



Division of Medicinal Chemistry
Scientific Abstracts
for the
256th National Meeting and Exposition

August 19-23, 2018
Boston, MA

MEDI

Division of Medicinal Chemistry

A. Stamford, *Program Chair*

OTHER SYMPOSIA OF INTEREST:

Diminutive Molecules, Big Impact: The Chemistry of ADC Linker-Payloads (see *ORGN*, Wed)

Drug Design (see *COMP*, Tue, Wed, Thu)

Frontiers in Organofluorine Research for Biological Chemistry & Drug Discovery (see *BIOL*, Wed)

Glycoprotein & Carbohydrate-Based Drugs for Human Health (see *CARB*, Tue, Wed)

Nanomaterials in Drug Delivery: Efficacy & Toxicity Considerations (see *TOXI*, Wed)

SOCIAL EVENTS:

MEDI Posters & Social, 7:00 PM: Sun, Wed

MEDI Hall of Fame Reception, 5:30 PM: Tue

BUSINESS MEETINGS:

Business Meeting, 5:30 PM: Sun

SUNDAY MORNING

Section A

Boston Convention & Exhibition Center
Room 210 B/C

Small-Molecule Approaches to the Treatment of Inflammatory Bowel Disease

K. S. Currie, *Organizer, Presiding*

8:30 Introductory Remarks.

8:35 MEDI 1. Oral peptide macrocycle antagonists of integrin $\alpha 4\beta 7$ for the treatment of IBD. **A.L. Roughton**, M. Pérez Vázquez, M.M. Morshed, A.P. Kafal, R. Mendoza Sanchez, Y. Boutin, A.K. Yudin, L. Bergeron, J.A. Coull

9:05 MEDI 2. Discovery & development PTG-100, an oral peptide antagonist of $\alpha 4\beta 7$ integrin, for the treatment of inflammatory bowel disease. **A. Bhandari**

9:35 MEDI 3. Small molecule approaches to the treatment of IBD. **G.D. Glick**

10:05 Intermission.

10:15 MEDI 4. Small-molecule antagonists targeting the NLRP3 inflammasome for treatment of inflammatory diseases. **W.R. Roush**, D. Shen, S. Venkatraman, J. Katz, E.J. Olhava, K. Byth, D. Winkler, A. Stutz, D. Bertheloot, S. Braams, A. Kitanovic, I. Kitanovic, P. Trippner, B. Sanchez, X. Lu, L. Franchi, E. Latz, S. Ghosh, D. Dean, A. Opiari, M. Seidel, G.D. Glick

10:45 MEDI 5. Discovery of a cross-species potent and selective inhibitor of receptor-interacting protein kinase 1 (RIPK1) providing protection in a *Nemo* deletion model of IBD. **S.D. Patel**

11:15 MEDI 6. BT-11: A new first-in-class oral therapeutic for Crohn's disease and ulcerative colitis that targets LANCL2. **R.D. Gandour**, J. Bassaganya-Riera

Section B

Boston Convention & Exhibition Center
Room 210A

General Oral Session

A. W. Stamford, *Organizer*

M. Lu, *Presiding*

8:30 MEDI 7. Impact of synthetic chemistry methodologies in drug discovery. J. Boström, D.G. Brown, R. Young, **G.M. Keseru**

8:50 MEDI 8. Rank ordering compound designs for synthesis: When do methods work and what are some known limitations? **K.P. Cusack**, M. Argiriadi, E. Breinlinger, J. Edmunds, D.M. George, F. Michael, M.Z. Hoemann

9:10 MEDI 9. Design, synthesis, and evaluation of nonretinoid retinol binding protein 4 antagonists for the potential treatment of atrophic age-related macular degeneration and Stargardt disease. **C. Cioffi**, K. Petrukhin

9:30 MEDI 10. Discovery of novel quinoline sulfonamide derivatives as potent, selective and orally active ROR γ inverse agonists. **D. Potin**, J. Amaudrut, M. Argiriadi, M.M. Barth, E. Breinlinger, D. Bressac, P. Broqua, D.J. Calderwood, M. Chatar, K.P. Cusack, S.B. Gauld, S. Jacquet, R.V. Kamath, V. Lepais, J. Luccarini, P. Masson, C. Montalbetti, L. Mounier, O. Poupardin, S. Rouaud, C.D. Wallace

9:50 MEDI 11. Development of thienopyridines as potent antiproliferative agents. **D. Barker**, L.I. Pilkington, M. van Rensburg, N.A. Haverkate, J. Reynisson, W.A. Denny, E. Leung

10:10 MEDI 12. Development of 4-oxazolidinone natural products as infectious disease lead compounds. **J.G. Pierce**

10:30 MEDI 13. Discovery of inhibitors of sirtuin and PARP enzymes from a DNA-encoded chemical library designed to target NAD⁺-binding pockets. **R.M. Franzini**, L. Yuen, S. Dana

10:50 MEDI 14. Complex-selective HDAC inhibitors promote synaptic resilience for therapeutic treatment of neurological disorders. **N.O. Fuller**, M.C. Hewitt, M. Ivarsson, J.A. Lowe, B. Lynch, T. McKee, A. Pirone, M. Quinton, A. Rosenberg

11:10 MEDI 15. Discovery of a novel pyrrolobenzodiazepine DNA-alkylator as an efficacious ADC payload. **B. Wei**, J. Dela Cruz Chuh, D. Zhang, Y. Ma, J. Chen, T. Pillow, P.S. Dragovich

11:30 MEDI 16. Medicinal chemistry centric approach to studying the delivery of diverse pyrrolobenzodiazepine dimers via antibody-drug conjugate technology. **L.R. Staben**

11:50 MEDI 17. Accelerating multiple medicinal chemistry projects using matched molecular pair analysis for knowledge based design: A review from the past 8 years of use at the front line. **A. Dossetter**, E.J. Griffen, A.G. Leach, S. Montague

Merck Research Award Symposium

Sponsored by WCC, Cosponsored by ANYL, COMP, MEDI and PROF

Bioactives & Neurodegenerative Diseases

Sponsored by AGFD, Cosponsored by MEDI

SUNDAY AFTERNOON

Section A

Boston Convention & Exhibition Center
Room 210 B/C

Awards Session

ACS Award for Creative Invention

Cosponsored by PROF
A. W. Stamford, *Organizer, Presiding*

1:30 MEDI 18. Award Address (ACS Award for Creative Invention sponsored by the ACS Corporation Associates). Design of kinase inhibitor medicines utilizing protein-ligand structures and property-based efficiency. **R. Kania**

2:10 MEDI 19. Discovery of AZD4573, a potent and selective inhibitor of CDK9 that enables transient target engagement for the treatment of haematological malignancies. **J.G. Varnes**, B. Barlaam, C. De Savi, L. Drew, A. Ferguson, D. Ferguson, C. Gu, J. Hawkins, A. Hird, M.L. Lamb, N. O'Connell, K. Pike, T. Proia, M. San Martin, M. Vasbinder, J. Wang, W. Shao

2:35 MEDI 20. Hit-selection and optimization strategy en route to FGF401, a reversible-covalent inhibitor of FGFR4 for the treatment of hepatocellular carcinoma. **T. Knoepfel**, P. Furet, P. Nimsgern, S. Ripoche, M. Kiffe, C. Leblanc, N. Buschmann, R. Mah, D. Graus-Porta, A. Weiss, M. Wartmann, I. Galuba, J. Trappe, R.A. Fairhurst

3:00 MEDI 21. Discovery of ORIC-101, a potent and selective glucocorticoid receptor antagonist. **Y. Rew**, X. Du, J. Eksterowicz, H. Zhou, N. Jahchan, L. Zhu, H. Kawai, X. Yan, L.R. McGee, J.C. Medina, T. Huang, C. Chen, T. Zavorotinskaya, D. Sutimantanapi, J. Waszczuk, E. Jackson, E. Huang, Q. Ye, V. Fantin, D. Sun

3:25 MEDI 22. Structure based design: Identification of the clinical candidate ABBV-744, a first-in-class highly BDII-selective BET bromodomain inhibitor. **L.**

Wang, G.S. Sheppard, S.D. Fidanze, L.A. Hasvold, D. Liu, J.K. Pratt, M. Bui, E. Faivre, X. Huang, X. Lin, D. Wilcox, Y. Shen, D.H. Albert, W. Kati, K.F. Mc Daniel

3:50 MEDI 23. Developing inhibitors of BRAF and RAS mutant cancers. **K. Dalby**

4:15 MEDI 24. Discovery and optimization of potent, selective, and orally available IDO1 heme-binding inhibitors featuring a novel A-pocket piece. **H. Zhang, A. Achab, M.J. Ardolino, X. Chai, M. Cheng, Y. Deng, A. Doty, H. Ferguson, X. Fradera, I. Knemeyer, C. Li, K. Liu, T.A. Martinot, M. McGowan, R. Miller, K. Otte, Q. Pu, B. Purakattle, N. Sciammetta, N. Solban, X. Song, P. Spacciapoli, A. Wise, W. Yu, H. Zhou, D.J. Bennett, Y. Han**

4:40 MEDI 25. Discovery of a selective, non-nucleoside small molecule inhibitor of DNA methyltransferase 1 (DNMT1). **B.W. King, A.B. Benowitz, J. Briand, C. Burt, C. Carpenter, M. Cockerill, K.A. Evans, D.T. Fosbenner, J. Handler, D.A. Heerding, A.M. Jordan, K. Keenan, R. Kruger, M. Li, J. Luengo, M. McCabe, C. McHugh, E. Minthorn, H. Mohammad, M.B. Pappalardi, M. Patel, A. Raoof, S. Romeril, L. Rueda, C. Sherk, A. Stowell, I. Waddell, K. Wong**

5:05 MEDI 26. Preventing regulatory T cell trafficking into the tumor microenvironment: Discovery of potent and selective CCR4 antagonists. **D.X. Hu, B. Abraham, B. Biannic, M.H. Bui, D. Chian, G. Cutler, J.J. Jackson, S. Jacobson, E. Karbarz, P. Kassner, J.M. Ketcham, L. Marshall, J. McKinnell, D. Pookot, M. Reilly, O. Robles, H. Shunatona, O. Talay, J. Walker, A. Wadsworth, A. Younai, M. Zibinsky, D.J. Wustrow**

Section B

Boston Convention & Exhibition Center
Room 210A

Emerging Trends in Target Identification

N. A. Meanwell, *Organizer*

A. K. Mapp, S. Niessen, P. M. Scola, K. Yeung, *Organizers, Presiding*

1:30 Introductory Remarks.

1:35 MEDI 27. Enabling chemical biology in oncology discovery. **S. Niessen**

2:10 MEDI 28. Revealing the druggable genome using chemical proteomics. **L. Jones**

2:45 MEDI 29. Expanding the druggable proteome: Ligand and target discovery by fragment-based screening in cells. **C. Parker**, A. Galmozzi, Y. Wang, B. Correia, E. Saez, B. Cravatt

3:20 MEDI 30. Target class platform accelerates deubiquitinase early discovery efforts. **S. Buhrlage**, E. Weisberg, N. Schauer, X. Liu, J. Yang, I. Lamberto

3:55 MEDI 31. Molecular visualization of tissues by MALDI imaging MS: Applications in drug discovery and development. **S. Castellino**

Structures & Functions of Glycans

Sponsored by CARB, Cosponsored by ANYL, BIOL, CELL, MEDI and ORGN

Bioactives & Neurodegenerative Diseases

Sponsored by AGFD, Cosponsored by MEDI

SUNDAY EVENING

Section A

Boston Convention & Exhibition Center
Exhibit Hall B1

General Poster Session

A. W. Stamford, *Organizer*

7:00 - 9:00

MEDI 32. Drug repurposing for schistosomiasis with assay central. **K.M. Zorn**, E.K. Chen, C.L. McConnon, A. Clark, C.R. Caffrey, S. Ekins

MEDI 33. Diaminopurines: structure activity relationships and structure property relationships towards a lead for human African trypanosomiasis inhibitors. **B. Singh**, R. Diaz, G. Ceballos, D. Rojas, M. Martinez-Martinez, P. Manzano-Chinchon, M. Navarro, M.P. Pollastri

MEDI 34. SAR exploration of a novel series of compounds for human African trypanosomiasis. **M.J. Buskes**, R. Diaz, G. Ceballos, M. Navarro, M.P. Pollastri

MEDI 35. Extraction and characterisation of an anti trypanosomal compound from the seeds of *Cassia occidentalis*. **S.A. Ogbuagu**

MEDI 36. Optimization of pyrazolo[1,5-*b*]pyridazines for the treatment of human African trypanosomiasis. **W. Tear**, S. Bag, R. Diaz, G. Ceballos, C. Cordon-Obras, D. Rojas, M. Martinez-Martinez, P. Manzano-Chinchon, M. Navarro, M.P. Pollastri

MEDI 37. SAR and ADME optimization of pyrazolopyridine-based human PDE4 inhibitors for human African trypanosomiasis. **A. Spaulding**, R. Leurs, H. de-Koning, D. Brown, M.P. Pollastri

MEDI 38. Hit-to-lead optimization of 3,5-disubstituted-7-azaindoles for human African trypanosomiasis. **D. Klug**, L. Silva, K.C. Forbes, R. Diaz, G. Ceballos, C. Cordon-Obras, M. Martinez-Martinez, P. Manzano-Chinchon, M. Navarro, M.P. Pollastri

MEDI 39. Repurposing as a strategy for the discovery of a new antileishmanial. **R. Charlton**, P.G. Steel, P. Denny, B. Rossi Bergmann

MEDI 40. Probing key elements of teixobactin-lipid ii interactions in membrane. **P. Wen**, J.M. Vanegas, S.L. Rempe, E. Tajkhorshid

MEDI 41. Design and synthesis of dual-acting quorum sensing inhibitors to suppress the virulence program of *Pseudomonas aeruginosa*. **A. Hossain**, N.A. German

MEDI 42. TAT-functionalized pH-sensitive liposomes for the treatment of bacterial meningitis. **C. Bartomeu Garcia**, D. Shi, T. Webster

MEDI 43. Strategies for restoring β -lactam activity against antibiotic resistant bacteria. **M.A. Boudreau**

MEDI 44. Bio-orthogonal chemistry-based approach for targeted treatment of bacterial infections. **N. Yee**, J. Mejia Oneto, M. Royzen, K. Wu

MEDI 45. Development of aminoglycoside resistance enzyme inhibitors as a means to rescue antibiotic activity. **M.R. Leung**, K.C. Leckett, X. Li, A. Chaudhry, M. Keramane, A. Capretta

MEDI 46. Specific structure variations of chimera ligand molecules for controlling bacterial drug-tolerance and persister formation. **F. Burns**, Y.Y. Luk

MEDI 47. Non-traditional antibiotic strategies targeting siderophore utilization in human pathogenic *Acinetobacter baumannii*. **T. Bohac**, J.A. Shapiro, T.A. Wencewicz

MEDI 48. Semisynthetic analogues of anhydrotetracycline as potential inhibitors of tetracycline destructase enzymes. **J.L. Markley**, L. Fang, A.J. Gasparrini, C.T. Symister, H. Kumar, G. Dantas, N. Tolia, T.A. Wencewicz

MEDI 49. Potentiating penicillins, carbapenems, and cephalosporins to kill MRSA. **C.V. Rice**, M. Foxley, A.K. Lam, A. Ly, M. Harney, E. Moen, B.A. Wilson

MEDI 50. Discovery of indole- and indazole-acylsulfonamides as potent and selective Nav1.7 inhibitors for the treatment of pain. **G. Luo**, L. Chen, A. Easton, A. Newton, C. Bourin, E. Shields, K. Mosure, M. Soar, R. Knox, M. Matchett, R. Pieschl, D. Post-Munson, S. Wang, J. Herrington, J. Graef, K. Newberry, L. Bristow, N. Meanwell, L.A. Thompson, C.D. Dzierba

MEDI 51. Discovery of new indole-based acylsulfonamide Nav1.7 inhibitors. **Y. Wu**, B. Venables, J. Guernon, J. Chen, S. Sit, R. Rajamani, R. Knox, M. Matchett, R. Pieschl, J. Herrington, L. Bristow, N. Meanwell, L. Thompson, C.D. Dzierba

MEDI 52. Structure-based design to improve the selectivity of kinase inhibitors in cancer therapy. **A. Assadieskandar**, C. Yu, C. Zhang

MEDI 53. Design and synthesis of selective imidazo[1,2-*b*]pyridazine and pyrazolo[1,5-*a*]pyrimidine inhibitors of leucine-rich repeat kinase 2 (LRRK2) using a checkpoint kinase 1 (CHK1)-derived crystallographic surrogate. **S.C. Ray**

MEDI 54. Quantitative characterization of bivalent probes for the dual bromodomain protein transcription initiation factor TFIID subunit 1, TAF1. **J.L. Suh**, B. Watts, J.I. Stuckey, J.L. Norris-Drouin, S.H. Cholensky, B.M. Dickson, Y. An, S. Mathea, E.

Salah, S. Knapp, A. Khan, A.T. Adams, B.D. Strahl, C.A. Sagum, M.T. Bedford, L.I. James, D. Kireev, S.V. Frye

MEDI 55. Nanoparticles with targeting and ROS triggering properties as an antigen delivery system. X. Liang, J. Duan, Y. Chen, H. Li, C. Li, **J. Yang**

MEDI 56. Identification of receptor interacting protein kinase 3 (RIPK3) type II inhibitors using high-throughput mechanistic studies in hit triage. **A.C. Hart**, L.M. Abell, C. Weigelt, J. Guo, M. Mertzman, C. Chaudhry, H. Lu, R. Padmanabha, M. Pokross, K. Kish, A. Douglas, D. Columbar, P. Zhang, B. Carpenter, J.E. Macor, W.J. Pitts

MEDI 57. Application of organocatalysis in bioorganometallic chemistry: Asymmetric synthesis of multifunctionalized spirocyclic pyrazolone-ferrocene hybrids as novel RalA inhibitors. **B. Han, W. Huang**, C. Peng

MEDI 58. Organocatalytic cascade reaction for asymmetric synthesis of novel chromane-fused spirooxindoles that potently inhibit cancer cell proliferation by inhibiting MDM2-p53 interaction. **W. Huang**, B. Han, C. Peng

MEDI 59. Discovery of EOS789: A novel inhibitor of NaPi-IIb, Pit-1 and Pit-2 for hyperphosphatemia. **N. Hori**, A. Kimbara, N. Okamoto, Y. Murata, Y. Ohtake, Y. Ono, S. Tanaka, E. Mizuguchi, T. Harada, K. Tachibana, M. Ide, K. Nomura, H. Kashiwagi, R. Hirokane, K. Morikami, S. Ohtomo, Y. Ichida, Y. Tsuboi, N. Horiba, K. Yamaguchi, T. Takahashi

MEDI 60. Novel conformational-restricted endocannabinoid probes with improved metabolic stability. **L. Ji**, S. Nikas, Y. Liu, M. DSouza, S.N. Kudalkar, O. Benchama, A. Korde, C. Honrao, S. Mallipeddi, S. Wu, S. Xu, N. Zvonok, L.J. Marnett, A. Makriyannis

MEDI 61. Mono and bifunctional cannabinoid receptor probes. **S. Jiang**, S. Nikas, C. Iliopoulos Tsoutsouvas, W. Zhang, S. Wu, J. Raghav, J. Anderson, A. Makriyannis

MEDI 62. Discovery of small-molecule Bax activators for the treatment of triple-negative breast cancer. G. Liu, D. Li, H. Chen, Y. Ding, Q. Shen, **J. Zhou**

MEDI 63. Design, synthesis, and structure-activity relationships (SARs) of novel series of irreversible LSD1 inhibitors with improved hematological liability. **Y. Hattori**, S. Morimoto, M. Toyofuku, S. Matsumoto, S. Matsuda, R. Baba, Y. Tominari, M. Iwatani, H. Oki, S. Iwasaki, M. Ito

MEDI 64. Folic acid derived-P5779 mimetics regulate DAMP-mediated inflammation through disruption of HMGB1:TLR4:MD-2 axis. **S. Sun**, M. He, Y. Wang, H. Yang, Y. Al-Abed

MEDI 65. Design, synthesis, and evaluation of functionalized 5-(phenoxyethyl)-1,3-dioxane analogs as potential treatments for metabolic syndrome. **B.E. Blass**, P. Iyer, M. Abou-Gharbia, W.E. Childers, J.C. Gordon, M. Ramanjulu, G.C. Morton, P. Arumugam, J. Boruwa, J.W. Ellingboe, S. Mitra, R. Nimmareddy, S. Paliwal, J. Rajasekhar, S. Shivakumar, P. Srivastava, R.S. Tangirala, K. Venkataramanaiah, M. Yanaandra, R. Bobbala, K.R. Leleti

MEDI 66. New class of mononuclear ruthenium complexes as antimicrobial agents. **B. Sun**, R. Keene, G. Collins

MEDI 67. Suitable chemical library for academic researchers in Japan. **H. Kojima**

MEDI 68. Antisense-mediated knockdown of host selenoprotein expression in ZIKV infected cells via targeting of cellular mRNA by viral RNA. **G.P. Dailey**

MEDI 69. Inhibitors of cytochrome P450 17A1 that spare 21-hydroxylase activity. **C.D. Vogt**, C. Fehl, R. Yadav, K. Li, E.E. Scott, J. Aube

MEDI 70. Highly selective purine based covalent CDK12 inhibitors. **J.W. Johannes**, C. Denz, N. Su, A. Wu, A. Impastato, S. Mlynarski, J. Varnes, B. Prince, J. Cidado, N. Gao, M. Haddrick, N. Jones, S. Li, X. Li, Y. Liu, T. Nguyen, N. O'Connell, E. Rivers, D. Robbins, R. Tomlinson, T. Yao, X. Zhu, A. Ferguson, M.L. Lamb, J. Manchester, S. Guichard

MEDI 71. Discovery, characterization and anti-Parkinsonian effect of a novel mGluR4 PAM chemical series. **A. Blayo**, B. Manteau, S. Mayer, S. Schann, M. Frauli, D. Charvin

MEDI 72. Investigation of the chemical space for brain penetrable, carboxylic acid-containing compounds: Expanding the area available for CNS drug discovery. **Y. Ohashi**, D. Hasegawa, M. Kotake, T. Kurokawa, T. Nishioka, I. Kushida, T. Yoshida, T. Mochizuki, M. Yamamoto, T. Komori, Y. Yoshida, K. Takeda, T. Terauchi

MEDI 73. Discovery of the clinical candidate OWL833 as an orally active non-peptide GLP-1R agonist. **H. Yoshino**, S. Tsuchiya, A. Matsuo, M. Nishimoto, K. Takami, K. Hiroko, Y. Nishimura, Y. Furuta, T. Kamon, N. Hori, T. Shiraishi, H. Kashiwagi, A. Mizutani, F. Kawagishi, M. Ide, T. Haneishi, S. Yeu, M. Sugiyama, T.

Emura, S. Niizuma, M. Wadamoto, T. Kawai, S. Yoshida, Y. Suzuki, K. Ogawa, S. Nagao, S. Tanida, M. Aoki, T. Sato, H. Sato

MEDI 74. Fluorinated (*R*)-(-)-aporphines as potential agonist positron emission tomography ligands for serotonergic 5-HT_{1A} receptor. **Y. Xu**, A.W. Sromek, J.L. Neumeyer

MEDI 75. Synthesis of ergoline-based analogs. **Á. Szabolcs**, V. Ujj, J. Gerencsér, M. Guzman, T. Armer, S. Borland

MEDI 76. Syntheses of 2-substituted oxetan-3-amines . **L. Zhang**, G. Liu, H. Li, X. Wu, M. Yang

MEDI 77. Exploration of strained saturated heterocycles as isosteres in medicinal chemistry. **C. Choi**, J. Mousseau, J.A. Bull

MEDI 78. Synthesis and evaluation of novel BACE1 inhibitors based on the *N*-amidino nitrogen-containing ring structure. **K. Kobayashi**, D. Joho, C. Taniguchi, M. Tanaka, R. Kimura, K. Komurasaki, Y. Kawasaki, Y. Hattori, K. Akaji

MEDI 79. Design of potent and selective inhibitors for human b-secretase 1 (memapsin 2), a target for Alzheimer's disease. A.K. Ghosh, **E.L. Cardenas**

MEDI 80. Design, synthesis and validation of small molecules that sensitize HIV-1 infected cells to antibody dependent cellular cytotoxicity (ADCC). **M.C. Grenier**, S. Ding, A. Finzi, A.B. Smith

MEDI 81. Porphyrins - A gift of nature to eradicate cancer? (Photodynamic therapy). **Z.S. Berhe**, E.C. Ojadi

MEDI 82. Discovery of novel phosphonate prodrugs by *de novo* rational design. **M. De Lera Ruiz**, I.T. Raheem, M.T. Rudd, J. McCauley, J. Schreier, T.J. Hartingh, B. Ma, H. Aloysius, S. Carroll, M. Lai, J. Balsells-Padros, A. Bennet

MEDI 83. Design, synthesis and *in vitro* evaluation of dual inhibitors of phosphatidylinositol-3-kinase delta (PI3K δ) and histone deacetylase 6 (HDAC6). **A. Thakur**, G. Grewal, G.J. Tawa, M. Henderson, C. Danchik, T.D. Lee, A. Simeonov

MEDI 84. Development of chemical probes targeting ASH1L histone methyltransferase. **H. Li**, J. Deng, D. Rogawski, S. Klossowski, T. Purohit, K. Kempinska, E. Kim, M. Szewczyk, Z. Jin, D. Borkin, D. Montgomery, J. Ndoj, H. Cho, H. Miao, J. Grembecka, T. Cierpicki

MEDI 85. Discovery of leniolisib (CDZ173), a potent and selective new generation PI3Kdelta inhibitor for autoimmune and inflammatory diseases. **N.G. Soldermann**

MEDI 86. Efficacy of compounds derived from a native medicinal plant against common wound-colonising bacteria. **V.A. Agampodi**, T. Collet

MEDI 87. Novel 2-arachidonoyl glycerol analogs with enhanced bio-activities and stabilities: Design, synthesis and *in vitro* biochemical evaluation. **Y. Liu**, S. Nikas, L. Ji, A. Korde, A. Ciesielski, A. Straiker, O. Benchama, A. Dhopeswarkar, C. Honrao, K. Mackie, A. Makriyannis

MEDI 88. Indole-based positive allosteric modulators for targeting CB₁ receptor to overcome neuropathic pain. **A. Resendez**, K. Kumar, V. Kumar, B.K. Kobilka, S. Malhotra

MEDI 89. Synthesis of new benzodiazepines that function as α_5 -GABA_A receptor ligands to target group 3 medulloblastomas. **F. Rashid**, G. Li, T. Ahmed, O. Jonas, S. Sengupta, J.M. Cook

MEDI 90. Synthesis and biological evaluation of novel imidazo[2,1-b]oxazole derivatives as V600E BRAF inhibitors for treatment of melanoma. **M.S. Abdel-Maksoud**, M.I. El-Gamal, U.M. Ammar, E.M. Ali, K.I. Mersal, H.S. Choi, C.H. Oh

MEDI 91. Using bacterial cytological profiling to determine the mechanism of action of antimicrobial peptides. **S.A. Juliano**, S.S. Duay, A.M. Angeles Boza

MEDI 92. Novel CMKLR1 inhibitors and structure activity relationship studies for application in demyelinating disease. V. Kumar, M. LaJevic, B.A. Zabel, **S.V. Malhotra**

MEDI 93. Small molecules facilitating DNA repair in breast cancer cells. M. Pandrala, K. Hastak, V. Kumar, M. Gardiner, J.M. Ford, **S.V. Malhotra**

MEDI 94. Novel chalcone derivatives as potential therapeutic agents for triple negative breast cancer. **V. Kumar**, C.C. Going, D. Tailor, M. Pandrala, A.M. Birk, S. Pitteri, **S.V. Malhotra**

MEDI 95. Prevention of trigeminal neuropathic pain development in rats using novel deuterated GABA_AR- α_6 subtype selective ligands. **D.E. Knutson**, D. Vasovic, B. Divovic, M. Treven, F. Steudle, P. Scholze, B. Brković, W. Sieghart, M. Ernst, J.M. Cook, M.M. Savic

MEDI 96. Design and synthesis of proanthocyanidin derivatives as an inhibitor of amyloid β aggregation. **M. Mizuno**, K. Mori, I. Nakanishi, K. Matsumoto, M. Shibamura, K. Fukuhara

MEDI 97. Efficient synthetic methodology for the construction of dihydronaphthalene and benzosuberone molecular scaffolds with application as potent inhibitors of tubulin polymerization. **H. Niu**, D. Mondal, T.E. Strecker, J. Gerberich, J.W. Campbell III, D. Saha, D.J. Chaplin, E. Hamel, R.P. Mason, M.L. Trawick, K.G. Pinney

MEDI 98. Design, synthesis, and structure-activity relationships of pyrido[3,2-*d*]pyrimidines as microtubule targeting agents that are effective against Pgp and β III-tubulin overexpressing cancer cells. A. Gangjee, **A.B. Doshi**, E. Hamel, S. Mooberry

MEDI 99. Pyrazolo[4,3-*d*]pyrimidines: A novel scaffold for microtubule-targeting agents (MTAs). **F. Islam**, T.M. Quadery, R. Bai, E. Hamel, A. Gangjee

MEDI 100. Investigating the binding modes and structure-activity relationships of small molecule FPR2 agonists using receptor homology modelling. **M. Maciuszek**, T. Chapman, G. Nicoales, K. Birchall, C. Reutelingsperger, M. Perretti, A. Merritt

MEDI 101. Synthesis and characterization of imidazopyrazine derivatives as VAV1 inhibitors. **M. Gerspacher**, P. Skaanderup, P. Imbach-Weese, L. Doumampouom Metoul, E. Roehn-Carnemolla, D. Arz, A. Garlot, A. Remond, V. Eric, M. Knapp, A. Lingel, V. Stucke, P. Chene, F. Hofmann

MEDI 102. Synthesis of novel chloramphenicol derivatives as ribosome-targeting antibiotics. **P.I. Fernando**, S.T. Gregory, S. Donhue, B.L. DeBoef, P. Cesana, J. Gerwald

MEDI 103. Synthesis and evaluation of α,β -unsaturated phosphonate esters as DXR inhibitors. **K. Heidel**, R. Edwards, S. Arnett, H.I. Boshoff, M.J. Meyers, A.R. Odom, C.S. Dowd

MEDI 104. Design, synthesis and evaluation of novel antimalarials targeting apicoplast DNA polymerase (apPOL) from *P. falciparum*. **P. Chheda**, R.J. Kerns

MEDI 105. Microwave assisted synthesis and characterization of 4-aminopyridine (ampyra) derivatives and their applications. **M.A. Abusultan**, Y.M. Hijji

MEDI 106. Preliminary evaluation of novel serotonin antagonists as potential antidepressant agents. **H. Giratallah**, K.M. Blattner, J.C. Gordon, D.A. Pippin, B.E. Blass, D.J. Canney

MEDI 107. Design, synthesis and bioactivity testing of *azotochelin* analogs as potential antibiotics. **N.M. Karadkhelkar**

MEDI 108. Discovery of AM-2995, a potent, selective and orally bioavailable APJ agonist for the treatment of heart disease. **Z. Ma**, X. Wang, M. Wanska, L. Heumann, R. Connors, F. Kayser, J.C. Medina, Q. Guo, Y. Chen, R. Chen, Y. Zhang, J. Ma, J. Shi, J. Wong, G. Swaminath, J.B. Houze

MEDI 109. Chemical modification and structure activity relationship (SAR) evaluation of Fellutamide B. **N. Acharekar**, **S. Yoganathan**

MEDI 110. Tantalum oxide nanoparticles for use in contrast enhanced computed tomography. **T. Lawson**, A. Patwa, J. Freedman, B.D. Snyder, M.W. Grinstaff

MEDI 111. Small molecule quinolinone derivatives that increase survival motor neuron protein via an SMN2 gene transcription enhancing mechanism. **D.K. Fiejtek**, J. Ahn, A. Rietz, H. Li, E.J. Androphy, K.J. Hodgetts

MEDI 112. Biostructural optimisation of a piperazine amide based series of Liver X Receptor (LXR) agonists. **A. Cooke**, X. Fradera, D.J. Bennett

MEDI 113. Synthesis and evaluation of the metabolites of GLS362E, an anti-*Clostridium difficile* lead compound. **A. Marashio**, B. Urbina, W. Xu, R. Lima

MEDI 114. Comparing and validating machine learning models for *Mycobacterium tuberculosis* drug discovery. **T. Lane**, D.P. Russo, K.M. Zorn, A. Clark, A. Korotcov, V. Tkachenko, R. Reynolds, A.L. Perryman, J.S. Freundlich, S. Ekins

MEDI 115. Selective sulfa drug acylations for antitubercular drug design. **M.J. Hearn**, C. Pugh, M.H. Cynamon

MEDI 116. Strained amine heterocycles as non-hydrolyzable β -lactam surrogates: Mechanistic probes for *Mycobacterium tuberculosis*. **S.M. Scarry**, D. Cesta, T. Abramyan, B. Gold, L. Lopez Quezada, K. Saito, D. Kireev, S. Somersan Karakaya, C.F. Nathan, J. Aube

MEDI 117. Synthesis of Pan-CMP mimics to inhibit CoaBC. **H. Butman**, X. Wang, R.C. Brothers, V. Mizrahi, J.C. Evans, E. Strauss, C.S. Dowd

MEDI 118. Synthesis and antimycobacterial activity of new *N*-oxide compounds active against multi-resistant tuberculosis. P.C. Souza, G.F. Fernandes, L.B. Marino, C.M. Ribeiro, P.B. da Silva, M. Chorilli, C.S. Siva, D.M. Hunt, L.S. de Carvalho, C.D. Costa, S.H. Cho, Y. Wang, S.G. Franzblau, C. ManChin, F.R. Pavan, **J.L. Dos Santos**

MEDI 119. Development of high affinity agonist ligands for the D2 receptor: Potential PET imaging agents. **A. Nurani**, Y. Xu, A.W. Sromek, J.L. Neumeyer

MEDI 120. Pharmacophore models for inhibitors of DNA methyltransferases. J. Ruiz-Rios, F.I. Saldívar-González, **J.L. Medina-Franco**

MEDI 121. Alpha-substituted tropolones as potential anti-blood cancer therapeutics. **J. Li**, E. Falcone, D. Wright, A.J. Wiemer

MEDI 122. HIV protease as a target for novel antiretroviral therapies. **I.W. Windsor**, B. Gold, D.M. Dudley, B. Graham, M.J. Palte, J.C. Lukesh, T.P. Smith, K.T. Forest, D.H. O'Connor, R.T. Raines

MEDI 123. Structure-based design, synthesis, evaluation and x-ray crystal structure analysis of HIV-1 protease inhibitors with modified P1, P1' and P2' groups. **L. Rusere**, A. Ali, G.L. Lockbaum, S. Lee, R. Swanstrom, C.A. Schiffer

MEDI 124. Design and synthesis of novel tricyclic 3,4-dihydro-2H-pyrido[1,2-a]-pyrazine-1,6-dione derivatives as gamma-secretase modulators. **F. Bischoff**, F. Van den Keybus, F. Rombouts, M. Mercken, H. Gijzen

MEDI 125. Enterovirus inhibitory activity of substituted urea and thiourea derivatives of *p*-benzene sulfonamide. **P. Chakrasali**, H. Soo Bong, Y. Jung

MEDI 126. Design and synthesis of some novel 6,7-dimethoxyquinazoline analogs as multi-target-directed ligands for the treatment of hypertension. **R.B. Ghuge**, N. Agrawal, B. Pithwa, A. Khadse, P.R. Murumkar, M. Yadav

MEDI 127. Synthesis and characterization of ibuprofen and diclofenac prodrugs. **J.J. James**, H.D. Tappa, Y.M. Hijji

MEDI 128. 4,6-Disubstituted quinazoline derivatives as inhibitors of the MEK5/ERK5 pathway. **S. Patel**, A.J. Motta, P.T. Flaherty, A. Bhatt, T. Wright, J. Cavanaugh

MEDI 129. Selective allosteric inhibition of MEK5: novel target for cancer therapeutics. **M. Gupta**, D. Shah, P.T. Flaherty, T. Wright, A. Bhatt, J. Cavanaugh

MEDI 130. SAR study of novel heterocyclic acylhydrazones as anti-fungal agents targeting the synthesis of fungal GlcCer. **Y. Sun**, K.H. Haranahalli, C. Lazzarini, M.D. Poeta, I. Ojima

MEDI 131. 1H-pyrrolo[3,2-b]pyridine GluN2B-selective NMDA antagonists. **A. Soyode-Johnson**

MEDI 132. Discovery of linear and cyclic tetrapeptides inhibitors of Y-49 β -lactamase by structure-based drug design (SBDD) and molecular docking platforms empowered by MOE, AutoDock Vina and StarDrop-ADMET (Optibrium) module. **J. Gonzalez, C.C. Clement**

MEDI 133. Strategies for synthesis of various aza- β -lactam derivatives as potential β -lactamase inhibitors. **J. Fifer**, M.A. Boudreau

MEDI 134. Development of thiol containing open lactam analogues targeting metallo-beta-lactamases. **M. Ohoueu**, M.A. Boudreau

MEDI 135. Synthesis and structure-activity relationships of quinolinone and quinoline-based P2X7 receptor antagonists and their anti-sphere formation activities in glioblastoma cells. S. Kwak, **B. Ko**, W. Kim, J. Lee, J.H. Jung, Y. Kim

MEDI 136. Synthesis of CD437 analogs: compounds with MRSA persister cell activity and antibiotic synergy. W. Kim, **C. Keohane**, A. Steele, W.M. Wuest, F.M. Ausubel, E. Mylonakis

MEDI 137. Synthesis, pharmacological activity and molecular modeling studies of a series of 2-amino-1,4,5,6-tetrahydropyrimidine-5-carboxylic acid analogues as betaine/GABA transporter 1 (BGT1) substrate-inhibitors. **S. Kicking**, A. Al-Khawaja, A. Stæhr Haugaard, R. Löffler, M. Damgaard, G.F. Ecker, B. Frølund, P. Wellendorph

MEDI 138. Development of chemical tools for epigenetic reader proteins. **J. Waybright**, K.D. Barnash, J. Rectenwald, S.V. Frye, L.I. James

MEDI 139. Novel and highly selective dopamine D₃ receptor antagonists/partial agonists as potential treatments for opioid use disorders. **A. Shaik**, A. Bonifazi, S. Cemaj, J. Giancola, A. Gadiano, R. Rais, B. Slusher, A.H. Newman

MEDI 140. Annulation rescues the rodent potency of a series of inhibitors of receptor-interacting protein kinase 1 (RIPK1). **G. Hamilton**

MEDI 141. Design, synthesis and biological evaluation of nitrate ester analogs of SCP-1. **M. Das**, N.G. Bazan, M. Trudell

MEDI 142. Small organic molecules to modulate apoe, abca1, & LDLR protein levels for Alzheimer's therapy. **B.S. Bajwa, P. Kumar**, B. Kim, H. Karahan, I. Bal, J. Kim, S. Maitra

MEDI 143. Discovery, synthesis and characterization of a series of (1-alkyl-3-methyl-1*H*-pyrazolo-5-yl)-2-(5-aryl-2*H*-tetrazol-2-yl)acetamides as novel GIRK1/2 potassium channel activators. **S. Sharma**, K.A. Kozek, K.K. Abney, D. Weaver, C. Hopkins

MEDI 144. Structure-based drug discovery of a selective, covalent KRas G12C inhibitor with oral activity in animal models of cancer. **J.P. Fischer**, B.R. Baer, J. Ballard, J.F. Blake, K. Bouhana, B.J. Brandhuber, D.M. Briere, L.E. Burgess, M.R. Burkard, H. Chiang, M.J. Chicarelli, J.G. Christensen, K. Davidson, J.J. Gaudino, J. Hallin, L. Hanson, K. Hee, E.J. Hicken, R.J. Hinklin, M.A. Marx, M.J. Mejia, P. Olson, P. Savechenkov, N. Sudhakar, T.P. Tang, G.P. Vigers, H. Zecca, J.B. Fell

MEDI 145. Disruption of D1-D2 heterooligomers via synthetic peptides: A new therapeutic tool? **M. Champion**, P. Khazaei, H. Evans, D. Heyl-Clegg

MEDI 146. Synthesis and structure–activity relationship (SAR) studies of novel *Pyrazolopyridine* derivatives as inhibitors of *Enterovirus* replication. **Y. Xing**, J. Zuo, P. Krogstad, M.E. Jung

MEDI 147. Template alignment modeling of the structure-activity relationships of opioid ligands. **Z. Wu**, V.J. Hruby

MEDI 148. Overcoming fluoroquinolone resistance in bacterial with new binding interactions. **B.H. Williamson**, R.J. Kerns

MEDI 149. Towards the design of proteolysis targeting chimeras (PROTACs) for the degradation of polycomb group proteins. **F.M. Potjewyd**, K.N. Lamb, O. Bell, L.I. James, S.V. Frye

MEDI 150. Characterization of new CRBN binders: Impact on protein degradation efficiency and differentiated pharmacology compared to IMiDs. N. Ji, **Y. Zhang**, M. Weiss, K. Hari, K. Yuan, J. Chen, J.F. Kelleher, C. Loh, N. Mainolfi

MEDI 151. Identification of novel cyclic peptide-peptoid hybrid CXCR7 modulators. **C. Limberakis**, M. Boehm, K. Beaumont, R. Jones, A.S. Kalgutkar, L. Zhang, K. Atkinson, G. Bai, J. Brown, H. Eng, G.H. Goetz, B. Khunte, S. Lazzaro, S. Ryu, L. Tylaska, R. Turner, S. Leung, M. Ramaseshan, D. Price, S. Liras, M.P. Jacobson, D.J. Earp, S. Lokey, A. Mathiowetz, E. Menhaji-Klotz

MEDI 152. Synthesis and biological evaluation of N9-cis-cyclobutylpurine derivatives for use as cyclin-dependent kinase(CDK) inhibitors. **J. Ha**, S. Park, E. Kim, M. Yoo, J. Lee, C. Park, J. Hwang

MEDI 153. CXCR2 receptor antagonists for the treatment of colorectal cancer. **C. Black**, K.C. Nagulapalli Venkata, M. Labonte Wilson, H. Lenz, S.G. Louie, N.A. Petasis

MEDI 154. Pheophorbide a suppresses toll-like receptor signaling via IKK β /NF κ B/TBK1/IRF3 to improve survival in septic mice. **K. Taekyun**

MEDI 155. Fragment-based discovery of pyrazolopyridones as JAK1 inhibitors with excellent subtype selectivity. **A. Ritzen**, T. Vifian, R. Sindet, B.B. Hansen, M. Larsen, T.H. Jepsen, J. Larsen, J.G. Seitzberg, S. Rai, V.R. Nasipireddy, M.A. Carnerup, A. Jerre, C. Mølck

MEDI 156. Synthesis and biological evaluation of some novel heterocyclic compounds as potential anti-thrombotic agents. **A.N. Khadse**, S. Khan, N. Prajapati, R.B. Ghuge, P.R. Murumkar, S. Rajput, M. Yadav

MEDI 157. Inducing the activity of NK cells with NKp30 small organic ligands. **P. Pinheiro**, G.C. Justino, J.P. Miranda, M. Marques

MEDI 158. Exploration of (hetero)aryl derived thienylchalcones for antiviral and anticancer activities. V. Patil, S.A. Patil, R. Patil, A. Bugarin, K. Beaman, **S. Patil**

MEDI 159. Rapid and accessible *in silico* macrocycle design – application to BRD4. **S. Sciammetta**, M. Bauer, R. Scoffin, G. Tedesco, M.D. Mackey

MEDI 160. Structure-based design of inhibitors for STE20-like kinase (SLK). **R.A. Serafim**, S. Vasconcelos, W. Zuercher, T. Willson, J. Bennett, F. Sorrell, K.B. Massirer, J.M. Elkins

MEDI 161. Discovery and structure–activity relationship study of dihydropyrano [2,3-c] pyrazoles as inhibitors of USP7. **A. Pepe**, N. Hjortland, A.D. Mesecar

MEDI 162. Discovery of novel hVMAT2 ligands. **B.A. Provencher**, A.J. Eshleman, R.A. Johnson, O. Kryatova, J. Nelson, J. Tian, P.C. Meltzer, A. Janowsky

MEDI 163. Discovery of selective filviral inhibitors through phenotypic screening of an aryl-naphthalene lignan library. **A. Lindstrom**, D.P. Petrov, V.J. Davisson

MEDI 164. How far can we use human serum transferrin to transport drugs? **G.C. Justino**, M. Marques

MEDI 165. Optimization of penfluridol for use in anticancer therapy. **M. Ashraf Uz Zaman**, M. Sajib, C. Mikelis, N.A. German

MEDI 166. Photochemical release of glycine from excited state dendrimer: An example of novel drug delivery. **J.I. Lee**, J. Kang

MEDI 167. Metal binding antimicrobial peptoids. **J. Portelinha**, A.M. Angeles Boza, S. Cobb

MEDI 168. Roles of mitochondrial fusion promoter in ischemia/reperfusion injury. **S. Hou**

MEDI 169. Synthesis, characterization, cytotoxic and genotoxic evaluation of *N*⁶-benzylquinazoline-2,4,6-triamine derivatives. **A. Matus-Meza**, M. Herrera-Martínez, B. Chávez-Munguía, P. Talamás-Rohana, M. Velasco-Velazquez, C. Ordaz-Pichardo, F. Hernández-Luis

MEDI 170. Homology model template selection benchmarking: Global versus local similarity measures. **P. Castleman**, A.L. Parrill-Baker, D.L. Baker

MEDI 171. Phototoxicity of 7-oxycoumarins with keratinocytes. **J. Saxena**, J. Laskin, D. Heck, C.D. Guillon, N.D. Heindel

MEDI 172. Antibacterial activities of aurofin analogs. **B. Wu**, X. Yang, M. Yan

MEDI 173. Selective targeting of breast cancer brain metastases by cisplatin prodrug nano-formulation. **B. Surnar**, S. Dhar

MEDI 174. NAADP-BODIPY dye conjugates for characterizing NAADP binding proteins. **Z. Guan**, J. Slama

MEDI 175. Design, synthesis, and SAR of inhibitors of lipid chaperones (FABPs) toward next-generation therapeutic agents for chronic pain and cancer. **M. Awwa**, S.

Yan, M. Elmes, J. Li, K. Ziadkhanpour, M. Kaczocha, R.C. Rizzo, D. Deutsch, I. Ojima

MEDI 176. Exploiting solvent effects in drug design and optimization. A. Ajamian, C. Williams

MEDI 177. Hepatitis C virus NS3/4A protease inhibitors incorporating flexible P2 quinoxalines target drug resistant viral variants. J. Zephyr, A.N. Matthew, N. Kurt-Yilmaz, C.A. Schiffer, A. Ali

MEDI 178. Investigating the efficacy of functionalized hybrid gold nanoparticles as theranostic platforms in dialysis related amyloidosis and Alzheimer's disease. R. Burke, D.J. Swinton, M.P. Washington, H. Zhang, A. Boroujerdi

MEDI 179. Discovery and optimization of macrocyclic peptide dimerization inhibitors of BRAFwt. C. Beneker, M. Rovoli, M. Roring, G. Kontopidis, T. Brummer, C. McInnes

MEDI 180. Anticancer properties of ruthenium(II) complexes and their application for photodynamic therapy and photoactivated chemotherapy. R. Ryan, D.K. Heidary, K.C. Stevens, J.P. Selegue, E.C. Glazer

MEDI 181. Alternative synthetic pathway for a cytotoxic compound for lymphocytic leukemia. D. Belmona, L. Sanchez

MEDI 182. Development of structure-activity relationships of cjoc42 for targeting Gankyrin. J. Almasri, P. Farrales, E. Abo-Ali, Y. Otmankhel, A. Shaik, V. Dukhande, V. Gupta, A. Muth

MEDI 183. Development of small molecule- and peptide-based probes for targeting Gankyrin. D. Kanabar, A. Muth

MEDI 184. Lobaric acid and pseudodepsidones from the lichen *Stereocaulon paschale* inhibit NF- κ B signaling pathway. C. Carpentier, X. Barbeau, D. Grenier, P. Lagüe, N. Voyer

MEDI 185. Synthesis and biological evaluation of novel 6-substituted thieno[3,2-*d*]pyrimidines as targeted antifolates. T.M. Quadery, F. Islam, L.H. Matherly, A. Gangjee

MEDI 186. Regulation of AIMP2-DX2, oncogenic splicing variant using small molecule. S. Huddar, S. Lee, C. Park

MEDI 187. Re-defining the oxindole chemotype to identify narrow spectrum inhibitors of the dark kinases TLK2 and PKMYT1. **C.R. Asquith**, M.P. East, T. Laitinen, G.J. Tizzard, D.H. Drewry, G.L. Johnson, T. Willson

MEDI 188. Design, synthesis and biological evaluation of novel aromatic/heterocyclic sulfonamides as carbonic anhydrase inhibitors with selectivity for tumor-overexpressed isozyme IX. **U.K. Mondal**, E. McDuffie, S. Zamanova, C.T. Supuran, M.A. Ilies

MEDI 189. Design and synthesis of anxiolytic, anticonvulsant and antinociceptive benzodiazepine/GABA(A)ergic receptor subtype selective ligands as potential non-sedating treatment for anxiety disorders, epilepsy and pain disorders. **G. Li**, J. Witkin, J. Schkeryantz, R. Cerne, J. Li, L. Lewter, K. Freeman, D. Stafford, L. Arnold, J.M. Cook

MEDI 190. Cholesteryl ester vesicle mediated delivery of nucleic acids into neural cells *in vitro*. **S. Andres**, M.Q. Irving, A. Kovacs, J. Fraser-McArthur, J. Hughes, J. Schentag, **L. Mielnicki**, M. McCourt

MEDI 191. Isolation and synthesis of luffariellolide derivatives and evaluation of antibacterial activities against Gram-negative bacteria. **J. Lee**, A. Shin, H. Lee

MEDI 192. Electro-responsive ceria nanoparticle-embedded ferrocene-polyethyleneimine nanocarriers for the treatment of bacterial infections. **S. Zhao**, N. Bassous

MEDI 193. New insights into salvinorin A from an activated kappa opioid receptor structure. **P.D. Mosier**, T. Che, B.L. Roth

MEDI 194. Structure-activity relationship study of otilonium bromide as an antimicrobial agent. **J. Rhodes**, H. Wang, A. Cunningham, B. Daives, S.F. McHardy

MEDI 195. Interactions of pyridine based aromatic hydrazides and amides with model membrane interfaces. B.J. Peters, C. an Cleave, K. Giffen-Kent, D. Crick, A. Sostarecz, **D.C. Crans**

MEDI 196. Multi-target molecular profiling using MOE: A CYP450 isoform selectivity case study. **M.R. Goldsmith**, C. Williams

MEDI 197. Computational approach for performing medicinal chemistry transformations within a 3D active site. N. Thorsteinson, **A. Deschenes**

MEDI 198. MOEsaic: Application of matched molecular pairs to interactive SAR exploration. **A. Ajamian**

MEDI 199. Organizing 3D project data for structure-based drug design. **A. Ajamian**

MEDI 200. Direct electrochemical differentiations of cancer and normal cells on the titanate. **H. Alismail**, Y. Du, J. Zhou, Z. Tian

MEDI 201. Application of extended Huckel theory to pharmacophore modeling. **A. Ajamian**

MEDI 202. Discovery of highly potent PI4KIII β inhibitors against rhinovirus replication. **P. Chakrasali**, H. Soo Bong, Y. Jung

MEDI 203. Amphipathic fatty acyl-cyclic [W₄R₄K] peptides as antimicrobial agents against pathogenic bacteria. **A.D. Akinwale**, J. Yamaki, K. Parang, R. Tiwari

MEDI 204. Modular synthesis of peptide-based single and multimodal targeted molecular imaging agents. **H.F. Schmitthener**, T. Barrett, S. Beach, L. Heese, A. Sweeny-Jones, C. Weidman, K. Jones, d. Dobson, X. Xu, H. Ophardt, K. Embong, I. Evans

MEDI 205. Vinblastine and effects of its metabolites on nausea associated receptors. **C.M. Chagas**, L. Alisaraie

MEDI 206. Pro-soft drug modulators of sphingosine-1-phosphate receptor 1 (S1PR1). **C. Robinson**, M. Bell, D. Foley, C. Naylor, G. Wood, J. Riley, O. Epemolu, L. Ellis, P. Scullion, Y. Shishikura, D. Fletcher, E. Katz, W. McLean, P. Wyatt, K. Read, A. Woodland

MEDI 207. Synthesis of novel, potent phosphatidyl-choline specific phospholipase C inhibitors. **L.I. Pilkington**, M. van Rensburg, J. Reynisson, E. Leung, W.A. Denny, D. Barker

MEDI 208. Investigating the scope of 3-oxabicyclo[4.1.0]heptane as a bioisostere for morpholine in kinase hinge binding fragments. **D.M. Summers**, S. Peace, C. Jamieson, H. Hobbs, S. Pal

MEDI 209. Mechanism-based inhibitors of the human sirtuin 5 deacylase. **K. Troelsen**, N. Rajabi, A.S. Madsen, C.A. Olsen

MEDI 210. Generation of cell-permeable protein mimetics through structural stabilization of protein fragments by membrane anchoring. **N. Tarasova**, K. Stefanisko, L. Khavrutskii, S. Tarasov

MEDI 211. Synthesis and evaluation of hydrogen peroxide sensitive prodrugs of methotrexate and aminopterin for the treatment of rheumatoid arthritis. **V. Previtali**, J.P. Cadahía, N. Andersen, M. Clausen

MEDI 212. Development of a potent blood-brain barrier penetrating EGFR tyrosine kinase inhibitor against malignant brain tumors. **L.M. Urner**, J. Tsang, G. Kim, P.M. Clark, T.F. Cloughesy, M.E. Jung, D.A. Nathanson

MEDI 213. Fluorescence quenching studies of the human serum albumin (HSA) - quercetin complex by addition of divalent cations. **R.M. Savizky**, U. Okorafor, C. Kim

MEDI 214. Modular synthesis of allosteric inhibitors of p97 AAA ATPase. **E. Carder**, D.M. Huryn, P. Wipf

MEDI 215. Discovery of a novel class of orally active CGRP receptor antagonists for the treatment of migraine. **I.M. Bell**

MEDI 216. Pharmacodynamics-driven skeleton synthesis with unravel of unique chemical reactivity feature: Exploring promising pharmaceutical agent. **M. Saini**, D. Sumkaria, V. Chaudhary, S. Guchhait

MEDI 217. Discovering drugs from plants or drugs in plants? **J. Nielsen**

MEDI 218. Synthesis and evaluation of functionalized benzoboroxoles as potential anti-cancer agents. **S.C. Jonnalagadda**

MEDI 219. Design of Baylis-Hillman template based betulinic acid derivatives as potential anti-cancer agents. **S.C. Jonnalagadda**

MEDI 220. Potent and selective inhibition of sirtuin 2 deacylation. **A. Nielsen**, N. Rajabi, A.S. Madsen, C.A. Olsen

MEDI 221. Novel nitroxide derivatives combined with low-level laser irradiation for the treatment of acute limb ischemia/reperfusion injury. **X. Yan**, L. Bi

MEDI 222. Generalization of a CNS-targeting prodrug strategy for nuclear receptor modulators. **S.J. Ferrara**, T.S. Scanlan

MEDI 223. Exploring conformational changes associated with antimicrobial agent, colicin E3 during receptor binding on targeted bacteria. **T.D. Nilaweera**, D.S. Cafiso

MEDI 224. Structure-activity relationship analysis of TNF receptor inhibitors for elucidation of inhibition mechanisms and therapeutic developments. **C. Lo**, W. Fiers, D. Thomas, C.C. Aldrich, J. Sachs

MEDI 225. Scavenging activity of flavonoids present in okra seed extracts against methylglyoxal, a neurotoxin and reactive dicarbonyl species derived from glucose linked to diabetes and neurodegenerative diseases. **B. Dayal**, M.A. Lea

MEDI 226. Semi-synthesis of albocycline analogs and biological evaluation for better mechanistic understanding. **S. Daher**, K. Franklin, V. Chatare, R.B. Andrade

MEDI 227. Design, synthesis, and molecular modeling of novel 6-substituted pyrido[2,3-*d*]pyrimidines as dihydrofolate reductase inhibitors and potential anti-opportunistic agents. **F. Islam**, D.W. Seybert, A. Gangjee

MEDI 228. Discovery of a 40-year-old sequence error unveils new understanding of allosteric ligand binding to glutamate dehydrogenase. **O. Nassar**, B.M. Pettitt, T. Smith

MEDI 229. Does β -lapachone isomerize in human body? **S. Cho**, B. Kim, Y. Yoon

MEDI 230. Chemical synthesis and applications of a novel fluorescent probe for human complement C3a receptor. **C. Wu**, A.D. de Araujo, K. Wu, R.C. Reid, T. Durek, J. Lim, D.P. Fairlie

MEDI 231. Drug repurposing for nontuberculous mycobacteria with assay central. **K.M. Zorn**, S. Murcia, A. Clark, M. Braunstein, S. Ekins

MEDI 232. Evaluation of butyrophilin (BTN3A1) ligands for gamma delta T cell stimulation. **M.M. Poe**, C.C. Hsiao, A.J. Wiemer

MEDI 233. Structure-guided design and SAR studies of hepatitis C virus NS3/4A protease inhibitors incorporating flexible P2 quinoxalines. **A. Ali**, A.N. Matthew, N. Desaboini, L. Rusere, A. Newton, C.J. Petropoulos, W. Huang, N. Kurt-Yilmaz, C.A. Schiffer

MEDI 234. Monitoring macrolide-induced changes to membrane properties of living bacteria by using second-harmonic light scattering. **M. Sharifian Gh.**, M.J. Wilhelm, H. Dai

MEDI 235. Synthesis and spectroscopic study of polymer - based nonsteroidal analgesic prodrugs. **H.D. Tabb**

MEDI 236. Potentially bioactive ferrocene-substituted nitro and amino complexes: Synthesis, structural interpretation, and DFT calculations. **F. Asghar**, A. Badshah, I.S. Butler

MEDI 237. Novel theranostic tools for Alzheimer's disease. **L. Sun**, N. Bandara, Y. Huang, H. Cho, B.E. Rogers, L.M. Mirica

MEDI 238. Design and antiviral activity evaluation of small molecule compounds against viruses from *Flavivirus* and *Enterovirus* genera. **A. Orlov**, M. Drenichev, V. Oslovsky, K. Frolov, A. Nikitina, E. Khvatov, A. Eletsкая, A. Golinec, S.N. Mikhailov, V. Palyulin, G. Karganova, V. Dotsenko, L. Kozlovskaya, D.I. Osolodkin

MEDI 239. Synthesis and base pairing studies of 5-cyanomethyluridine (cnm⁵U) and 5-cyanouridine (cn⁵U) in RNA duplexes. **S. Mao**, J. Sheng

MEDI 240. Synthesis and crystal structure studies of 2'-5'-linked RNA duplexes. **F. Shen**

MEDI 241. Molecular dynamics simulations of the absorption of dodecaborate hydride clusters by Feraheme medicine. **P. Rehak**

MEDI 242. Understanding the effect of arsenic treatment on breast cancer cell lines using gene expression analysis. **L.L. Pruteanu**, C. Braicu, D. Módos, A. Jurj, L. Raduly, R. Cojocneanu-Petric, A. Moldovan, A. Bender, I. Berindan-Neagoe

MEDI 243. 2,3-Difluoro sialic acid analogs as potential bacterial sialidase inhibitors. **W. Li**, A. Santra, H. Yu, Y. Li, T. Slack

MEDI 244. Potent zwitterionic anticancer agent: Selective killing of cancer by targeting cancer redox metabolism. **J. Song**, **J. Mi**, **L. Jin**, B. Liang, D.P. Jones, H. Fu, C.L. Hill, S. Nie

MEDI 245. Prodrug of doxorubicin and biomaterial allow for targeted treatment of soft tissue sarcoma. **K. Wu**, M. Royzen, J. Mejia Oneto, N. Yee

MEDI 246. Polyelectrolytes, potent excipients for protein drugs. **A. Mancuso**, N. Pillarella, A. Sadek, M. Bazrouk, K.S. Raja

MEDI 247. Vitamin B12 derivatives for photopharmaceutical therapy. **J.R. Shell,** D.C. Zites, T.A. Shell, J. Gunn, B. Pogue

MEDI 248. Membrane association controls substrate specificity of lipolytic enzymes. **V. Mouchlis,** J. McCammon, E.A. Dennis

MEDI 249. Amphiphilic cell-penetrating hybrid cyclic-linear peptides as a drug delivery system. **S. Mozaffari,** K. Tavakoli, B. Khungar, R. Tiwari, K. Parang

MEDI 250. Selective metabolic blackout in hepatocellular carcinoma cells by submicromolar iodoacetate-loaded galactosylated nanoparticles. **A.M. Reda**

MEDI 251. Rapid estimation of relative binding affinities of G-protein coupled receptor (GPCR) ligands using precomputed ensembles based free energy approaches. **S.K. Lakkaraju,** S. Jo, A.D. Mackerell

MONDAY MORNING

Section A

Boston Convention & Exhibition Center
Room 210B

Best Practices in Fragment-Based Drug Design

A. C. Hart, D. Marcoux, H. Perez, *Organizers, Presiding*

9:00 MEDI 252. Progress, pitfalls, and best practices for fragment-based drug discovery. **D.A. Erlanson**

9:35 MEDI 253. Strategizing fragment libraries and screening methods for hit identification against metabolic enzyme targets. **A. Padyana**

10:10 MEDI 254. Fragment-based discovery of KAT II inhibitors via high-throughput chemistry. **M. Harner, C.L. Cavallaro**

10:45 MEDI 255. Discovery of potent orally bioavailable Factor D inhibitors by exploiting non-validated very weak binding affinity fragments. **A. Vulpetti**

11:20 MEDI 256. Fragment-based discovery of an orally bioavailable ERK1/2 inhibitor which reduces the level of phosphorylated ERK. **D. Norton**

Section B

Boston Convention & Exhibition Center
Room 210A

New Advances in Treating Rare Diseases

A. A. Scholte, K. Yeung, *Organizers, Presiding*

8:30 Introductory Remarks.

8:35 MEDI 257. Identification of novel CNS active glucosylceramide synthase (GCS) inhibitors for the treatment of neuronopathic lysosomal storage diseases. **J.P. Leonard**

9:10 MEDI 258. Discovery of sarcomere modulator mavacamten. **J. Oslob**

9:45 MEDI 259. Discovery and development of avapritinib: A highly targeted therapy for systemic mastocytosis. **K.J. Wilson**

10:20 MEDI 260. Discovery of CFTR correctors for the treatment of cystic fibrosis. **X. Wang**

10:55 MEDI 261. ACH-4471, the first clinically investigated orally administered small-molecule inhibitor of complement factor D for the treatment of rare chronic diseases including C3 glomerulopathy. **J.A. Wiles**, V.R. Gadhachanda, A.S. Phadke, S.D. Podos, Y. Huang, W. Yang, H. Kocinsky, M. Deshpande, M. Huang

11:30 MEDI 262. Sulfur-halogen intramolecular conformational constraints: Identification of 1,3,4-thiadiazole analogs of LMI070 as SMN2 splicing modulators. **M. Sung**

Section C

Boston Convention & Exhibition Center
Room 210C

General Oral Session

A. W. Stamford, *Organizer*
A. J. Roecker, *Presiding*

8:30 MEDI 263. Chemical insights into human aldehyde oxidase-mediated metabolism. **S. Lepri**, N. Milani, S. Tortorella, G. Cruciani

8:50 MEDI 264. Discovery of potent and selective BRD4 inhibitors capable of blocking TLR3-induced acute airway inflammation. Z. Liu, B. Tian, H. Chen, P. Wang, A.R. Brasier, **J. Zhou**

9:10 MEDI 265. Discovery of potent BET inhibitors as potential treatments for cancer. **M.D. Hill**, H. Fang, D. Norris, W.D. Schmitz, C. Huang, R. Westhouse, M. Kramer, J. Morrison, C. Tye, E. Shields, H. Zhang, M. Sinz, J. Simmermacher-Mayer, F. Lee, A.V. Gavai, A.P. Degnan

9:30 MEDI 266. Development of a YEATS-domain chemical probe. **M. Moustakim**, O. Monteiro, J. Bennett, C. Giroud, T. Christott, L.D. Saez, I. Panagakou, L. Felce, V. Gamble, K. Huber, G. Farnie, J. Heer, D. Dixon, P. Brennan, O. Federov

9:50 MEDI 267. Development of KDM5 covalent inhibitors as chemical probes. **S. Vazquez-Rodriguez**, M. Wright, P. Brennan

10:10 MEDI 268. Antitubercular drug discovery enabled by Bayesian modeling. A.L. Perryman, T.P. Stratton, J.S. Patel, X. Wang, S. Ekins, **J.S. Freundlich**

10:30 MEDI 269. Discovery of a highly potent and orally bioavailable selective estrogen receptor degrader (SERD) GNE-149 for ER-positive breast cancer. **J. Liang**

10:50 MEDI 270. Discovery of a series of selective inhibitors of the sodium-phosphate co-transporter NaPi2a (SLC34A1). **K.J. Filipski**

11:10 MEDI 271. Discovery and application of 3-oxabicyclo[4.1.0]heptane, a non-nitrogen containing morpholine isostere, through predictive quantum mechanical modelling. **H. Hobbs**, G. Bravi, I. Campbell, M. Convery, H. Davies, G. Inglis, S. Pal, S. Peace, J. Redmond, D.M. Summers

11:30 MEDI 272. Exploration of novel chemical space by the interplay of drug design and method development: Neglected sulfur (VI) pharmacophores in drug

discovery. **U.T. Luecking**, F. Izzo, J. Sirvent, R.A. Stockman, F. von Nussbaum, M. Bauser, M. Brands

11:50 MEDI 273. Assessment of AstraZeneca secondary pharmacology profiling assays and applications to lead optimization efforts. **D.G. Brown**

Structures & Functions of Glycans

Sponsored by CARB, Cosponsored by ANYL, BIOL, CELL, MEDI and ORGN

Bioactives & Skin Health

Sponsored by AGFD, Cosponsored by MEDI

MONDAY AFTERNOON

Section A

Boston Convention & Exhibition Center
Room 210B

Confronting the Opioid Epidemic: Novel Treatments for Chronic Pain

S. McKerrall, *Organizer, Presiding*

1:30 Introductory Remarks.

1:35 MEDI 274. NKTR-181: Separating euphoria from analgesia in a full MOR agonist. **S.K. Doberstein**, N.K. Anand

2:05 MEDI 275. Evaluation of opioid antinociceptive tolerance with G-protein signaling biased opioid agonists. **L.M. Bohn**, T.D. Bannister

2:35 MEDI 276. NYX-2925 is a novel NMDA receptor-specific spirocyclic- β -lactam that induces rapid and long-lasting analgesia in multiple rat models of neuropathic pain. **R.A. Kroes**, M. Khan, N. Ghoreishi-Haack, C. Cearley, J.R. Moskal

3:05 MEDI 277. Strategic advances in the identification of small molecule inhibitors of Nav1.7 for the treatment of chronic pain. **B. Milgram**

3:35 MEDI 278. Structure-based drug discovery in a sodium channel: Discovery of chromane arylsulfonamide Nav1.7 inhibitors for the treatment of chronic pain. **S. McKerrall**, P. Bergeron, B. Safina, D.F. Ortwine, S. Shields, L. Deng, D. Hackos, J. Chen, J. Pang, J. Chang, K.W. Lai, W. Liu, Z. Liu, C.M. Dehnhardt, J. Johnson, G. Bankar, C. Cohen, D.P. Sutherlin

4:05 MEDI 279. Discovery of novel arylsulfonamide Nav1.7 inhibitors: *In vitro-in vivo* correlations, development of multiparameter optimization (MPO) methods, and optimization of selectivity profiles. **A.J. Roecker**, M.E. Layton, M.J. Kelly, J.E. Pero, T.J. Greshock, T. Zhang, R.L. Kraus, Y. Li, C. Daley, A. Jovanovska, B. Klein, M. Clements, J. Wang, D. Henze, G. Varty, J. Ballard, D. Wang, F. Zhao, C.P. Regan, H. Regan, L.A. Joyce, E.C. Sherer, C.T. John, X. Peng, X. Wang, H. Sun, A.K. Houghton, C.S. Burgey

Section B

Boston Convention & Exhibition Center
Room 210A

Biology's Magic Methyl: Methyltransferases & Demethylases as Epigenetic & Neurotransmitter Regulators

J. Barrow, J. Panarese, *Organizers, Presiding*

1:30 Introductory Remarks.

1:35 MEDI 280. Discovery of selective inhibitors for histone methyltransferases. **J. Jin**

2:15 MEDI 281. Discovery, optimization and biological activity of EED binders allosterically inhibiting the methyltransferase PRC2. **A. Lingel**, Y. Huang, D. Bussiere, J. Gu, L. Li, W. Qi, M. Sendzik, Y. Wang, Z. Yu, H. Zhang, J. Zhang, M. Zhang, K. Zhao, C. Oyang, E. Li

2:55 MEDI 282. Structural rationalization of bioactivity trends that led to identification of the EZH2 development candidate (PF-06821497). **P. Kung, S. Bergqvist, P. Bingham, J.F. Braganza, A. Brooun, M.R. Collins, W. Diehl, Y. Deng, D. Dac, C. Fan, V. Fantin, K. Gajiwala, H. Gukasyan, W. Hu, B. Huang, R. Kania, W. Liu, S. Kephart, M. Kraus, C. Krivacic, R. Kumpf, G. Li, K. Maegley, I.J. McAlpine, L. Nguyen, S. Ninkovic, M.A. Ornelas, D. Richter, E. Rui, M. Ryskin, S.A. Scales, J. Spangler, A. Stewart, S.C. Sutton, J. Tatlock, C. Tsao, D. Verhelle, F. Wang, H. Wang, M. Wythes, S. Yamazaki, B. Yip, X. Yu, L. Zehnder, W. Zhang, P. Zhu, J. Zhu, R. Rollins, S. Sharma, M.P. Edwards**

3:35 MEDI 283. Targeting histone methyltransferases and demethylases. **V. Gehling**

4:15 MEDI 284. Discovery and development of opicapone, a third generation catechol-*O*-methyltransferase inhibitor. **P. Soares-da-Silva, L. Kiss**

4:55 Concluding Remarks.

Section C

Boston Convention & Exhibition Center
Room 210C

Drug Discovery for the Treatment of Childhood Neuromuscular Diseases

A. S. Kamlet, *Organizer, Presiding*

1:30 MEDI 285. Spinal muscular atrophy from gene to treatment. **A. Burghes**

2:10 MEDI 286. Small molecule SMN splicing modifiers to treat SMA. **M.G. Woll, G.M. Karp, A. Turpoff, N.A. Naryshkin, A. Dakka, J. Narasimhan, V. Gabbeta, M. Weetall, X. Zhao, N. Risher, J. Sheedy, J. Baird, H. Ratni, F. Metzger, S. Paushkin, K.S. Chen**

2:50 MEDI 287. Spinal muscular atrophy: Advancing small molecule splicing modulators from phenotypic screen to the clinic. **B. Hurley**

3:30 Intermission.

3:40 MEDI 288. Exon skipping therapy for Duchenne muscular dystrophy – it takes more than an antisense oligonucleotide. **A. Aartsma-Rus**

4:20 MEDI 289. Small molecule utrophin modulators for the therapy of Duchenne muscular dystrophy (DMD). **A.J. Russell**, A. Vuorinen, N.J. Willis, D. Conole, M. Chatzopoulou, E. Emer, I. Wilkinson, S.G. Davies, S. Guiraud, S.E. Squire, A. Babbs, H. Dugdale, B. Edwards, S. Hemming, L. Moir, K. Perkins, S. Harriman, F. Wilson, G.M. Wynne, J.M. Tinsley, K.E. Davies

Structures & Functions of Glycans

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Undergraduate Research Posters

Medicinal Chemistry

Sponsored by CHED, Cosponsored by MEDI and SOCED

Tetrahedron Prize

Sponsored by ORGN, Cosponsored by BIOL, CARB and MEDI

MONDAY EVENING

Section A

Boston Convention & Exhibition Center
Exhibit Hall B2/C

Sci-Mix

A. W. Stamford, *Organizer*

8:00 - 10:00

39, 50, 54, 60, 73-74, 80, 86, 95, 98, 100-101, 104, 111, 113, 118, 123, 128, 135, 138-139, 143, 145-146, 149, 163, 165, 167-170, 173, 179, 184, 186-187, 189, 192. See previous listings.

357, 371-372, 378, 385, 431, 436, 440-441. See subsequent listings.

TUESDAY MORNING

Section A

Boston Convention & Exhibition Center
Ballroom West

Awards Session

Cosponsored by PROF
A. W. Stamford, *Organizer*
P. L. Ornstein, *Presiding*

8:30 MEDI 290. Design and synthesis of novel opioid peptidomimetics for potential treatment of cocaine addiction. **D. Montgomery**, J.P. Anand, N.W. Griggs, J.R. Traynor, H.I. Mosberg

8:55 MEDI 291. Total syntheses of highly oxidized bioactive natural products. **H. Chu**

9:20 MEDI 292. Towards the development of an *in vivo* chemical probe for Polycomb chromodomains. **K.N. Lamb**, J.I. Stuckey, S.N. Dishman, J.L. Norris-Drouin, S.H. Cholensky, O. Bell, S. Musetti, L. Huang, C.A. Sagum, M.T. Bedford, L.I. James, S.V. Frye

9:45 MEDI 293. Development of predictive guidelines for small-molecule accumulation in Gram-negative bacteria. **M. Richter**

10:10 MEDI 294. Novel strategies for treating estrogen receptor positive metastatic breast cancer. **R. Xiong**, J. Zhao, L. Gutgesell, Y. Li, Y. Lu, C. Rosales, H. Zhao, D. Tonetti, G.R. Thatcher

10:35 MEDI 295. Structure and physicochemical property guided design of small molecule kinase inhibitors and further opportunities. **T.P. Heffron**

11:20 MEDI 296. In recognition of those who deserve the Philip S. Portoghese lectureship award but did not receive it. **M. Cushman**

Section B

Boston Convention & Exhibition Center
Room 210B

Projects of NCI Chemical Biology Consortium: A Unique, Collaborative Approach to Cancer Drug Discovery

Cosponsored by BIOL[‡]
M. Arkin, D. M. Huryn, *Organizers, Presiding*

8:30 Introductory Remarks.

8:35 MEDI 297. NCI Chemical Biology Consortium. **B. Mroczkowski**

8:55 MEDI 298. Design and characterization of a chemical fragment library of mercaptophiles. **P. Wipf**, T. Maskrey, M. Arkin, D.M. Huryn

9:20 MEDI 299. Discovery and structure-based optimization of potent, covalent inhibitors of Taspase1. **J. Neitz**, M. Arkin, A.G. Waterson, L. Sambucetti

9:45 MEDI 300. Discovery, optimization and characterization of allosteric inhibitors of the AAA ATPase p97, an emerging cancer target. **D.M. Huryn, M. Arkin**

10:30 MEDI 301. Discovery of novel tricyclic Mcl-1 inhibitors that exhibit selective anti-proliferative activity and *in vivo* efficacy. **T. Lee**, J.C. Tarr, B. Zhao, Z. Bian, S. Shaw, J. Belmar, A. Arnold, J.L. Sensintaffar, W.J. Moore, G.M. Stott, M. Hollingshead, A. Srivastava, C.J. Thomas, M.M. Davis, O.W. Rossanese, E.T. Olejniczak, S.W. Fesik

11:05 MEDI 302. Discovery and characterization of cell active inhibitors of lactate dehydrogenase (LDH) using structure-based design. **A.G. Waterson, M.D. Hall, G. Rai, K. Brimacombe, B. Mott, D.J. Urban, K. Kim, P.P. Christov, A.P. Lamers, I.M. Romaine, S. Jana, X. Hu, S. Yang, T.D. Lee, D. Cheff, J. Kouznetsova, G.A. Benavides, K. Pohida, E.J. Kuenstner, D.K. Luci, C.M. Lucaks, D.R. Davies, D. Dranow, H. Zhu, G.A. Sulikowski, W.J. Moore, G.M. Stott, A.J. Flint, V.M. Darley-Usmar, J.P. Norenberg, L.A. Sklar, L.M. Neckers, C.V. Dang, A. Simeonov, A. Jadhav, D.J. Maloney**

11:50 MEDI 303. MRX-2843, a dual MERTK/FLT3 inhibitor enabled by the NCI Chemical Biology Consortium (CBC) entering Phase 1 clinical trials. **X. Wang, D. DeRyckere, D. Kireev, D. Graham, H. Earp, S.V. Frye**

12:25 Concluding Remarks.

DARPA Make-It Program: Automating Small Molecule Route Design, Optimization & Synthesis

Flow Synthesis

Sponsored by COMSCI, Cosponsored by ANYL, COMP, MEDI and ORGN

TUESDAY AFTERNOON

Section A

Boston Convention & Exhibition Center
Ballroom West

Structure-Based Drug Design for GPCRs & Other Difficult Targets

T. D. Bannister, C. de Graaf, *Organizers, Presiding*

1:30 MEDI 304. Structure-based drug discovery of G protein-coupled purine receptor ligands. **K.A. Jacobson**

2:10 MEDI 305. Application of MD-simulations in GPCR drug design – exemplified by case studies. **C. Tautermann**

2:50 MEDI 306. Navigating structural GPCR-ligand interaction space for crafted computer-aided drug design. **C. de Graaf**, B.G. Tehan, F. DeFlorian, J. Mobarec, C.C. Scully, R.T. Smith, G. Bottegoni, J.S. Mason, M. Congreve

3:30 MEDI 307. Orthosteric and allosteric antagonism of chemokine receptors: Structural insights into compound affinity and selectivity. K.K. Chahal, G.E. Baker, Y. Zheng, A. Tebben, T.M. Handel, **I. Kufareva**

4:10 MEDI 308. Opportunities for advanced computational modeling in GPCR drug discovery. **A. Bortolato**, K. Zhu, K.W. Borrelli, T. Beuming, I. Aloni, R. Abel

4:50 MEDI 309. Identifying inter-helical interactions involved in GPCR structure-function and the forces that determine ligand residence time. **A. Heifetz**, A. Potterton, I. Morao, T. James, M. Southey, D.G. Fedorov, M. Bodkin, A. Townsend-Nicholson

Section B

Boston Convention & Exhibition Center
Room 210B

General Oral Session

A. W. Stamford, *Organizer*
M. Visser, *Presiding*

1:30 MEDI 310. Lead repurposing for neglected tropical diseases: Strategies for optimization of ADME properties of kinase inhibitor chemotypes. **L. Ferrins**, A. Sharma, K.A. Bachovchin, S. Bag, L. Silva, D. Klug, N. Mehta, J. Woodring, W.G. Devine, J. Wiedman, K. Mensa-Wilmot, M.P. Pollastri

1:55 MEDI 311. Design of a potent and selective GPR40 agoPAM with low projected human dose. **D. DeMong**, Z. Hu, M.W. Miller, R. Orr, A. Weinglass, G. Eiermann, K. Mitra, J. Ehrhart, C. Plummer, H. Chen, H.R. Chobanian, A.R. Angeles, M. Maddess, E. Ashley, J. DiSalvo, B. Thomas-Fowlkes, S. Souza, B. Cheewatrakoolpong, M. Trujillo, J. Gorski, M. Pachanski, D. Kosinski, M. Kirkland, J. Mane, J. Baldassari, D. Szeto, J. Xue, G. Forrest, K. Samuel, R. Tschirret-Guth, D. Tatosian, Q. Chen, M. Hafey, R. Houle, A. Thomas, J. Shang, T. Pereira, A. Howard, S.L. Colletti

2:20 MEDI 312. Harnessing intramolecular hydrogen bonds in the design of potent and selective CREBBP bromodomain ligands. **S.J. Conway**

2:45 MEDI 313. Identification and *in vivo* evaluation of novel IRAK4 inhibitors in murine models of lupus. **J. Hynes**

3:10 MEDI 314. Discovery of TAK-137 and TAK-653, clinical candidates of α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor potentiators with reduced agonistic activities. **S. Nakamura**, M. Toyofuku, E. Honda, T. Imaeda, A. Yokota, S. Sogabe, A. Kunugi, H. Kuno, Y. Kosugi, M. Kori, T. Miki, H. Kimura, T. Kuroita, T. Kaku

3:35 MEDI 315. First class of orally available mono-saccharide galectin-3 inhibitors for treatment of fibrosis (NASH) and cancer. **F. Zetterberg**

4:00 MEDI 316. Discovery of orally bioavailable non-catechol atropisomer dopamine D₁ agonists with reduced desensitization. **J.E. Davoren**, D.L. Gray, D. Nason, A. Harris, W. Xu, S. Mente, J.W. Coe, R. Kozak

4:25 MEDI 317. DRX-065, the deuterated (*R*)-enantiomer of pioglitazone, as a nonalcoholic steatohepatitis (NASH) drug candidate: Preclinical and phase 1 results. **V. Jacques**, L. Van der Ploeg, S.H. Dewitt

4:50 MEDI 318. Discovery of novel potent and selective first in class calpain inhibitors for the potential treatment of neurodegenerative disorders. **H. Mack**, K. Jantos, A. Kling, C.W. Hutchins, W. Hornberger, G. Backfisch, M. Nijssen

DARPA Make-It Program: Automating Small Molecule Route Design, Optimization & Synthesis

Reaction Planning & Screening

Sponsored by COMSCI, Cosponsored by ANYL, COMP, MEDI and ORGN

WEDNESDAY MORNING

Section A

Boston Convention & Exhibition Center
Ballroom West

First Time Disclosure of Clinical Candidates

E. F. DiMauro, *Organizer, Presiding*

9:00 Introductory Remarks.

9:05 MEDI 319. Discovery of the TYK2 selective inhibitor PF-6826647 for the treatment of Crohn's disease, and other autoimmune conditions. **B.S. Gerstenberger**, E.P. Arnold, M. Banker, M.F. Brown, J.D. Clark, A. Dermenci, M. Dowty, A. Fensome, M.M. Hayward, M. Hegen, B.D. Hollingshead, J.D. Knafels, D.W. Lin, T. Lin, D. Owen, E. Saiah, R. Sharma, F.F. Vajdos, F. Vincent, S.W. Wright, L. Xing, X. Yang, X. Yang, L. Zhang

9:45 MEDI 320. Discovery of AZD5718, a novel 5-lipoxygenase activating protein (FLAP) inhibitor. **M. Lemurell**, D. Pettersen, J. Ulander, M. Hayes, C. Whatling, M. Swanson, J. Broddefalk, H. Emtenas, E. Lindstedt

10:25 MEDI 321. Discovery of LY3154207, a potent and selective dopamine receptor D1 positive allosteric modulator for the treatment of Parkinson's disease dementia. **J. Hao**, J.P. Beck, J.H. Krushinski, J.M. Schaus, X. Wang, B. Heinz, R.F. Bruns, D.M. Bender, J.W. Cramer, K.A. Svensson

11:05 MEDI 322. Discovery of AMG986, a potent, selective and orally bioavailable APJ agonist for the treatment of heart disease. **P.J. Dransfield**, Z. Ma, J. Ma, V. Pattaropong, S. Lai, M.R. Kaller, N. Nishimura, N. Chen, D. Kopecky, D. Horne, K. Hoagland, S. Hedley, J.B. Houze, J. Mihalic, J. Heath, Y. Chen, Q. Guo, X. Chen, J.C. Medina, Z. Fu, J. Deignan, S. Wang, T. Judd, R. Connors, S. Olson, G. Swaminath, W. Sutherland, M. Fielden, B. Farrell, J. Harvey

11:45 Concluding Remarks.

Section B

Boston Convention & Exhibition Center
Room 210B

Antibiotic Resistance: Recent Advances in Drug Discovery & Development

S. Dong, C. Gonzalez-Bello, J. Su, *Organizers, Presiding*

8:30 MEDI 323. Obstacles to the discovery of novel antibacterials & approaches towards a new strategy. **R.A. Tommasi**

9:00 MEDI 324. Disabling unexplored key enzymes in bacteria to unlock resistance to antibiotics. **C. Gonzalez-Bello**

9:30 MEDI 325. Resetting the antibacterial arms race by enabling a novel Gram negative target. **M. Koehler**, H.S. Girgis, C.E. Heise, R.I. Higuchi, J. Murray, T.C. Roberts, P. Paraselli, L. Rougé, P.A. Smith

10:00 MEDI 326. Systematic conversion of Gram-positive-only compounds into broad-spectrum antibiotics. **P.J. Hergenrother**

10:30 MEDI 327. Can sideromycins (siderophore-antibiotic conjugates) be effective antibiotics? Challenges and opportunities. **M.J. Miller**

11:00 MEDI 328. Microbiome: A key player in modulating infectious diseases and antibiotic resistance. **O. Danilchanka**

Nanomaterials in Drug Delivery: Efficacy & Toxicity Considerations

Sponsored by TOXI, Cosponsored by MEDI

WEDNESDAY AFTERNOON

Section A

Boston Convention & Exhibition Center
Ballroom West

First Time Disclosure of Clinical Candidates

E. F. DiMauro, *Organizer, Presiding*

1:30 Introductory Remarks.

1:35 MEDI 329. Discovery of a once-weekly NNRTI clinical candidate: A new paradigm for treating HIV-1 infection. **Y. Han**, C.S. Burgey, K. Menzel, M. Lai

2:15 MEDI 330. Discovery, structure disclosure, and early clinical development of LY3202626, a low-dose, CNS-penetrant BACE inhibitor. **D.J. Mergott**, J.E. Audia, M. Barberis, J.P. Beck, L.N. Boggs, R.D. Boyer, R.A. Brier, A.N. Borders, L.L. Daugherty, R.A. Dean, L. Ereshefsky, J.A. Erickson, P. Garcia-Losada, H. Gevorkyan, S.J. Green, E.J. Hembre, M.C. Irizarry, D.E. James, S. Jhee, Q. Lin, J.E. Lopez, A. Lo, S.L. Lowe, B.M. Mathes, P.C. May, D.L. McKinzie, S.A. Monk, M. Nakano, W.J. Porter, Y. Shi, S.L. Stout, D.E. Timm, B. Watson, B.A. Willis, L.L. Winneroski, Z. Yang, J.A. Zimmer

2:55 MEDI 331. Discovery of PF-05251749 a selective casein kinase 1 (CK1 δ /e) inhibitor for the treatment of circadian rhythm disorders. **T.T. Wager**

3:35 MEDI 332. Discovery of pyrrolidinamides, a novel chemical class for malaria treatment: First time disclosure of the orally bioavailable clinical candidate GSK701. **H. Rami**, I. Castellote, F. Gamo, J. Haselden, F. Calderon Romo

4:15 Concluding Remarks.

Section B

Boston Convention & Exhibition Center
Room 210B

General Oral Session

A. W. Stamford, *Organizer*
S. K. Cyr, *Presiding*

1:30 MEDI 333. Discovery of highly isoform-selective Nav1.6 inhibitors that show potent anticonvulsant activity in mouse models for focal seizures and severe childhood epilepsy. **T. Focken**, M.E. Grimwood, V. Lofstrand, K. Burford, W. Gong, Q. Jia, A. Hasan, M. Taron, W. Zhang, M. Wilson, P. Tari, K. Nelkenbrecher, K. Khakh, S.J. Goodchild, N. Shuart, S. Lin, R. Kwan, L. Sojo, R.J. Devita, S. Wesolowski, C. Cohen, J. Johnson, C.M. Dehnhardt, J.R. Empfield

1:50 MEDI 334. Synthesis, biological activity and druglikeness profile of new leishmanicidal candidates. **L.M. Lima**, M.A. Alves, A.C. Queiroz, M. Alexandre Moreira, S.E. Haas, E.J. Barreiro

2:10 MEDI 335. Discovery of 2,4-substituted azaindoles as multi-parasite inhibitors: Utilizing a parasite-hopping approach to drug-discovery. **K.A. Bachovchin**, R. Diaz, G. Ceballos, M. Martinez-Martinez, P. Manzano-Chinchon, R.J. Sciotti, M. Navarro, M.P. Pollastri

2:30 MEDI 336. Click chemistry *In Cellulo*: Bacterial cell as reaction vessel selectively synthesizes macrolide antibiotics. **X. Jin**, S. Daher, M. Lee, B. Buttaro, R.B. Andrade

2:50 MEDI 337. Structural requirements for the effective myostatin inhibition of myostatin prodomain-derived peptide derivatives. **K. Takayama**, T. Asari, M. Saitoh, Y. Roppongi, A. Nakamura, A. Taguchi, A. Taniguchi, Y. Hayashi

3:10 MEDI 338. Design, synthesis and biological evaluation of a series of novel 2-benzamide-4-(6-oxy-N-methyl-1-naphthamide)-pyridine derivatives as potent fibroblast growth factor receptor (FGFR) inhibitors. **A. Zhang**

3:30 MEDI 339. Design and synthesis of vesicular monoamine transporter 2 (VMAT2) inhibitors. **J.P. Williams**, N.D. Harriott, S.R. Hoare, N.J. Ashweek, J. Pires, J. Fan

3:50 MEDI 340. Design and evaluation of immunoproteasome-selective inhibitors for the treatment of autoimmune diseases. **C.E. Stivala**

4:10 MEDI 341. Peptidomimetics that interact with Rpn-6 as new anti-cancer molecules. W. Tian, **D.J. Trader**

4:30 MEDI 342. Evolution of efficient purine PI3Kdelta inhibitors with excellent selectivity and physicochemical properties. **J.L. Methot**, H. Zhou, M. McGowan, N.J. Anthony, S. Kattar, M. Christopher, Y. Garcia, A. Achab, K. Lipford, Y. Deng, M. Altman, X. Fradera, C. Lesburg, T. Fischmann, C. Li, S. Alves, C. Chappell, R. Jain, P. Goldenblatt, A. Hill, L. Shaffer, D. Chen, V. Tong, R. McLeod, H. Lee, H. Yu, A. Bass, R.A. Kemper, T. Guzi, Y. Ducharme, B. Trotter, S. Shah, J. Katz

4:50 MEDI 343. Discovery of tarantula venom-derived Nav1.7-inhibitory peptide with systemic block of histamine-induced pruritis. **B. Wu**

WEDNESDAY EVENING

Boston Convention & Exhibition Center
Exhibit Hall B1

General Poster Session

A. W. Stamford, *Organizer*

7:00 - 9:00

MEDI 344. Catalytic difluoroalkylations through controllable difluorocarbene and radical cross-couplings and their applications in medicinal chemistry. **X. Zhang**

MEDI 345. Developing selective SETD8 inhibitors for treating high-risk neuroblastoma. **A. Ma**, V. Veschi, W. Yu, N. Babault, F. Li, K. Butler, J. Wang, M. Luo, M. Vedadi, P. Brown, C. Arrowsmith, C. Thiele, J. Jin

MEDI 346. Development of chemical probes for the TRIM33 bromodomain. **L. See**, A.R. Scolah, J.P. Bluck, J.K. Reynolds, A.R. Sekirnik (née Measures), S.J. Conway

MEDI 347. Synthesis and anti-bacterial activities of derivatives of 2-aminoimidazoles. **R. Alshehry**, S. Rasapalli

MEDI 348. Hypoxia-activated prodrugs of the KDAC inhibitor panobinostat. **E.D. Calder**, I.N. Mistry, E.M. Hammond, S.J. Conway

MEDI 349. Development of a covalent proteasome inhibitor and kinetic analysis of its inhibitory mechanism. **S. Kitahata**, F. Yakushiji, S. Ichikawa

MEDI 350. Synthesis and evaluation for antibacterial and antibiofilm activities of 2-aminoimidazole Derivatives. S. Rasapalli, **V. Sammeta**, Z. Murphy, S. Parker

MEDI 351. Development of BCL6 protein-protein interaction inhibitors using a fragment-based approach. **B. Linhares**, H. Cheng, W. Yu, M.G. Cardenas, Y. Ai, W. Jiang, A. Melnick, A.D. MacKerell, F. Xue, T. Cierpicki

MEDI 352. Synthesis and ¹⁹F NMR-based screening of a library of diverse and three-dimensional fluorinated fragments. **N. Andersen**, M. Clausen

MEDI 353. Development of 8-pyridopyrimidinone-based covalent inhibitors of KDM5B. **M. Wright**, S. Vazquez-Rodriguez, P. Brennan, A. Kawamura

MEDI 354. Structure-based design of extracellular FLT3 inhibitors: First-in-class preclinical candidates for the treatment of neuropathic pain. C. RIVAT, C. Sar, J. Leyris, C. Sonrier, Y. Philipson, M. Schmitt, P. Sokoloff, J. Valmier, **D. Rognan**

MEDI 355. Wnt signaling pathway inhibitors for non-alcoholic fatty liver diseases (NAFLD). **F. Xue**, Y. Ai, Y. Li, Y. Shu, W. Yang

MEDI 356. Study of L-neplanocin analogues: Synthesis and antiviral property. **Q. Chen**, N. Miller, A. Smith, G. Imhoff

MEDI 357. Design, synthesis and biological evaluation of D3 antagonists with an aryl linker motif. **P. Cordone**, B. Muniz, E. Gallicchio, R. Pal, T.P. Kurtzman, W. Harding

MEDI 358. 4-Fluoropiperidine amides as fatty acid synthase inhibitors. **C.A. Zificsak**, N.C. Becknell, A.K. Ghose, T.S. Angeles, M.A. Ator, L.D. Aimone, S.J. Miknyoczki, P. Dobrzanski, B.A. Ruggeri, R.L. Hudkins

MEDI 359. Optimization of aryl sulfonamides as CNS penetrant, isoform-selective Nav1.6 inhibitors with efficacy in mouse models of epilepsy. **K. Burford**, T. Focken, J. Andrez, M.E. Grimwood, A. Zenova, M. Taron, W. Gong, S. Decker, S. Chowdhury, N. Shuart, P. Tari, R. Kwan, L. Sojo, R.J. Devita, C. Cohen, J. Johnson, S.S. Wesolowski, J.R. Empfield, C.M. Dehnhardt

MEDI 360. Carbon dot@NaTbF₄ for imaging and *in vivo* drug delivery. **R. Li**

MEDI 361. Synthesis and evaluation of ¹⁸F-radiolabeled anticancer agents as tracers of nucleic acid metabolism. **A.K. King**, A. Doepner, D. Turton, D.M. Ciobota, G. Kramer-Marek, G. Smith

MEDI 362. First asymmetric synthesis of dihydro-thieno-indol scaffold, the alkylation subunit of NMS-P528, a new highly promising agent for ADC generation. **P. Orsini**, M. Caruso, I. Candiani, N. Colombo, M. D'Anello, R. Frigerio, F. Gasparri, D. Ramella, B. Valsasina, D. Donati

MEDI 363. Design and synthesis of potent DNA alkylating indolino-benzodiazepine compounds (BIAs) linked with a DNA binding moiety for use in antibody-drug conjugates (ADCs). **E.E. Reid**, **K.E. Archer**, M. Shizuka, M.A. McShea, E.K.

Maloney, O. Ab, L. Lanieri, A. Wilhelm, J.F. Ponte, N.C. Yoder, R.V. Chari, M.L. Miller

MEDI 364. Imidazo[1,2-*b*]pyridazines as potent glycogen synthase kinase-3 β inhibitors for the potential treatment of Alzheimer's disease. **R.A. Hartz**, V. Ahuja, P. Sivaprakasam, C. Burton, H. Xiao, C. Krause, W. Clarke, K. Kish, H. Lewis, J.E. Macor, G.M. Dubowchik

MEDI 365. Embrace the sulfonamide! The unusual pathway from the identification to the optimization of PERK inhibitors. **D. Carenzi**, E. Casale, M. Fasolini, I. Motto, I. Beria, M. Silvagni, C. Perrera, B. Valsasina, D. Donati, E.R. Felder, A. Galvani, A. Isacchi, M. Pulici

MEDI 366. *N*-(2,4-difluoro-3-((6-(2-fluoropyridin-3-yl)quinazolin-4-yl)amino)phenyl)propane-1-sulfonamide (DRF-0529) as a novel RAF kinase inhibitor. **S. Peng**, C. Liao, M. Kuo, S. Yen, H. Huang, J. Yang, Y. Liu, S. Ciou

MEDI 367. Improving peptide pharmacokinetics through tryptophan late-stage lipidation. **C. Huang**, H. He, V. Reddy, R.P. Nargund, S. Lin, A. Palani

MEDI 368. Discovery of new oxindoles derivative as potent and selective AMPK activators. **O. Venier**, C. Namane, E. Fett, e. Nicolai, P. Mougnot, P. Paul, B. Cornet, P. Chamiot-Clerc

MEDI 369. Discovery of 2-aminoisobutyric acid ethyl ester (AIBEE) phosphoramidate prodrugs that deliver high levels of the active triphosphate of nucleoside HCV inhibitors in human hepatocytes and in dog liver biopsy studies. **J.T. Randolph**, T. Li, A.C. Krueger, H.R. Heyman, H. Chen, D. Bow, C. Van Handel, V. Peterkin, R.A. Carr, D. Stolarik, T. Dekhtyar, M. Irvin, P. Krishnan, R. Wagner, D.A. DeGoey

MEDI 370. Design, synthesis and biological evaluation of novel 4-phenylisoquinolinone BET bromodomain inhibitors. M. Bennett, Y. Wu, A. Bloor, J. Matuszkiewicz, S. O'Connell, L. Shi, R. Stansfield, J. Del Rosario, J. Veal, D. Hosfield, J. Xu, S. Kaldor, J. Stafford, **J.M. Betancort**

MEDI 371. Anti-filarial activity of natural neurolelin D and synthetic neurolelin derivatives. **L. Perez-Perez**, S.A. Williams, K.M. Shea

MEDI 372. Identifying compounds that restore normal cellular function in Frontotemporal dementia caused by progranulin haploinsufficiency. **M.**

Telpoukhovskaia, K. Liu, F. Sayed, J. Etchegaray, Y. Zhou, D. Le, M. Xie, M.S. Bogyo, S. Ding, L. Gan

MEDI 373. Metal-free and mild approach to 1,3,4-oxadiazol-2(3*H*)-ones via oxidative C-C bond cleavage using molecular oxygen. **B. Lim**, S. Park, J. Park, J. Gam, S. Kim, J. Yang, J. Lee

MEDI 374. Design and synthesis of dimeric tetrahydroxanthenes as anticancer agents. **R. Ali**, G.A. Bradshaw, A.N. Leveille, A.E. Mattson

MEDI 375. Four series of estrane derivatives as selective inhibitors of cytochrome P450 (CYP 1B1): Design, synthesis and evaluation. **D. Poirier**, R. Dutour, J. Roy, R. Maltais, F. Cortés-Benitez

MEDI 376. REAL database a comprehensive database of synthetically feasible molecules: an update. **Y. Moroz**, **M. Vybornyi**, P. Mykhailiuk

MEDI 377. Synthesis of novel bicyclic amines and their application for drug design. **P. Mykhailiuk**

MEDI 378. Design, synthesis, and evaluation of improved aminoglycosides. **M.G. Pirrone**, T. Matsushita, G.C. Sati, T. Kato, S.N. Hobbie, T. Schrepfer, J. Schacht, A. Vasella, E.C. Bottger, D. Crich

MEDI 379. Fully automated radiosynthesis of carbon-11-labeled 5-HT₆R antagonists as new candidate PET radioligands for imaging of Alzheimer's disease. **M. Wang**, M. Gao, Q. Zheng

MEDI 380. Interaction of novel immunogenic cell death-inducing azonafides with DNA: A biophysical study. **S.G. Tarasov**, P. Andrade Bonilla, W. Zhang, S. Sinha, N. Tarasova

MEDI 381. Kinetic isotope effects of a 1,2,3,6-tetrahydropyridine-derived MAO-B substrate. **L. Drake**, A. Mufarreh, J. Pham, A.F. Brooks, M. Kilbourn, P. Scott

MEDI 382. Two strategies for imaging the receptor for advanced glycation end products. **L. Drake**, A.F. Brooks, P. Scott

MEDI 383. Aromatic sulfonamide library of human carbonic anhydrase IX inhibitors – towards anticancer drug design through chemical and crystallographic structure correlations with the thermodynamics of binding. V. Linkuviene, A. Zubriene, V. Paketuryte, A. Smirnov, V. Petrauskas, **D. Matulis**

MEDI 384. Elucidating the enzymatic activity of HDAC11. **C. Moreno Yruela**, I. Galleano, A.S. Madsen, C.A. Olsen

MEDI 385. Conformationally locked UDP and U_{P3}U analogues as P2Y₆ receptor agonists. **K.S. Toti**, S. Jain, A. Ciancetta, R. Balasubramanian, S. Chakraborty, R. Surujdin, Z. Shi, K.A. Jacobson

MEDI 386. Synthesis, structural characterization and butyrylcholinesterase inhibition studies of ferrocene based anilides. **A. Altaf**, **A. Badshah**, D.C. Crans

MEDI 387. Design, synthesis, insecticidal activity and structure–activity relationship (SAR) of (1*R*)-(+)-verbenone derivatives. **M. Kim**, K. Lee, Y. Choi

MEDI 388. Potential lead compounds for the treatment of Alzheimer’s disease: A peptide that blocks amyloid β induced neurotoxicity. **K. Fukuhara**, T. Arai, A. Ohno, K. Mori, M. Shibanuma, N. Miyata, H. Nakagawa

MEDI 389. Unprecedented enantiomeric discrimination of the two chiral-forms of DNA “light-switching” Ru(II) cationic complex by living-cells via ion-pairing with achiral counter-anions. **B. Zhu**

MEDI 390. *N*-glycosylation inhibitors towards novel anti-cancer chemotherapeutics. K. Mitachi, S. Eslamimehr, S.M. Kurosu, **M. Kurosu**

MEDI 391. Design, synthesis and biological evaluation of novel discodermolide analogues leading to suppression of senescence and an increase cancer cell death. **B. Guo**, A.B. Smith, H.M. Mcdaid, S.B. Horwitz

MEDI 392. Insight into the drug likeness of 4-aminoantipyrine based thioureas: Synthesis, biological evaluation, molecular docking and molecular dynamic simulation studies. **A. Khurshid**, A. Saeed

MEDI 393. Colorectal cancer inhibition and cellular activities of (Z)-2-cinnamamido-3- phenyl-*N*-propylpropanamide (MOS-1512A). **K. Alireza**

MEDI 394. *In vitro* and *in vivo* activity of peptidomimetic compounds that target the periodontal pathogen *Porphyromonas gingivalis*. P. Patil, J. Tan, D.R. Demuth, **F.A. Luzzio**

MEDI 395. Synthesis of fluorescent goldnanocluster used in metal pollution sensing. **K. Sanyal**

MEDI 396. Synthesis of the analogs of oxazolidine moiety contained in antitumor agents. **T. Yang**, S. Huang, Y. Shih

MEDI 397. Synthesis and identification of prodrug: Using diclofenac sodium as the main drug. **I. Gunawan**, H.D. Tabba

MEDI 398. Novel biochemical insights in cerebrospinal fluid of patients with Neurosyphilis based on metabonomics study. **S. Qi**, R. Luo, Q. Chen, D. Xu

MEDI 399. Synthesis and anti-microbial evaluation of novel dihydrophthalazine-1, 4-diones congeners via green synthetic methodology. **V. Chittireddy**

MEDI 400. Chemical synthesis and biological evaluation of unnatural analogs of Amorphutin. **L. Barasa**

MEDI 401. Drug-drug interactions severity prediction using PASS approach. **A. Dmitriev**, D. Filimonov, A. Lagunin, A. Rudik, D. Karasev, K. Murtazalieva, **V. Poroikov**

MEDI 402. Discovery of pharmacological potential of 9,10-anthaquinone dithiocarbamates: Virtual screening and experimental study. **M. Stasevych**, V. Zvarych, V. Novikov, S. Zagorodnya, O. Povnitsa, M. Chaika, M. Nesterkina, I. Kravchenko, T. Glorizova, **V. Poroikov**

MEDI 403. Structure activity relationship (SAR) studies of NNRTI (non-nucleoside reverse transcriptase inhibitors) and nucleotide reverse transcriptase (NRTI) used to combat HIV, using Gaussian computational techniques. **S. Narayan**, D.Z. Burgan, K.Y. Baldwin

MEDI 404. Discovery and characterization of small molecules of long noncoding MALAT1 triple helix with anti-cancer therapeutic potential. **F. Abulwerdi**, W. Xu, A. Ageeli, M. Yonkunas, G. Arun, J. Schneekloth, N.J. Baird, D. Spector, S. Le Grice

MEDI 405. Detection of butyrylcholinesterase in living systems using a highly specific near-infrared fluorogenic substrate. **G. Yang**, S. Liu, W. Yang

MEDI 406. Biological activity of photoactivated iron metallocene anti-cancer compounds. **P. Olsen**, J.M. O Connor

MEDI 407. Asymmetric total synthesis of novel resolvin conjugates in tissue regeneration (RCTR). **T.F. Lam**, R. Nshimiyimana, N.A. Petasis

MEDI 408. Stereocontrolled total synthesis of novel resolvin-related sulfidoconjugates. **R. Nshimiyimana**, T.F. Lam, N.A. Petasis

MEDI 409. Improved synthesis of *cis*-1, 4-cyclohexanediol. **W. Liu**, H. Li, M. Yang

MEDI 410. PPAR δ modulators improve mitochondrial function: Potential treatment for Duchenne muscular dystrophy (DMD). **B. Lagu**, A.F. Kluge, E. Tozzo, M. Goddeeris, P. Dwyer, A. Basinsky, R. Fredenburg, R. Senaiar, M. Jaleel, N. Krishnamurthy, A. Lakshminarasimhan, N. Tiwari, T. Takahashi, M.A. Patane

MEDI 411. Novel synthetic method for 5-aminooxan-3-ol hydrochloride. **J. Li**, L. Qi, Q. Fei, H. Li, M. Yang

MEDI 412. Synthesis and application of unnatural proline analogues: Advanced building blocks for medicinal chemistry. P. Mykhailiuk, **Y. Moroz**, O. Michurin

MEDI 413. Design, synthesis and application of novel building blocks to “Escape the Flatland” in medicinal chemistry. **Y. Moroz**, **P. Mykhailiuk**, A. Tolmachev

MEDI 414. [2+2]-photochemical synthesis and application of bicyclic amines: Advanced building blocks for medicinal chemistry. **Y. Moroz**, **P. Mykhailiuk**, V. Levterov

MEDI 415. Polyfunctional building blocks for drug discovery. **O. Gavrylenko**, Y. Moroz, B. Rogovoy

MEDI 416. Design, synthesis and application of novel morpholine surrogates. **P. Mykhailiuk**

MEDI 417. Design and synthesis of novel fluorinated amines. **P. Mykhailiuk**

MEDI 418. Total synthesis of nosokophic acid. **D. Pena**, T. Tetrault, M.A. Boudreau

MEDI 419. Distorted phthalocyanines via click-chemistry: synthesis, photoacoustic, photothermal and cell studies. **W. Rizvi**, E. Khwaja, N.K. Bhupathiraju, A. Rizvi, C.M. Drain

MEDI 420. Click chemistry on chlorins. **N. Bhupathiraju**, W. Rizvi, C.M. Drain

MEDI 421. Using adducts and fragments to identify compounds in mass-directed flash column chromatography. **J.R. Bickler**

MEDI 422. Calibration of analytical HPLC to generate preparative LC gradients. **J.E. Silver**, R. Sorgo, A. Darter

MEDI 423. Methanol as an alternative mobile phase solvent for reversed-phase peptide purification. **E. Denton**, J.R. Bickler, J.J. Urh

MEDI 424. Development of HPLC methods for analysis of cholesteryl esters with alkyl chains of odd number length. **K. Lilly**, M.Q. Irving, J. Hughes, J. Schentag, **L. Mielnicki**, M. McCourt

MEDI 425. *pro*-Pyrrolobenzodiazepine (*pro*-PBD) bioconjugates, part 3: Design and synthesis of *pro*-PBD conjugates containing a self-immolative substituted disulfide linkers. I.R. Vlahov, L. Qi, **H.K. Santhapuram**, G.L. Parham, K.Y. Wang, J.F. Vaughn, S.J. Hahn, M. Vetzal, M. Nelson, J. Reddy, C.P. Leamon

MEDI 426. *pro*-Pyrrolobenzodiazepine (*pro*-PBD) bioconjugates, part 4: Design of novel oxime-based *pro*-PBD conjugates that release active drug via intramolecular diazepine-ring-closure. I.R. Vlahov, **A. Felten**, N. Zou, K.Y. Wang, S.J. Hahn, J.F. Vaughn, M. Vetzal, M. Frieden, M. Nelson, J. Reddy, C.P. Leamon

MEDI 427. Drug delivery of xanthohumol to adipocytes using ultrasmall superparamagnetic iron oxide nanoparticles (USPIO). **I. Khaki Najafabadi**, V.V. Mody, J. Samuels, R. Dansby-Sparks, S. Raylam, A. Singh, R. Deshmukh

MEDI 428. Hygromycin A, an antimicrobial with selective activity against *Borrelia burgdorferi* for treatment of Lyme disease. Y. Imai, X. Wu, M. Caboni, Q. Favre-Godal, S. Niles, K. Megan, **A. Iinishi**, K. Lewis

MEDI 429. Evaluation of antibacterial activity of *Vangueria volkensii* extracts. **A.K. Addo-Mensah**, D. Holland

MEDI 430. Synthesis and biological evaluation of benzimidazoles as FKBF inhibitors. **S.K. De**

MEDI 431. Disabling the resistance of methicillin-resistant *Staphylococcus epidermidis* (MRSE). **A.K. Lam**, M. Foxley, C.V. Rice

MEDI 432. Regioselectivity of N-substituted 3-nitropyrazole alkylations. **S. Bao**, J. Perea, N. Norman, A. Huang

MEDI 433. Targeting trimethylamine oxide biosynthesis pathway discovery of new inhibitors against TMA lysate protects against atherosclerosis lesion, MI and stroke. **A. Duzan**

MEDI 434. Targeting the trimethylamine oxide biosynthesis pathway: Discovery new novel inhibitors against gut microbial TMA lysate protects against atherosclerosis lesion, MI and stroke. **A. Duzan**, A. Roberts, J. Buffa, S. Hazen, V. Gogonea

MEDI 435. DCBCO1303-a promising inhibitor of smo-mediators of hedgehog pathway signalling. **M. Kuo**

MEDI 436. Studies into the enzymatic action and immunomodulatory activity of isopentenyl-diphosphate isomerase. **M.A. Schladetsch**, A.J. Wiemer

MEDI 437. Practical modular synthesis of targeted imaging agents for MRI, PET and PET-MRI. **K. Jones**, A. Sweeny-Jones, J. Perez, S. Beach, C. Weidman, M. Regan, S. Williams, H.F. Schmitthenner

MEDI 438. Activity prediction by target fingerprinting. **P. Schneider**

MEDI 439. Prenylated isoflavones: Comparison of distribution coefficients, hydrogen bonding acidity values and positions within detergent micelles. **S. Tuck**, W.L. Whaley, M. Abraham

MEDI 440. Theranostic antibody-drug conjugates for potential dual application in targeted therapy and fluorescence imaging of colorectal cancer. **S. Ren**, X. Sun, H. Xu, T. Nguyen, C. Kang, N. Sadeghipour, X. Xu, N. Wu, Y. Chen, K. Tichauer, D.D. Minh, H.S. Chong

MEDI 441. New bifunctional ligands of Zr-89 for potential applications in antibody-targeted positron emission tomography (PET) imaging and precision medicine. **Y. Chen**, S. Ren, C. Kang, Y. Liu, S. Zhang, H.S. Chong

MEDI 442. Targeted nanoparticles for pathogen-specific drug delivery. **L. Schnorbus**, L.J. Perez

MEDI 443. Fructose-enhanced antimicrobial activity of self-assembled nano peptide amphiphiles for treating antibiotic resistant infections. **M. Gao**, K. Chang, d. Wang, Y. Li, L. Sun, S. Lustig, T. Webster

MEDI 444. Solid lipid nanoparticles (SLN) from ketogenic diet lipids: Anxiolytic and anticonvulsant effect. **E.V. Toledo**

MEDI 445. Aminolipid structure-activity relationships in lipid nanoparticle *in vivo* performance. **M.A. Cornebise**, K. Benenato, L. Brito, W. Butcher, K. Davis, j. deterling, k. hassett, N. Jordan, L. Knowles, E.S. Kumarasinghe, D. Mampreian, J. Milton, K. Olsen, S. Sabnis, T. Salerno, J. Sanabria, A. Sengooba, P. Shah, M. Stanton, A. Woods

MEDI 446. Preparation and characterization of new solid micro and nanodispersions of amorphous drugs. **J. Cruz**, P. Morales, C. Martínez, M. Videá, L.M. Martínez

MEDI 447. Design and development of small molecule RelA/RSH inhibitors. **D.C. Hall**, H. Ji, G.D. Ehrlich, J. Krol

MEDI 448. Reducing tau phosphorylation using synthetic peptides: Developing peptide-based inhibitors of microtubule affinity regulating kinase 2 (MARK2). **J.M. Holub**, N. Alqaeisoom, C. Qian, D. Arachchige, R. Colvin

MEDI 449. Synthesis of water soluble anthraquinoneaminoacrylamides and their glioblastoma cell viability. **N. Pianovich**, B.S. Jursic

MEDI 450. Synthesis and characterization of aspirin and indomethacin prodrugs. **A. Mahmoud**, H.D. Tabbá, Y.M. Hijji

MEDI 451. Homology models of G protein-coupled receptors: quantitative studies to assess feasibility and applicability to drug discovery. **S. Costanzi**

MEDI 452. Way2drug platform – ligand-based approach to drug repurposing. **D. Druzhilovskiy**, A. Rudik, D. Filimonov, G. Sastry, V. Poroikov

MEDI 453. Cholesteryl ester vesicle-mediated delivery of GFP plasmid into retinal epithelial cells *in vitro*. **R. Meechan**, M.Q. Irving, J. Hughes, J. Fraser-McArthur, J. Schentag, L. Mielnicki, M. McCourt

MEDI 454. Fragment-based approaches to targeting the CoA pathway. **A.G. Coyne**

MEDI 455. Three new cytotoxic steroidal glycosides isolated from *Conus pulicarius* collected in Kosrae, Micronesia. **Y. Lee**, S. Kim, H. Lee, J. Lee, J. Lee

MEDI 1

Oral peptide macrocycle antagonists of integrin $\alpha 4\beta 7$ for the treatment of IBD

Andrew L. Roughton¹, aroughton@cogeco.ca, Manuel Pérez Vázquez¹, M. M. Morshed¹, Adam P. Kafal¹, Rodrigo Mendoza Sanchez¹, Yvan Boutin², Andrei K. Yudin³, Louise Bergeron⁴, Jeffrey A. Coull⁴. (1) Chemistry, Encycle Therapeutics, Inc., Toronto, Ontario, Canada (2) Biology, TransBIOTech, Levis, Quebec, Canada (3) Dept of Chem Univ of Toronto, Toronto, Ontario, Canada (4) Biology, Encycle Therapeutics, Inc., Toronto, Ontario, Canada

T cell trafficking to the gut initiates mucosal inflammation in the intestine, a hallmark of Inflammatory Bowel Disease (IBD). Legacy and current agents for IBD have provided clinicians with effective treatment options comprised largely of biologics, including vedolizumab (Entyvio®), a monoclonal antibody targeting integrin $\alpha 4\beta 7$. Orally available agents that can mitigate shortcomings in low colon perfusion, loss of response or extra-intestinal adverse events would provide attractive alternatives. Encycle Therapeutics employs proprietary cyclization chemistries to prepare nacellins, our brand of macrocycles, that exhibit drug-like properties including stability, amphipathicity and exposure. We conducted a discovery campaign starting from linear peptide ligands of integrin $\alpha 4\beta 7$, focused on macrocyclization to optimize potency, selectivity against integrin $\alpha 4\beta 1$ and DMPK. In pre-clinical mouse models of dextran sulfate sodium-induced colitis, nacellin antagonists of integrin $\alpha 4\beta 7$ evoke prolonged receptor internalization in memory T cells in blood and exclusion of $\alpha 4\beta 7+$ memory T helper cells from gut-associated lymphoid tissues. Several nacellins exhibit a balanced gut-plasma exposure profile and persistently suppress mechanisms of disease. Key features of the medicinal chemistry optimization will be presented.

MEDI 2

Discovery & development PTG-100, an oral peptide antagonist of $\alpha 4\beta 7$ integrin, for the treatment of inflammatory bowel disease

Ashok Bhandari, ashokbhandari@gmail.com. Protagonist Therapeutics, Menlo Park, California, United States

PTG-100, a potential first-in-class oral peptide antagonist of $\alpha 4\beta 7$ integrin, is being developed for the treatment of patients with ulcerative colitis and Crohn's disease. Protagonist's oral peptide technology platform was utilized to discover PTG-100 as a potent, selective, and orally stable peptide that alters trafficking of gut homing T cells in animal models of colitis. Target engagement was assessed in the peripheral blood of colitis and healthy mice, and translated to the demonstration of pharmacodynamic proof-of-concept in a Phase 1 trial with normal healthy volunteers. We initiated a Phase 2b clinical trial in patients with active ulcerative colitis. The discovery process and Phase 1 clinical results of PTG-100 will be discussed.

MEDI 3

Small molecule approaches to the treatment of IBD

Gary D. Glick, *gglick@umich.edu. Univ of Michigan, Ann Arbor, Michigan, United States*

Inflammatory bowel disease (IBD) encompasses a spectrum of autoimmune disorders effecting up to 2,000,000 Americans. Although anti-TNF-alpha therapies are effective in IBD, their use is associated with systemic side effects including re-activation of latent pathogens, cancer, and the formation of autoantibodies. Some patients are inherently resistant to anti-TNF-alpha drugs, and over time, almost half of all patients that initially respond, develop resistance. Side effects and gaps in efficacy of current treatments result in significant morbidity for IBD patients and a need for better treatment options. Recent studies have demonstrated that gut-resident pathogenic immune cells driving IBD have a metabolic phenotype wherein they abnormally rely on oxidative phosphorylation for survival and effector function. Niclosamide is a gut-restricted salicylanilide antihelmintic drug possessing an outstanding safety profile based on human use over 50 years. Its antihelmintic effect results from uncoupling mitochondria of cestodes, disrupting their oxidative phosphorylation and causing death of the parasites. Here we describe an experimental therapeutic approach leveraging the chemical biology of niclosamide to target pathogenic immune cells in IBD, that similar to cestodes depend on oxidative phosphorylation. Results in several preclinical models of IBD. highlight the potential of niclosamide to be developed as a new, cost-effective treatment for IBD (both mild-to-moderate and moderate-to-severe forms of the disease) and underlie the rationale for current clinical evaluation of the drug in ulcerative colitis.

MEDI 4

Small-molecule antagonists targeting the NLRP3 inflammasome for treatment of inflammatory diseases

William R. Roush¹, *roush@scripps.edu*, **Dong-Ming Shen**¹, **Shankar Venkatraman**¹, **Jason Katz**¹, **Edward J. Olhava**¹, **Kate Byth**¹, **David Winkler**¹, **Andrea Stutz**², **Damien Bertheloot**², **Simona Braams**², **Ana Kitanovic**², **Igor Kitanovic**², **Pascal Trippner**², **Brian Sanchez**³, **Xiaokang Lu**³, **Luigi Franchi**^{1,3}, **Eicke Latz**², **Shomir Ghosh**¹, **Dennis Dean**¹, **Anthony Pipari**^{1,3}, **Martin Seidel**¹, **Gary D. Glick**¹. (1) IFM Therapeutics, Boston, Massachusetts, United States (2) IFM Therapeutics, Bonn, Germany (3) IFM Therapeutics, Ann Arbor, Michigan, United States

Danger signals appear in many common inflammatory diseases and can lead to activation of the cytosolic innate signaling receptor NLRP3. Active NLRP3 induces the assembly of an inflammasome which triggers caspase-1 mediated activation of IL-1 β family cytokines and induces inflammatory pyroptotic cell death. Pharmacological interference with NLRP3 activation has proven to be successful in a variety of preclinical models of inflammatory diseases, validating NLRP3 as an attractive target for drug

development. In this presentation, an overview of recent advances in the development of small-molecule antagonists targeting NLRP3 for treatment of inflammatory diseases will be provided.

MEDI 5

Discovery of a cross-species potent and selective inhibitor of receptor-interacting protein kinase 1 (RIPK1) providing protection in a *Nemo* deletion model of IBD

Snahel D. Patel, *patel.snahel@gene.com*. *Discovery Chemistry, Genentech, Inc., South San Francisco, California, United States*

Regulation of cell death signaling is critical for the maintenance of homeostasis and prevention of disease. A variety of cell death stimuli can lead to the activation of kinases RIPK1 and RIPK3 culminating in inflammatory cell death pathways including apoptosis and necroptosis. One such trigger is the dysfunction of the nuclear factor (NF)- κ B essential modulator (NEMO) that is critical for intestinal epithelial cell homeostasis and gut integrity. We will present the development of a cross-species potent and selective small molecule inhibitor of RIPK1 that blocks TNF-induced hypothermia in a systemic inflammatory response syndrome (SIRS) model and prevents the colitis and ileitis caused by intestinal *Nemo* deletion. Therefore targeting the kinase RIPK1 has potential in treating patients with *NEMO* mutations that lead to inflammatory diseases and conceivably in IBD.

MEDI 6

BT-11: A new first-in-class oral therapeutic for Crohn's disease and ulcerative colitis that targets LANCL2

Richard D. Gandour, *gandour@vt.edu*, *Josep Bassaganya-Riera*. *Landos Biopharma, Blacksburg, Virginia, United States*

Lanthionine synthetase C-like 2 (LANCL2), a novel therapeutic target for inflammatory and autoimmune diseases, and diabetes, exerts anti-inflammatory and insulin-sensitizing effects. This study reports the first LANCL2-based therapeutics for inflammatory bowel disease (IBD). New chemical entities were screened by molecular docking, then synthesized and analyzed for binding to LANCL2 by surface plasmon resonance. Piperazine-1,4-diylbis((6-benzo[d]imidazole-2-yl)pyridine-2-yl)methanone, BT-11, was identified as the lead LANCL2-binding compound for treating IBD. Oral BT-11 is effective in five mouse models of IBD exhibiting consistent downregulation of inflammatory markers and decreased presence of colonic lesions with a dependency on the presence of LANCL2. Similarly, in cells isolated from IBD patients, BT-11 decreases inflammatory markers while increasing IL-10 and FOXP3 expression. In toxicity, safety pharmacology, and genetic toxicity studies, BT-11 has a benign safety profile. With robust preclinical safety and efficacy supporting data, BT-11, a first-in-class, orally

active, gut-targeting therapeutic, enters clinical trials for Crohn's disease and ulcerative colitis in 2018.

MEDI 7

Impact of synthetic chemistry methodologies in drug discovery

Jonas Boström², Dean G. Brown³, Robert Young⁴, Gyorgy M. Keseru¹, keseru.gyorgy@ttk.mta.hu. (1) Research Centre for Natural Sciences, HAS, Budapest, Hungary (2) AstraZeneca, Mölndal, Sweden (3) AstraZeneca Pharmaceuticals, Waltham, Massachusetts, United States (4) Medicines Research Centre, GSK, Stevenage, United Kingdom

The key objectives of medicinal chemistry are to efficiently design and synthesize bioactive compounds that lead to safe and efficacious drugs, which can ultimately be produced on a large scale. Most medicinal chemistry programs benefit from screening collections populated by a range of molecules derived from a set of known and robust chemistry reactions. A number of papers analyzed the role of synthetic organic chemistry in drug discovery, suggesting that the same set of reactions is used in most of the optimizations and the impact of many new methodologies is limited. Starting from the known limitations of reaction parameters, synthesis design tools, synthetic strategies and innovative chemistries, we highlight opportunities for expansion of medicinal chemists' synthetic toolbox. More intense crosstalk between synthetic and medicinal chemists in industry and academia should enable enhanced impact of new methodologies through widening of synthetic diversity in future drug discovery.

MEDI 8

Rank ordering compound designs for synthesis: When do methods work and what are some known limitations?

Kevin P. Cusack, kcuse@mac.com, Maria Argiriadi, Eric Breinlinger, Jeremy Edmunds, Dawn M. George, Friedman Michael, Michael Z. Hoemann. AbbVie, Worcester, Massachusetts, United States

The small molecule drug design cycle is comprised of multiple discreet steps including target identification, target druggability assessment, ligand identification/design, ranking of designs, ranking difficulty of synthesis, preparation, testing and data analysis. A critical step in maximizing the efficiency of the design cycle is the ability to rank order target molecules prior to synthesis. Simple docking is often not sufficient to separate out acceptable and unacceptable target molecules and designers frequently rely on additional information from various tools such as shape and electrostatic analysis, molecular dynamics simulations, and free energy perturbation (FEP) scoring. The argument can be made that absolute scoring of a concept molecule is not required and relative ranking against a known data point is sufficient to decide whether a proposal is worth investing in. In addition more difficult synthetic targets that require increased

investment in synthetic resources can easily be justified when there is clear data to support the value of a proposed molecule. The use of reliable scoring methods to rank order compounds is therefore of critical interest to medicinal chemists.

MEDI 9

Design, synthesis, and evaluation of nonretinoid retinol binding protein 4 antagonists for the potential treatment of atrophic age-related macular degeneration and Stargardt disease

Christopher Cioffi¹, christopher.cioffi@acphs.edu, **Konstantin Petrukhin**². (1) *Basic and Clinical Sciences and Pharmaceutical Sciences, Albany College of Pharmacy and Health Sciences, ALBANY, New York, United States* (2) *Ophthalmology, Columbia University, New York, New York, United States*

Accumulation of lipofuscin in the retina is associated with the pathogenesis of atrophic age-related macular degeneration (AMD) and Stargardt disease. Evidence has shown that bisretinoids such N-retinylidene-N-retinylethanolamine mediate lipofuscin toxicity. The synthesis of lipofuscin bisretinoids is a natural outcome of the visual cycle and is dependent upon the influx of retinol from serum to the retina. Thus, agents that modulate the visual cycle by impeding ocular uptake of serum retinol show promise as potential pharmacotherapies by which to stem further neurodegeneration and concomitant vision loss associated with geographic atrophy of the macula. Specifically, we have shown that compounds antagonizing the retinol-dependent interaction of retinol-binding protein 4 (RBP4) with transthyretin (TTR) reduce serum RBP4 and retinol levels and inhibit bisretinoid formation in the retina of *Abca4*^{-/-} mice. This lecture will highlight work conducted as part of the NIH Blueprint Neurotherapeutics Network whereby novel RBP4 antagonists with exquisite in vitro RBP4 binding affinity and favorable drug-like characteristics were identified. Furthermore, we will show that standout analogues exhibited robust in vivo efficacy by reducing circulating plasma RBP4 levels by greater than 90% in rodents.

MEDI 10

Discovery of novel quinoline sulfonamide derivatives as potent, selective and orally active ROR γ inverse agonists

Dominique Potin¹, dominique.potin@inventivapharma.com, **Jérôme Amaudrut**¹, **Maria Argiriadi**², **Martine M. Barth**¹, **Eric Breinlinger**², **Didier Bressac**¹, **Pierre Broqua**¹, **David J. Calderwood**², **Mohamed Chatar**¹, **Kevin P. Cusack**², **Stephen B. Gauld**³, **Sébastien Jacquet**¹, **Rajesh V. Kamath**², **Valérie Lepais**¹, **Jean-Michel Luccarini**¹, **Philippe Masson**¹, **Christian Montalbetti**¹, **Laurent Mounier**¹, **Olivia Poupardin**¹, **Sylvie Rouaud**¹, **Craig D. Wallace**². (1) *Inventiva, Daix, France* (2) *AbbVie, Worcester, Massachusetts, United States* (3) *AbbVie, North Chicago, Illinois, United States*

Targeting the IL-17 pathway has become in recent years a very attractive approach for the treatment of immuno-inflammatory diseases. IL-17 antibodies such as secukinumab have validated the interest of blocking IL-17 secretion for such therapy. The nuclear receptor ROR γ t is a master player in the regulation of IL-17. It does indeed play a key role in the differentiation and development of Th17 cells which secrete IL-17A and other pro-inflammatory cytokines like IL-17F and IL-22. Small molecule ROR γ t inhibitors could be useful for the treatment of various diseases such as rheumatoid arthritis, multiple sclerosis, psoriasis or inflammatory bowel disease.

An HTS has been run on Inventiva's library (248000 Compounds) using a GAL4 transactivation assay leading to the discovery of a new series of quinoline sulfonamides as ROR γ inhibitors, eventually giving rise to a lead compound showing a nice activity *in vivo* when administered *p.o.* both in a target engagement model as well as in a multiple sclerosis model (EAE). The synthesis, structure activity relationship (SAR) and biological activity of these derivatives will be presented.

MEDI 11

Development of thienopyridines as potent antiproliferative agents

David Barker¹, d.barker@auckland.ac.nz, **Lisa I. Pilkington**¹, **Michelle van Rensburg**¹, **Natalie A. Haverkate**¹, **Johannes Reynisson**¹, **William A. Denny**², **Euphemia Leung**². (1) *School of Chemical Sciences, University of Auckland, Auckland, New Zealand* (2) *Cancer Society Research Centre, University of Auckland, Auckland, New Zealand*

The antiproliferative activity of thieno[2,3-*b*]pyridine-2-carboxamides were initially discovered using virtual high throughput screening against the regulatory enzyme phospholipase C (PLC). Morphology and motility assays, using triple negative breast cancer cell lines, led to the conclusion that PLC is the most probable bio-molecular target. Using a combination of computer aided drug design and synthesis, further analogues have been prepared and tested for their antiproliferative activity allowing an SAR to be developed. Numerous analogues with low nano-molar growth inhibition against various cancers have been developed. SAR studies suggest that the core structure can be fine-tuned to specific cancers, potentially due to enzyme/isoform specificity. Additionally mouse xenograft assays showed significant reduction in tumour size after treatment, whilst showing no adverse effects to non-cancerous mice. Here we report on our recent development of novel thienopyridines and derivatives, expanding the SAR against PLC and our efforts preparing potent, more soluble and bioavailable, compounds.

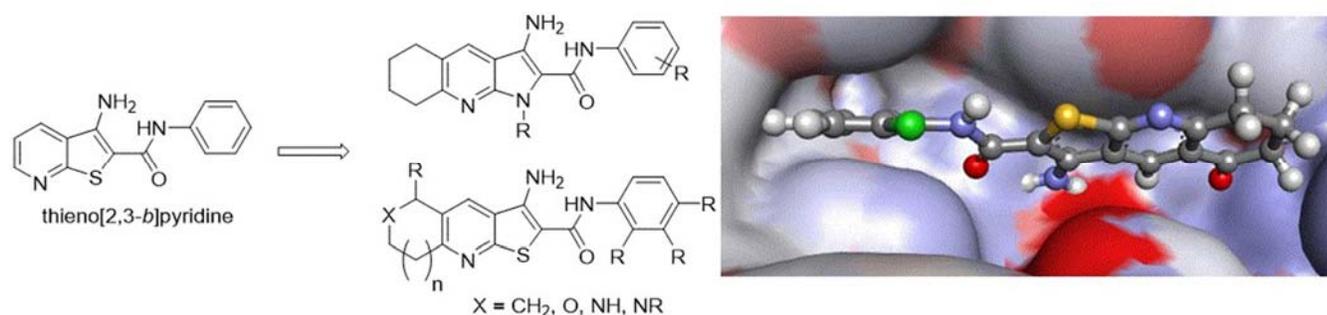


Figure 1: Thienopyridine analogues and docking of one example to PLC

MEDI 12

Development of 4-oxazolidinone natural products as infectious disease lead compounds

Joshua G. Pierce, joshuapierce6@me.com. Dept of Chemistry, NC State University, Raleigh, North Carolina, United States

4-oxazolidinone natural products, highlighted by lipoxazolidinone A, are unusual molecules isolated from marine sources. Through rapid chemical synthesis and medicinal chemistry/chemical biology efforts, we have demonstrated that these heterocycles are potent antimicrobial agents against a wide panel of drug resistant Gram-positive pathogens, and new derivatives also display activity against Gram-negative pathogens as well. This talk will focus on our development of the molecular scaffold, optimization of the molecular properties and the study of the mechanism of action and generation of resistance. Of great interest, these molecules possess a dual mechanism of action (cell wall and protein synthesis inhibitors) and do not display significant toxicity to mammalian cells. Further, resistance is slow to develop.

MEDI 13

Discovery of inhibitors of sirtuin and PARP enzymes from a DNA-encoded chemical library designed to target NAD⁺-binding pockets

Raphael M. Franzini, raphael.franzini@utah.edu, Lik Hang Yuen, Srikanta Dana. Medicinal Chemistry, University of Utah, Salt Lake City, Utah, United States

The efficient discovery of hit compounds for diverse target proteins is a key challenge in the development of chemical probes and therapeutic agents. DNA-encoded chemical libraries are emerging as a powerful hit discovery technology. It is widely believed that platforms of several ultra-large DNA-encoded libraries are needed to achieve consistent screening productivity, which are inaccessible to most medicinal chemists. We instead pursue the development of DNA-encoded chemical libraries designed for specific target classes. Based on this concept, we designed and synthesized a DNA-encoded chemical library to specifically target NAD⁺-binding pockets. Despite its simple design

and small overall size, this library enabled the discovery of potent and structurally novel inhibitors of several sirtuin and ADP-ribosyl transferase enzymes. The presented data provides evidence that even small and inexpensive DNA-encoded chemical libraries can provide robust screening success when designed carefully.

MEDI 14

Complex-selective HDAC inhibitors promote synaptic resilience for therapeutic treatment of neurological disorders

Nathan O. Fuller¹, nathan@rodintherapeutics.com, Michael C. Hewitt¹, Magnus Ivarsson¹, John A. Lowe², Berkley Lynch¹, Timothy McKee¹, Antonella Pirone¹, Maria Quinton¹, Adam Rosenberg¹. (1) Rodin Therapeutics, Cambridge, Massachusetts, United States (2) JL3 Pharma, Stonington, Connecticut, United States

Multiple studies have demonstrated that synaptic loss is a key event in many neurological disorders, including Alzheimer's disease. Indeed, synaptic pathology has been closely tied to disease symptoms. With the goal of improving synaptic resilience as a therapeutic intervention for neurological disorders with synaptic pathology, Rodin Therapeutics has designed complex-selective HDAC inhibitors which promote synaptic health. Importantly, these compounds have been optimized for CNS drug-like properties and decreased hematological toxicity, a key class-based safety concern. This profile enables treatment of neurological disorders with a chronic dosing paradigm, and represents a notable advance in the field of HDAC inhibition for treating these diseases. By enhancing the function of synapses critical for learning and memory, Rodin compounds have the potential to improve cognition, function, and other key endpoints in multiple neurodegenerative and neuropsychiatric diseases.

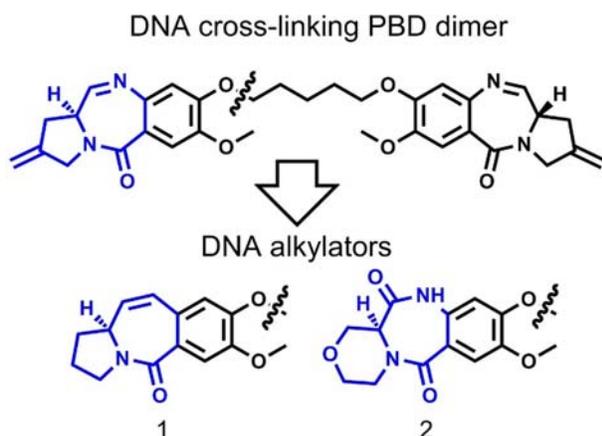
MEDI 15

Discovery of a novel pyrrolobenzodiazepine DNA-alkylator as an efficacious ADC payload

Binqing Wei¹, wei.binqing@gmail.com, Josefa Dela Cruz Chuh¹, Donglu Zhang¹, yong ma¹, Jinhua Chen², Thomas Pillow¹, Peter S. Dragovich¹. (1) Genentech, South San Francisco, California, United States (2) WuXi Apptec Inc., Shanghai, China

Delivery of cytotoxic drugs selectively to tumors using antibody-drug conjugates (ADCs) is a clinically validated therapeutic modality for cancer. DNA cross-linking pyrrolobenzodiazepine (PBD) dimers showed early promise as potent ADC payloads. However, emerging clinical data revealed that the doses achievable with this class of ADCs have been low due to systemic toxicity. Recent ADC advances involve the exploration of less potent PBD derivatives that may offer improvements over the legacy PBD-dimer payloads. Here we investigated two novel DNA-alkylating PBD-dimer analogs in both conjugated and unconjugated form (compounds 1-2). Despite the apparent structural similarity between these payloads, significant differences in ADC

efficacy were observed using both cancer cell lines and tumor xenografts. Surprisingly, when incorporated into an ADC, a membrane-permeable payload (1) showed much weaker activity than a less-permeable analog (2). To better understand these outcomes, we systematically characterized the DNA-alkylation activities and physicochemical properties of the payloads, as well as their intracellular concentrations following ADC-mediated delivery. This study identifies a novel PBD DNA-alkylator as efficacious ADC payload that is significantly less cytotoxic than the PBD dimers. Furthermore, this work sheds new light on the relationship between payload properties and ADC efficacy which may inform the development of related DNA-alkylators that are less cytotoxic than the majority of legacy ADC payloads.



MEDI 16

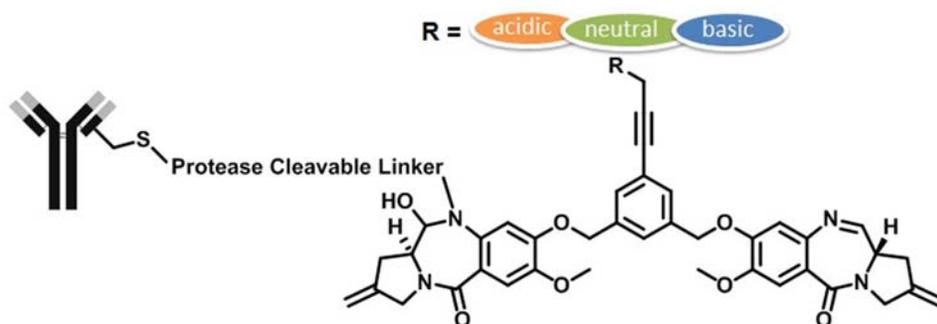
Medicinal chemistry centric approach to studying the delivery of diverse pyrrolobenzodiazepine dimers via antibody-drug conjugate technology

Leanna R. Staben, leannas@gene.com. MS 18b, Genentech, South San Francisco, California, United States

The use of antibody-drug conjugates (ADCs) to deliver highly cytotoxic agents in oncology settings as well as in other disease indications has been widely reported. The payloads employed in such ADC applications often display undesirable pharmacokinetic properties or safety concerns when examined in unconjugated form. While such challenging payload molecules can often be salvaged for therapeutic use by ADC technology, the optimization of their physicochemical properties for ADC applications is typically not performed. In an effort to better understand how payload physicochemical properties contribute to ADC performance, we modified these attributes in a well-known class of potent DNA alkylators, the pyrrolobenzodiazepene (PBD) dimers, and subsequently monitored how such alterations influenced the *in vitro* and *in vivo* activities of conjugates derived from these entities.

This presentation exhibits how we took a “medicinal chemistry approach” and made systematic changes to the pKa, lipophilicity, LogD, and PAMPA permeability parameters associated with a series of PBD-dimer ADC payloads. These physicochemical property

changes were introduced in the center of the PBD-dimer structure and thus had minimal impact on the ability of the molecules to bind to DNA minor groove (as determined via an in vitro DNA alkylation assay). When examined in unconjugated form, the new PBD-dimer molecules exhibited a wide range of anti-proliferation activities against the BJAB cancer cell line (IC₅₀ range = 3 to >20,000 pM). However, when the same PBD-dimers were conjugated to the anti-CD22 mono-clonal antibody through a protease cleavable Val-Cit linker, the resulting ADCs all displayed relatively potent anti-BJAB activities in cell culture experiments. The new CD22-targeting conjugates also exhibited varying levels of anti-tumor activity in a CD22 expressing WSU-xenograft tumor model. The tolerability of the conjugates in the xenografted mice also varied considerably with different PBD-dimer payloads. The relationships between PBD-dimer payload physiochemical properties and the in vivo efficacy and tolerability of the corresponding ADCs will be described.



MEDI 17

Accelerating multiple medicinal chemistry projects using matched molecular pair analysis for knowledge based design: A review from the past 8 years of use at the front line

Alexander Dossetter¹, *al.dossetter@medchemica.com*, **Edward J. Griffen**², **Andrew G. Leach**³, **Shane Montague**¹. (1) MedChemica Limited, Macclesfield, United Kingdom (2) Medchemica Ltd, Macclesfield, United Kingdom (3) MedChemica Limited, Staffordshire, United Kingdom

The technical methods and results of Matched Molecular Pair Analysis (MMPA) applied from a small, individual assay scale through large pharma scale, to multiple pharma data sharing scale have been published and reviewed. The drive behind these efforts has been to derive a medicinal chemistry knowledge base (i.e. definitive textbook) that can be applied to drug discovery projects. The aim is to greatly decrease the time in lead identification and optimization by the synthesis of fewer compounds. Given this context, how does this work on projects? How do the chemists make decisions? What are the results? The talk will answer these questions through project examples where MMPA has been applied and how this led to drug candidates. The projects disclosed are from multiple organisations and describe Cathepsin K inhibitors, Glucokinase

Inhibitors, 11β -Hydroxysteroid Dehydrogenase Type I Inhibitors (11β -HSD1), Ghrelin inverse antagonists and Tubulin Polymerization inhibitors. An overview of MMPA will be presented and each project will be briefly described with a focus on how the chemists used MMPA to understand SAR and design compounds. The impact of project progress to CD will be quantified.

MEDI 18

Award Address (ACS Award for Creative Invention sponsored by the ACS Corporation Associates). Design of kinase inhibitor medicines utilizing protein-ligand structures and property-based efficiency

Robert Kania, *robert.kania@pfizer.com*. Design Chemistry for Oncology, Pfizer Inc., San Diego, California, United States

The talk will cover some themes of drug discovery through several programs that advanced to advanced clinical development and to approval. The focus will be on the design and characterization of axitinib and key published clinical results to date. The data demonstrates that axitinib is differentiated in the class of VEGFR tyrosine kinase inhibitors (VEGFR TKIs). The class collectively has changed the landscape of how cancer is treated, particularly in renal cell carcinoma (RCC). The drug discovery team solved the first Xray structure of VEGFR2 kinase, and leveraged a computer-aided 3D molecular design platform of optimization, which was updated iteratively with structures of the inhibitor prototypes bound to the target VEGFR2 kinase. Principles of modern drug design, focused on potency-efficiency, were employed to achieve remarkable levels of potency against the target kinase, while also achieving selectivity across the 500+ members of the large kinase gene family of proteins. A number of key assays, with isolated protein and in whole cells, were required to inform the discovery effort, and help solve some big challenges and mysteries during the discovery effort. To fully understand the potency-efficiency of the best designs, crystallography relied on newly prepared constructs of protein, inclusive of the important juxtamembrane (JM) domain. Collectively, the studies elucidate unique drug-kinase interactions for axitinib that are dependent on distinct JM-domain conformations, resulting in significant potency and ligand-efficiency differences in the class. The identified structural trends are consistent with *in vitro* measurements, which also translate well to clinical performance in the class that clearly differentiates axitinib from other members. Additional oncology programs will be highlighted briefly to illustrate or support key lessons in modern medicinal chemistry.

MEDI 19

Discovery of AZD4573, a potent and selective inhibitor of CDK9 that enables transient target engagement for the treatment of haematological malignancies

Jeffrey G. Varnes¹, *jgvarnes@gmail.com*, **Bernard Barlaam**⁴, **Chris De Savi**¹, **Lisa Drew**¹, **Andrew Ferguson**², **Douglas Ferguson**¹, **Chungang Gu**¹, **Janet Hawkins**⁴, **Alexander Hird**¹, **Michelle L. Lamb**¹, **Nichole O'Connell**², **Kurt Pike**⁴, **Theresa Proia**¹,

Maryann San Martin¹, Melissa Vasbinder¹, Jianyin Wang³, Wenlin Shao¹. (1) Oncology, IMED Biotech Unit, AstraZeneca Pharmaceuticals, Waltham, Massachusetts, United States (2) Discovery Sciences, IMED Biotech Unit, AstraZeneca Pharmaceuticals, Waltham, Massachusetts, United States (3) Early Product Development, IMED Biotech Unit, AstraZeneca Pharmaceuticals, Waltham, Massachusetts, United States (4) Oncology, IMED Biotech Unit, AstraZeneca Pharmaceuticals, Cambridge, United Kingdom

Cyclin-dependent kinase 9 (CDK9) is a serine/threonine kinase that regulates elongation of transcription through phosphorylation of RNA polymerase II at serine 2 (p-Ser2-RNAPII). Transient inhibition of CDK9 results in reduced protein levels for genes that have short half-lives of transcripts and proteins, thus presenting a potential therapeutic opportunity in tumors dependent upon oncogenes fitting such criteria. One example is Mcl-1, an anti-apoptotic protein that plays a key role in cancer cell survival. A potent and selective CDK9 inhibitor having appropriate physical properties and pharmacokinetics (intravenous administration and short $t_{1/2}$) would enable short yet tuneable target engagement, allowing high flexibility in order to optimize the efficacy / tolerability balance in the clinic. We previously reported the identification of AZ5576 from an amidopyridine series as a potent, highly selective and orally bioavailable preclinical inhibitor of CDK9.

Here we report further optimization of this series with a focus on pharmacokinetic and physicochemical properties suitable for an intravenous agent with short target engagement. We discuss the Structure Activity Relationships (SAR) and Structure Property Relationships (SPR) in this series, specifically increasing human metabolic clearance (in order to achieve short half-life) and solubility whilst improving potency. This work led to the identification of AZD4573, a potent inhibitor of CDK9 (IC_{50} of $<0.004 \mu\text{M}$) with fast-off binding kinetics ($t_{1/2}$ 16 min) and high selectivity versus other kinases, including other CDK family kinases. AZD4573 exhibits a short half-life in multiple preclinical species (less than one hour in rat, dog and monkey) and good solubility for intravenous administration. Short-term treatment with AZD4573 led to a rapid dose- and time-dependent decrease in cellular pSer2-RNAPII, resulting in activation of caspase 3 and cell apoptosis in a broad range of haematological cancer cell lines (e.g. caspase activation EC_{50} $0.0137 \mu\text{M}$ in an acute myeloid leukemia model MV4-11). Correspondingly, in vivo efficacy was demonstrated in xenograft models derived from multiple haematological tumours (e.g. regression at 15 mg/kg twice weekly in MV4-11 xenografts). These results support AZD4573 as a clinical candidate for the treatment of haematological malignancies.

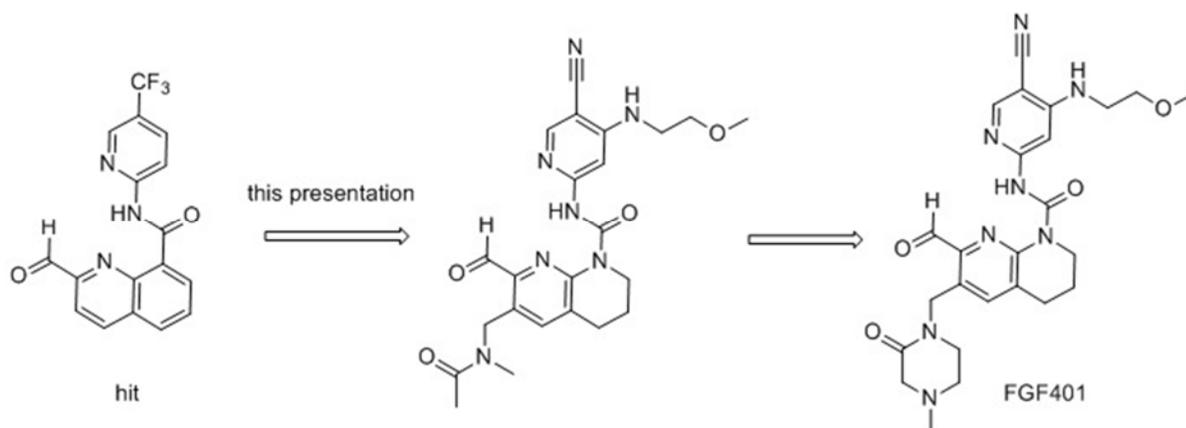
MEDI 20

Hit-selection and optimization strategy en route to FGF401, a reversible-covalent inhibitor of FGFR4 for the treatment of hepatocellular carcinoma

Thomas Knoepfel, thomas.knoepfel@novartis.com, Pascal Furet, Pierre Nimsgern, Sébastien Ripoché, Michael Kiffe, Catherine Leblanc, Nicole Buschmann, Robert Mah,

Diana Graus-Porta, Andreas Weiss, Markus Wartmann, Inga Galuba, Jörg Trappe, Robin A. Fairhurst. Novartis Pharma AG, Basel, Switzerland

The aberrant signaling of fibroblast growth factor 19 (FGF19) through the fibroblast growth factor receptor 4 (FGFR4) in combination with the co-receptor β -klotho (KLB) has been shown to be essential for the initiation and maintenance of a subset of solid tumors, and in particular hepatocellular carcinomas (HCC). This presentation will discuss our rationale for the selection of a 2-formyl quinoline starting point and the strategy behind the initial optimization into highly potent and selective, reversible-covalent inhibitors of the kinase activity of the FGFR4. Scaffold morphing to improve the physicochemical properties and for the metabolic stabilization of the aldehyde electrophile were required in order to obtain compounds that were suitable to demonstrate in vivo efficacy in tumor xenograft models after oral dosing. Further optimization then led to the identification of FGF401, our clinical first-in-class FGFR4 inhibitor.



MEDI 21

Discovery of ORIC-101, a potent and selective glucocorticoid receptor antagonist

Yosup Rew, yosup@oricpharma.com, Xiaohui Du, John Eksterowicz, Haiying Zhou, Nadine Jahchan, Liusheng Zhu, Hiro Kawai, Xuelei Yan, Lawrence R. McGee, Julio C. Medina, Tom Huang, Chelsea Chen, Tatiana Zavorotinskaya, Dena Sutimantanapi, Joanna Waszczuk, Erica Jackson, Elizabeth Huang, Qiuping Ye, Valeria Fantin, Daqing Sun. Oric Pharmaceuticals, South San Francisco, California, United States

The glucocorticoid receptor (GR) is a member of the nuclear receptor superfamily, which is activated by its endogenous steroid hormone ligand cortisol, and by synthetic glucocorticoid agonists such as dexamethasone. Numerous preclinical studies have revealed that GR mediates resistance to both targeted cancer therapies and cytotoxic chemotherapies in a variety of epithelial cancers including prostate, lung, bladder, renal, ovarian and triple-negative breast cancers. These findings suggest that targeted cancer therapies or cytotoxic chemotherapies in combination with a GR antagonist could be a

more efficacious approach to cancer treatment.

The title presentation will describe our extensive SAR studies toward finding selective GR antagonists. Lead optimization starting with mifepristone and employment of structure-based drug design led to the discovery of ORIC-101, a highly potent steroidal GR antagonist with reduced AR agonistic activity and lower CYP inhibition relative to mifepristone. Moreover, ORIC-101 has an excellent pharmacokinetic profile and demonstrated in vivo antitumor activity in a chemo-resistant OVCAR5 ovarian cancer xenograft model. ORIC-101 is currently being evaluated in human clinical trials for the treatment of cancer.

MEDI 22

Structure based design: Identification of the clinical candidate ABBV-744, a first-in-class highly BDII-selective BET bromodomain inhibitor

Le Wang², le.wang@abbott.com, George S. Sheppard², Steven D. Fidanze², Lisa A. Hasvold², Dachun Liu², John K. Pratt², Mai-Ha Bui¹, Emily Faivre¹, Xiaoli Huang¹, Xiaoyu Lin¹, Denise Wilcox¹, Yu Shen¹, Daniel H. Albert¹, Warren Kati¹, Keith F. Mc Daniel². (1) Dept. R460, AbbVie Inc., North Chicago, Illinois, United States (2) Dept. R4AB, Bldg. AP10, AbbVie Inc., North Chicago, Illinois, United States

The BET family of proteins consists of BRD2, BRD3, BRD4 and BRDT, with each of these proteins containing two distinct bromodomains (BDI and BDII). ABBV-075, our first generation BET family bromodomain inhibitor currently under clinical development, exhibits similar affinity to each of the 8 bromodomains. It also shows potent anti-proliferative activity against a wide range of tumor cell lines. It has been hypothesized that selective inhibition of specific subsets of the BET bromodomain might provide a better therapeutic window by targeting tumor types that are predominantly driven by the gene transcriptions induced by subtype specific BET bromodomain(s). Both BDI and BDII are highly conserved across BET family members with more than 70% identity, suggesting that the generation of compounds that are selective for either the BDI or the BDII bromodomains might be achievable. Based on project team X-ray protein structures, Asp144/His 437 and Ile146/Val439 sequence differences (BRD4 BDI/BDII numbering) were identified as potential targets for the generation of BDII-selective inhibitors. Initial medicinal chemistry efforts resulted in a tool compound with greater than 100-fold selectivity for BRD4 BDII over BRD4 BDI. In vivo xenograft experiments demonstrated that this BDII-selective tool compound was orally efficacious in an SKM-1 AML xenograft model over a wide dose range, suggesting a potential improvement in therapeutic index. With this encouraging result, further optimization of BDII-selectivity and drug-like properties led to the identification of the clinical asset ABBV-744.

MEDI 23

Developing inhibitors of BRAF and RAS mutant cancers

Kevin Dalby, *dalby@austin.utexas.edu*. University of Texas at Austin, Austin, Texas, United States

Rational: Most of the available ERK inhibitors are reversible inhibitors that either act through an allosteric mechanism, or by targeting the ATP binding site. Taking advantage of our understanding of ERK-docking interactions we set out to discover an irreversible substrate-selective inhibitor that targets the protein-binding site of ERK.

Methods: Biochemical, cell biology and in vivo studies have been employed to characterize the mechanism of action of the first covalent inhibitor of ERK docking interactions.

Results: Protein NMR, Mass spectroscopy, mutagenesis and molecular docking studies indicate a covalent interaction of the inhibitor with a conserved cysteine residue, Cys-159. Extensive biochemical studies provide an estimate of its kinetic parameters and its kinase-selectivity profile. The new ERK inhibitor inhibits ERK activation, as well as its ability to phosphorylate downstream substrates (e.g. p90RSK and Elk-1) in HEK293T and A375 melanoma cells. The targeting of ERK in HEK293T cells was confirmed using a chemical-genetic approach where the ERK2 C159A mutant was used to rescue the effects of this compound on ERK2 signaling and cell proliferation. Finally, the compound suppressed the growth of melanoma tumors in A375 melanoma cancer xenografts model when administered daily (10 mg/Kg) for 16 days.

Conclusion: This covalent inhibitor represents a potentially valuable lead molecule whose development may result in a novel class of pharmacologically useful ERK inhibitors for targeting resistant forms of melanoma

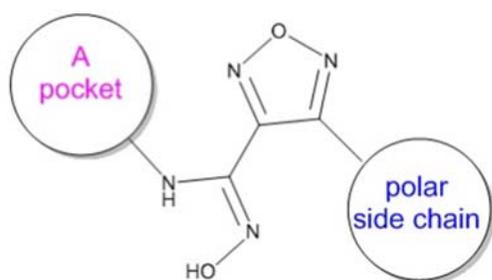
MEDI 24

Discovery and optimization of potent, selective, and orally available IDO1 heme-binding inhibitors featuring a novel A-pocket piece

Hongjun Zhang¹, *hzhang200@gmail.com*, **Abdelghani Achab**¹, **Michael J. Ardolino**¹, **Xiaomei Chai**¹, **Mangeng Cheng**¹, **Yongqi Deng**¹, **Amy Doty**¹, **Heidi Ferguson**¹, **Xavier Fradera**⁵, **Ian Knemeyer**¹, **Chaomin Li**¹, **Kun Liu**¹, **Theodore A. Martinot**¹, **Meredeth A. McGowan**¹, **Richard Miller**¹, **Karin Otte**¹, **Qinglin Pu**¹, **Biju Purakattle**¹, **Nunzio Sciammetta**¹, **Nicolas Solban**¹, **Xuelel (Sherry) Song**¹, **Peter Spacciapoli**¹, **Alan Wise**¹, **Wensheng Yu**¹, **Hua Zhou**¹, **David J. Bennett**¹, **Yongxin Han**¹. (1) Merck Research Laboratories, Boston, Massachusetts, United States (5) Structural Chemistry, Merck, Boston, Massachusetts, United States

Indoleamine-2,3-dioxygenase-1 (IDO-1), as well as the related Indoleamine-2,3-dioxygenase-2 (IDO2) and tryptophan 2,3-dioxygenase (TDO), are intracellular heme-containing enzymes which catalyze the first, and rate-determining, step in the metabolism of tryptophan to *N*-formylkynurenine. The depletion of tryptophan and accumulation of kynurenine pathway metabolites can lead to immunosuppression via T-

reg activation and T-eff suppression and apoptosis. Both IDO1 and TDO2 are up-regulated by many cancer cells, and increased IDO1 and/or TDO activity in tumors can give rise to suppressed host immune response to the tumor. The expression of IDO1 is highly correlated with PD-1 expression in tumors, and the clinical efficacy of an IDO1 inhibitor in combination with a PD-1 inhibitor has been demonstrated by the combination of Epacadostat (an IDO1-selective inhibitor, Incyte) and Pembrolizumab (anti-PD-1 antibody, Merck). In this presentation, we will describe the discovery and optimization of a novel class of hydroxyamidine-based heme-binding IDO1 inhibitors featuring a very unique A-pocket piece. The lead molecule from this chemical series demonstrates very good potency, isoform selectivity, and off-target profile as well as favorable pharmacokinetics. Additional studies to evaluate the chemical stability and to confirm the drug-like properties of the novel A-pocket piece will also be discussed.



MEDI 25

Discovery of a selective, non-nucleoside small molecule inhibitor of DNA methyltransferase 1 (DNMT1)

Bryan W. King¹, bryan.w.king@gsk.com, Andrew B. Benowitz¹, Jacques Briand¹, Charlotte Burt², Chris Carpenter¹, Mark Cockeril², Karen A. Evans¹, David T. Fosbenner¹, Jessica Handler¹, Dirk A. Heerding¹, Allan M. Jordan², Kathryn Keenan¹, Ryan Kruger¹, Mei Li¹, Juan Luengo¹, Michael McCabe¹, Charles McHugh¹, Elisabeth Minthorn¹, Helai Mohammad¹, Melissa B. Pappalardi¹, Mehul Patel¹, Ali Raoof², Stuart Romeril¹, Lourdes Rueda¹, Christian Sherk¹, Alexandra Stowell², Ian Waddell², Kristen Wong¹. (1) GlaxoSmithKline, Collegeville, Pennsylvania, United States (2) Cancer Research UK Manchester Institute, Manchester, United Kingdom

Aberrant DNA hypermethylation within gene promoter regions and subsequent gene silencing are near universal hallmarks of human cancer. Upon DNA replication, these methylation profiles are copied onto the newly synthesized DNA strand by DNA methyltransferase 1 (DNMT1), ensuring heritability of the epigenetic profile upon cell division.

Reversal of DNA methyl marks by a hypomethylating agent such as decitabine, delivers clinical benefit for the treatment of cancers such as acute myeloid leukemia. These agents have considerable drawbacks limiting their potential therapeutic benefit, including IV administration, poor PK properties, lack of selectivity and a mechanism that

requires incorporation into replicating DNA. This indirect, irreversible inhibition of the entire DNMT family (DNMT1, 3a and 3b), and subsequent DNA damage, induces significant dose-limiting toxicity, preventing sufficient target engagement required for maximal demethylation and limiting therapeutic utility. As a result, the past few decades have seen considerable interest in the pursuit of potent, selective DNMT1 inhibitors. However, these attempts have been fraught with difficulty and have delivered little, if any, success.

Here we report the outcome of a high-throughput screen and the development of a robust screening cascade to identify a series of molecules that were found to be non-DNA incorporating and highly selective for DNMT1 over DNMT3a or DNMT3b. Structure-activity relationship (SAR) optimization led to the discovery of potent tool compounds that induced robust decreases in global DNA methylation in cancer cells, induced transcriptional activation of many silenced genes, and inhibited cancer cell growth. Rodent *in vivo* studies with these agents demonstrated appreciable exposure, decreased DNA methylation and a dose-dependent decrease in tumor growth with regression at well-tolerated doses.

MEDI 26

Preventing regulatory T cell trafficking into the tumor microenvironment: Discovery of potent and selective CCR4 antagonists

Dennis X. Hu¹, dhu@flxbio.com, **Betty Abraham**², **Berenger Biannic**¹, **Minna H. Bui**¹, **David Chian**³, **Gene Cutler**², **Jeff J. Jackson**¹, **Scott Jacobson**³, **Emily Karbarz**¹, **Paul Kassner**², **John M. Ketcham**¹, **Lisa Marshall**², **Jenny McKinnell**¹, **Deepa Pookot**², **Maureen Reilly**¹, **Omar Robles**¹, **Hunter Shunatona**¹, **Oezcan Talay**³, **James Walker**¹, **Angela Wadsworth**³, **Ashkaan Younai**¹, **Mikhail Zibinsky**¹, **David J. Wustrow**¹. (1) Drug Discovery, FLX Biosciences, South San Francisco, California, United States (2) Quantitative Biology, FLX Biosciences, South San Francisco, California, United States (3) Discovery Biology, FLX Biosciences, South San Francisco, California, United States

Abstract: Recruitment of suppressive CD4⁺ Foxp3⁺ regulatory T cells (T_{reg}) to the tumor microenvironment (TME) is suspected to be a key driver in tumor immune evasion. Inhibiting mechanisms of T_{reg} recruitment to the TME is hypothesized to activate the immune system against tumors. A major mechanism of tumor T_{reg} recruitment is the chemoattraction of T_{reg} to the chemokines CCL17 and CCL22, which recruit T_{reg} by binding the chemokine receptor CCR4. The discovery of potent, selective, and orally bioavailable inhibitors of CCR4 and their effects in *in vivo* models is described. The design, synthesis, and ADME properties of key compounds will also be discussed.

MEDI 27

Enabling chemical biology in oncology discovery

Sherry Niessen, *sherryniessen@gmail.com. Pfizer, San Diego, California, United States*

This talk will describe how we are applying chemical biology techniques and tools across multiple projects in the oncology drug discovery program. For example, we generated clickable probes of several covalent EGFR T790M inhibitors to evaluate their proteome-wide selectivity across cell and animal models. In another example, we used covalent kinase chemical probes to determine target occupancy and selectivity of our next generation CDK inhibitors. Together these studies are enabling a deeper understanding of the mechanism of action of protein inhibitors and their cellular targets.

MEDI 28

Revealing the druggable genome using chemical proteomics

Lyn Jones, *lynhowardjones@gmail.com. Jnana Therapeutics, Boston, Massachusetts, United States*

Target identification continues to be a high-risk, high-reward endeavor and innovative technologies are required to advance our understanding of small molecule-protein interactions. Examples of successful target, and off-target, identification will be presented, and key learnings shared: the targets of cysteine-reactive natural products were elucidated using clickable chemical probes in conjunction with mass spectrometry proteomics; the antiviral mechanism of azithromycin was determined using orthogonal chemoproteomic profiling techniques; and unbiased reactivity-based protein profiling of sulfonyl fluoride probes uncovered a plethora of interesting targets across multiple gene families.

Through the development of these technologies and their resulting insights, new ligandable proteins were unearthed that provide confidence in expanding the druggable human genome. Additionally, structural chemogenomic methods were used to illuminate other potentially druggable targets of therapeutic significance.

MEDI 29

Expanding the druggable proteome: Ligand and target discovery by fragment-based screening in cells

Christopher Parker¹, *cparker0221@gmail.com*, **Andrea Galmozzi**¹, **Yujia Wang**¹, **Bruno Correia**², **Enrique Saez**¹, **Benjamin Cravatt**¹. (1) *The Scripps Research Institute, San Diego, California, United States* (2) *Ecole Polytechnique Federale De Lausanne, Lausanne, Switzerland*

Advances in DNA sequencing and editing technologies have revolutionized our understanding of the genetic basis of human disease. However, many disease-relevant genes encode proteins that are poorly characterized and/or are considered “undruggable”, hindering our understanding of disease mechanisms and translating this

knowledge into new therapies. Chemical probes offer a valuable way to directly interrogate the function and disease-relevance of proteins and can also serve as valuable leads for drug development, yet most proteins in the human proteome lack small-molecule ligands that can serve as probes. More generally, the boundaries, if any, on the ligandability, and therefore potential druggability, across native proteomes remains poorly understood. In this talk, I will describe a platform that integrates fragment-based ligand discovery with quantitative chemical proteomics to map thousands of reversible small molecule-protein interactions directly in cells. Many of these interactions can be site-specifically determined and involve proteins that fall outside of traditional druggable classes. We demonstrate that this knowledge can be advanced to furnish compounds that affect the activity of proteins previously lacking chemical probes. Furthermore, we integrated this platform with phenotypic screening to facilitate the identification of ligand-protein interactions that regulate complex cellular processes. Fragment-based screening in cells provides an extensive proteome-wide portrait of native protein ligandability, and therefore potential "druggability," and facilitates the coordinated discovery of bioactive small molecules and their molecular targets.

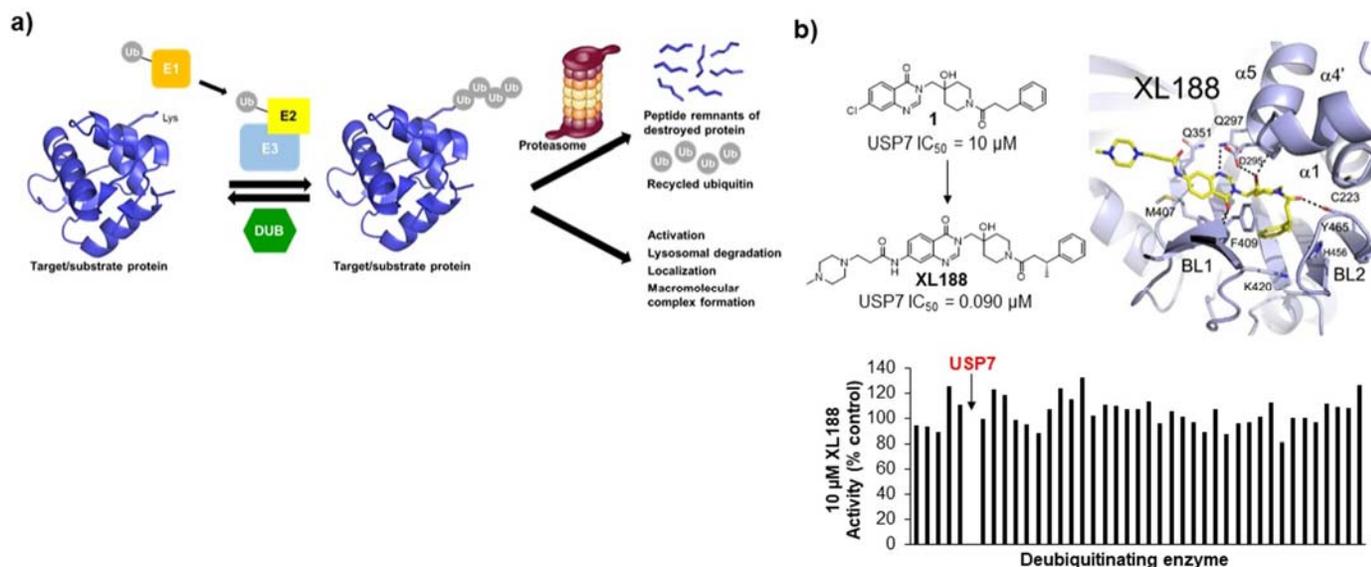
MEDI 30

Target class platform accelerates deubiquitinase early discovery efforts

Sara Buhrlage, *saraj_buhrlage@dfci.harvard.edu*, Ellen Weisberg, Nathan Schauer, Xiaoxi Liu, Jing Yang, Ilaria Lamberto. Dana-Farber Cancer Institute, Boston, Massachusetts, United States

The post-translational modification of proteins by ubiquitin mediates the concentration or activity of a large fraction of the proteome by impacting proteasomal and lysosomal degradation, localization, complexation, and susceptibility to other post-translational modification. Deubiquitinating enzymes (DUBs) are a family of more than 100 proteases that catalyze the removal of ubiquitin from substrate proteins (Figure 1a). As a result, DUBs perform key roles in virtually all normal physiology and human disease. In cancer, for example, USP6 fusion genes contribute to malignancy in aneurysmal bone cysts, while USP7 and USP8 stabilize oncogenic proteins HDM2 and mutant EGFR, respectively. DUBs have been linked to neurodegeneration through roles in regulating mitophagy, autophagy and acting directly on protein aggregates. Despite intense interest in their function and potential as therapeutic targets, there are few selective small molecule probes for DUBs and no approved DUB-targeting drugs. We have built a platform for developing and validating DUB inhibitors that includes library synthesis and medicinal chemistry, biochemistry and screening, chemical proteomics, structural biology, and cancer biology. This platform has enabled us to assemble DUB-targeted libraries annotated for selectivity across the gene family that have proven powerful in linking target and phenotype across multiple projects. In one example, the dataset revealed a highly selective inhibitor for USP7 that was subsequently optimized and utilized to pharmacologically interrogate reported functions of USP7 (Figure 1b). In a different type of example, we performed a cellular phenotypic screen of the annotated

DUB inhibitor library to identify compounds that could induce degradation of oncogenic FLT3. Subsequent target deconvolution efforts allowed us to identify USP10 as the critical DUB required to stabilize FLT3.



MEDI 31

Molecular visualization of tissues by MALDI imaging MS: Applications in drug discovery and development

Stephen Castellino, steve.x.castellino@gsk.com. GlaxoSmithKline, Durham, North Carolina, United States

Developing safe and efficacious drugs is linked to understanding the complex mechanistic relationships between molecular initiation events of pharmacologically active compounds and the cascade of biological consequences. Matrix-assisted laser desorption/ionization (MALDI) Imaging Mass Spectrometry (IMS) technology has taken us beyond “plasma centric” studies to directly mapping drug tissue disposition and molecular changes associated with pharmacology and disease pathogenesis. MALDI IMS correlates analyte tissue distributions with histology images, thereby integrating chemical structures and tissue morphology without the need for labeling techniques. This emerging technology provides high spatial resolution, sensitivity, and can be quantitative. Furthermore, MALDI IMS offers the opportunity to further our mechanistic understanding of drug disposition, disease progression and pharmacology (including toxicology) by providing snap shots of temporal and causal changes. While we have primarily employed MALDI IMS to determine the tissue distribution of drugs and their metabolites, it is becoming evident that more detailed understanding of biological systems can be gained by including the changes in endogenous compound distribution as a function of disease or pharmacology. This presentation will focus on our efforts to couple MALDI IMS and histology in drug

development to better understand tissue disposition and gain mechanistic insights into drug correlated toxicities and efficacy. Case studies from early and late stage drug development, where MALDI IMS was employed to investigate the mechanisms of adverse events, provide insights into disposition, and PK/PD relationships will be presented.

MEDI 32

Drug repurposing for schistosomiasis with assay central

Kimberley M. Zorn¹, kimzorn@gmail.com, Eric K. Chen³, Cecelia L. McConnon³, Alex Clark², Conor R. Caffrey³, Sean Ekins¹. (1) Collaborations Pharmaceuticals, Inc., Raleigh, North Carolina, United States (2) Molecular Materials Informatics, Inc., Montreal, Quebec, Canada (3) Center for Discovery and Innovation in Parasitic Diseases, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla, California, United States

Schistosomiasis, also known as snail fever, is a parasitic disease caused by the *Schistosoma* blood fluke that infects humans when freshwater snail larvae penetrate the skin. Although the worm itself is not found in the United States, the disease affects an estimated 240 million people worldwide and the only drug currently available for treatment is praziquantel (PZQ). Considering the possibility of resistance and the pharmacological and pharmaceutical drawbacks of PZQ, new treatments are needed. Sharing data and ideas is an important obstacle to overcome when developing any treatment, but particularly for neglected tropical diseases (NTDs) such as this, as experts are scattered globally and communication is limited.

Assay Central facilitates drug discovery collaboration by deploying a collection of predictive Bayesian models in a self-contained executable. Datasets of structure-activity relationships are collated and stored using the code-management system Git, from which molecular descriptors (extended-connectivity fingerprints) are calculated as contributing to activity against disease targets. Novel molecules are assigned a score reflecting predicted activity against a target of interest, while visualization of molecular features and training data solidify comprehension and compliment human intuition to make intelligent decisions.

Models of anti-schistosomiasis activity were created specific to time-point (from 1-6 days) and worm life stage (somule/larva or adult), initially from Caffrey group data only, but later from published data. Compounds are periodically selected for testing using these models and results are integrated appropriately. Somule models have larger datasets and cover a wider chemical space, but adult worm models have been bolstered with more published data. For all models, Receiver Operator Characteristic scores ranged from 0.58-0.80. A feedback loop of this nature can improve model predictions and drive drug discovery for NTDs, and Assay Central can reduce superfluous synthesis and testing by driving discussion between collaborators.

MEDI 33

Diaminopurines: Structure activity relationships and structure property relationships towards a lead for human African trypanosomiasis inhibitors

Baljinder Singh¹, *b.singh@neu.edu*, Rosario Diaz², Gloria Ceballos², Domingo Rojas³, Maria Martinez-Martinez⁴, Pilar Manzano-Chinchon⁵, Miguel Navarro⁶, Michael P. Pollastri¹. (1) Department of Chemistry and Chemical Biology, Northeastern University, Boston, Massachusetts, United States (2) Instituto de Parasitología y Biomedicina "López-Neyra" Consejo Superior de Investigaciones Científicas (CSIC), Granada, Spain (4) Tres Cantos Medicines Development Campus, DDW, GlaxoSmithKline, Tres Cantos, Spain

Human African trypanosomiasis, or sleeping sickness, is caused by the protozoan parasite *Trypanosoma brucei* and it is life threatening if left untreated. Current drugs for this disease are poor, with high toxicity and inconvenient dosing regimens. In the interest of identification of new kinase-targeting chemotypes against *T. brucei*, we have performed HTS screening of 42,444 focused inhibitors and identified 797 potent inhibitors of parasite growth with greater than 100-fold selectivity over human HepG2 cells. From this set of hits, a cluster of diaminopurine derived compounds was identified. In the present work, we have designed and synthesized several analogs around one of the HTS hits N²-(thiophen-3-yl)-N⁶-(2,2,2-trifluoroethyl)-9H-purine-2,6-diamine (NEU-0001106). Work involving exploration of structure activity relationships, structure property relationships, and identification of a potent lead compound with improved ADME properties will be reported, as well as progress towards establishing proof-of-concept translation of *in vitro* antiparasitic activity to *in vivo* efficacy.

MEDI 34

SAR exploration of a novel series of compounds for human African trypanosomiasis

Melissa J. Buskes¹, *m.buskes@northeastern.edu*, Rosario Diaz², Gloria Ceballos², Miguel Navarro², Michael P. Pollastri¹. (1) Department of Chemistry & Chemical Biology, Northeastern University, Waltham, Massachusetts, United States (2) Instituto de Parasitología y Biomedicina "López-Neyra", Consejo Superior de Investigaciones Científicas, Granada, Spain

Human African trypanosomiasis (HAT), also known as sleeping sickness, is one of 20 neglected tropical diseases, as classified by the World Health Organization. The disease affects a reported ~2000 people annually primarily in sub-Saharan Africa, with millions more living in endemic areas. HAT is caused by infection with the protozoan parasite *Trypanosoma brucei* of which there are two subspecies that cause human infection and, if left untreated, is ultimately fatal.

To identify new chemotypes, a high-throughput screen of 42,444 kinase-targeted

inhibitors from the GSK collection was performed against *T. brucei*. As a result, 797 sub-micromolar inhibitors of *T. brucei* growth were identified and were categorized into 59 clusters, based on common substructures. A series of substituted azaindoles were selected for medicinal chemistry optimization due to their potent activity against *T. brucei* and their overall good absorption, distribution, metabolism and excretion (ADME) profile. The structure-activity (SAR) and structure-property relationships (SPR) of this cluster will be discussed.

MEDI 35

Extraction and characterisation of an anti trypanosomal compound from the seeds of *Cassia occidentalis*

Stellamaris A. Ogbuagu, *as.ogbuagu@unizik.edu.ng*. Pure and Industrial Chemistry, Nnamdi Azikiwe University, Awka Nigeria, Awka, Anambra, Nigeria

Preliminary screening of the crude methanolic extracts of seeds of *Cassia occidentalis* for phytochemicals, elemental constituents, antimicrobial and acute toxicity (LD₅₀), revealed the presence of flavonoids, steroids, terpenes, fatty acids, resins, glycosides, tannins and anthraquinones. Zinc, selenium, iron, cadmium and chromium were also found in appreciable quantities. The extracts were not toxic even at 5000m/kg. Extraction with ethylacetate followed by isolation and purification using series of chromatographic techniques yielded two pure compounds with melting points of 190-193 and 206-208°C which were identified using UV, FTIR, MS, one and two Dimensional ¹HNMR and ¹³CNMR as 1,1',8,8'-tetrahydroxy-6,6'-methoxy-3,3'-dimethyl-10,10'-bianthracene-9,9' dione and 1, 8-dihydroxy-3-methoxy-6-methylanthraquinone. The compound 1,8-dihydroxy-3-methoxy 6-methyl anthraquinone showed strong activity against *Trypanosome brucei* a causative organism for African Trypanosomiasis.

MEDI 36

Optimization of pyrazolo[1,5-b]pyridazines for the treatment of human African trypanosomiasis

Westley Tear², *westear17@gmail.com*, Seema Bag², Rosario Diaz¹, Gloria Ceballos¹, Carlos Cordon-Obras¹, Domingo Rojas¹, Maria Martinez-Martinez³, Pilar Manzano-Chinchon³, Miguel Navarro¹, Michael P. Pollastri². (1) Consejo Superior de Investigaciones Cientificas (CSIC), Instituto de Parasitologia y Biomedicina "Lopez-Neyra", Granada, Spain (2) Department of Chemistry & Chemical Biology, Northeastern University, Waltham, Massachusetts, United States (3) Tres Cantos Medicines Development Campus, DDW and CIB, GlaxoSmithKline, Tres Cantos, Spain

Human African trypanosomiasis (HAT), a parasitic disease caused by two subspecies of *Trypanosoma brucei*, affects over 2,000 people annually in sub-Saharan Africa. Fatal if left untreated, HAT is most often diagnosed when it crosses the blood-brain barrier

into the central nervous system (CNS) in later stages of the disease. Many of the current treatments are inadequate, with lengthy treatment regimens and severe, sometimes fatal, side effects. To identify potential treatments for HAT a whole organism high-throughput screen was performed against *T.b. brucei* using 42,444 known human kinase inhibitors. Compounds were scored based on potency, selectivity, cidalty, rate of action, and the probability of CNS activity, then clustered based on structural similarity. One series contained a pyrazolo[1,5-*b*]pyridazine core; this series was pursued for structure-activity relationship (SAR) studies due to the cluster's high potency, cidalty, and predicted CNS penetration. This series has known activity against several human kinases (GSK-3 β , CDK-2, and CDK-4). Leveraging published crystal structures and potency data for these targets enabled the design of analogs that were predicted to have improved selectivity for *T.b. brucei*. The SAR trends, improvements to the overall adsorption, distribution, metabolism, and excretion (ADME) properties of the series, selectivity for the parasite over human kinases, and results of preliminary *in vivo* work will be discussed.

MEDI 37

SAR and ADME optimization of pyrazolopyridine-based human PDE4 inhibitors for human African trypanosomiasis

Andrew Spaulding¹, spaulding.an@husky.neu.edu, **Rob Leurs**², **Harry de-Koning**⁴, **David Brown**⁵, **Michael P. Pollastr**³. (1) Northeastern University, Boston, Massachusetts, United States (2) VU University Amsterdam, Amsterdam, Netherlands (4) University of Glasgow, Glasgow, United Kingdom (5) University of Kent, Canterbury, United Kingdom

Human African Trypanosomiasis (HAT) is a neglected tropical disease (NTD) caused by the parasite *Trypanosoma brucei* and affects nearly 70 million people that are at risk, with currently some 3,000 cases reported annually. We have previously reported that inhibition of an essential pair of enzymes in *T. brucei*, phosphodiesterase B1 and B2 (TbrPDEB1 and TbrPDEB2) leads to an increase in the cyclic adenosine monophosphate (cAMP) in the bloodstream form of the pathogen, which inhibits proliferation, blocks cytokinesis, and promotes parasite death. These trypanosomal enzymes exhibit 35% homology with human phosphodiesterase B4 (hPDE4B) but X-ray crystallography indicates variation in the binding region that could be leveraged for improved selectivity over human PDEs. In collaboration with GlaxoSmithKline, we performed a high-throughput screen that led to the identification of a series of pyrazolopyridines, and we have initiated initial structure activity relationship (SAR) studies. Guided by crystal structures with bound inhibitors we are working to decouple the hPDE activity and to promote selective binding to TbrPDE. Herein, the SAR of the pyrazolopyridine class will be discussed in conjunction with selectivity, absorption, distribution, metabolism, and excretion (ADME) properties.

MEDI 38

Hit-to-lead optimization of 3,5-disubstituted-7-azaindoles for human African trypanosomiasis

Dana Klug³, dana.klug@yahoo.com, **Lisseth Silva**³, **Katherine C. Forbes**³, **Rosario Diaz**¹, **Gloria Ceballos**¹, **Carlos Cordon-Obras**¹, **Maria Martinez-Martinez**², **Pilar Manzano-Chinchon**², **Miguel Navarro**¹, **Michael P. Pollastri**³. (1) Instituto de Parasitología y Biomedicina "López-Neyra", Consejo Superior de Investigaciones Científicas, Granada, Spain (2) Tres Cantos Medicines Development Campus, GlaxoSmithKline, Tres Cantos, Spain (3) Department of Chemistry & Chemical Biology, Northeastern University, Waltham, Massachusetts, United States

Human African trypanosomiasis (HAT) is a disease caused by two subspecies of the parasite *Trypanosoma brucei*. Prevalent in sub-Saharan Africa, HAT, along with 19 other indications, has been deemed a neglected tropical disease (NTD) by the World Health Organization. These diseases represent a significant global health burden but do not attract financial investment from the for-profit sector because they primarily affect those living in poverty, without the means to pay for treatment. Although drugs are currently available to treat HAT, some require extended IV dosing, and most are associated with severe side effects, aggravated by coinfection with other lethal diseases such as malaria or HIV. New treatments for HAT that are safe, effective, and easy to administer to patients without convenient access to health care facilities are therefore desperately needed.

In 2014, employing a lead repurposing strategy, our group undertook a high-throughput screen (HTS) of known human kinase inhibitors against *T. brucei*, in collaboration with the OpenLab Foundation and GlaxoSmithKline. In this HTS, we identified 53 clusters of structurally related compounds with <1 µM activity against *T. brucei* and >100x selectivity against HepG2 cells. We subsequently undertook hit-to-lead optimization on several of these clusters focused simultaneously on improving not only the potency against *T. brucei*, but also absorption, distribution, metabolism, and excretion (ADME) properties, such as aqueous solubility and human liver microsome clearance. We now report the results of this optimization centered on a cluster of 3,5-disubstituted-7-azaindoles.

MEDI 39

Repurposing as a strategy for the discovery of a new antileishmanial

Rebecca Charlton¹, r.i.charlton@durham.ac.uk, **Patrick G. Steel**², **Paul Denny**², **Bartira Rossi Bergmann**³. (1) University of Durham, Durham, United Kingdom (2) Department of Chemistry, University of Durham, Durham, United Kingdom (3) Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

Leishmaniasis is a vector-borne Neglected Tropical Disease, caused by protozoan parasites of the genus *Leishmania* for which there is a shortage of effective and viable non-toxic drugs. There are approximately 1.3 million new cases of leishmaniasis each year with the greatest impact on the poorest communities. This means that desperately needed new antileishmanial treatments have to be both affordable and accessible. Established medicines with cheaper and faster development times may hold the cure for this neglected disease. The repositioning of old drugs for new uses is not a new concept but, with the ambitious target of controlling or eradicating tropical diseases by 2020, this strategy is still an important one.

Previous work in our group identified *Leishmania major* inositol phosphorylceramide synthase (*Lmj*IPCS) as a potential drug target. *Lmj*IPCS is a membrane bound enzyme involved in the biosynthesis of sphingolipids and has a function that differs from its mammalian orthologue (sphingomyelin synthase), potentiating the development of safe, selective antileishmanials. Using a microtiter plate compatible assay, a set of 1040 pharmalogically active compounds were screened for activity against *Lmj*IPCS and parasites. Clemastine, an over-the-counter antihistamine, showed submicromolar potencies against different species of leishmania (*L. major*, *L. amazonensis*, *L. donovani* and *L. infantum*) and was effective against *L. amazonensis* intramacrophage amastigotes ($EC_{50} = 0.4$ mM). With successful *in vitro* results and a well-studied pharmacokinetic and mammalian safety profile, clemastine was chosen as an ideal candidate to progress into a mouse model. There was a significant reduction in parasite burden when clemastine was given *via* the IL route demonstrating its potential as a localised antileishmanial therapy.

This presentation will share these findings together with details of synthetic studies towards new active and more accessible analogues.

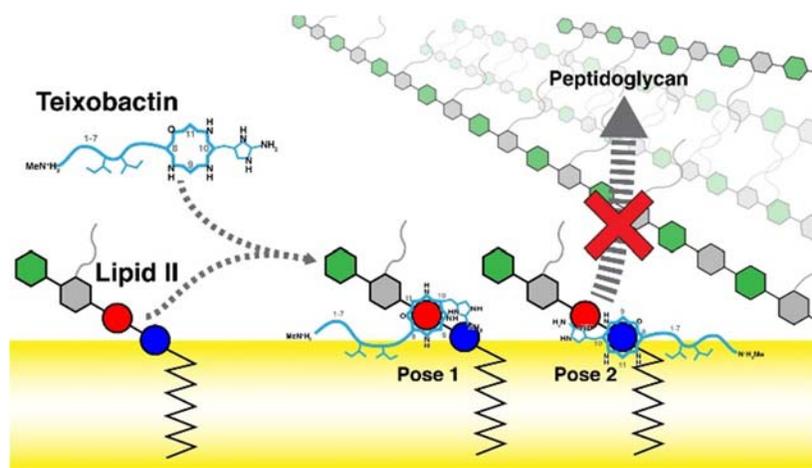
MEDI 40

Probing key elements of teixobactin-lipid ii interactions in membrane

Po-Chao Wen^{1,2}, pwen2@illinois.edu, Juan M. Vanegas³, Susan L. Rempe^{4,5}, Emad Tajkhorshid^{1,2}. (1) Department of Biochemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois, United States (2) Beckman Institute, University of Illinois at Urbana-Champaign, Urbana, Illinois, United States (3) Department of Physics, University of Vermont, Burlington, Vermont, United States (4) Department of Nanobiology, Sandia National Laboratories, Albuquerque, New Mexico, United States (5) Center for Biological and Engineering Sciences, Sandia National Laboratories, Albuquerque, New Mexico, United States

Teixobactin (Txb) is a recently discovered antibiotic against Gram-positive bacteria that induces no detectable resistance. The bactericidal mechanism is believed to be the inhibition of cell wall biosynthesis by Txb binding to lipid II and lipid III. Txb binding specificity likely arises from targeting of the shared lipid component, the pyrophosphate moiety. Despite synthesis and functional assessment of numerous chemical analogs of

Txb, and consequent identification of the Txb pharmacophore, the detailed structural information of Txb-substrate binding is still lacking. Here, we use molecular modeling and microsecond-scale molecular dynamics simulations to capture the formation of Txb-lipid II complex at a membrane surface. Two dominant binding conformations were observed, both showing characteristic lipid II pyrophosphate binding by the Txb backbone amides near the C-terminal cyclodepsipeptide (D-Thr8—Ile11) ring, as well as by the side chains of Ser7 and the unique L-*allo*-enduracididine. Interestingly, those conformations differ by swapping two groups of hydrogen bond donors that coordinate the two phosphate moieties of lipid II, resulting in opposite orientations of lipid II binding. In addition, residues D-*allo*-Ile5 and Ile6 serve as the membrane anchors in both conformations, regardless of the detailed phosphate binding interactions near the cyclodepsipeptide ring. Based on the Txb-lipid II interactions captured in their complexes, as well as their partitioning depths into the membrane, we propose that the bactericidal mechanism of Txb is to arrest cell wall synthesis by selectively inhibiting the transglycosylation of peptidoglycan, while possibly leaving the transpeptidation step unaffected. The observed "pyrophosphate caging" mechanism of lipid II inhibition appears to be similar to some lantibiotics, but different from that of vancomycin or bacitracin.



Two binding poses of the teixobactin-lipid II complex were captured with MD simulations at the membrane surface.

MEDI 41

Design and synthesis of dual-acting quorum sensing inhibitors to suppress the virulence program of *Pseudomonas aeruginosa*

Anwar Hossain, anwar.hossain@ttuhsc.edu, Nadezhda A. German. Pharmaceutical Sciences, Texas Tech University Health Sciences Center, Amarillo, Texas, United States

Pseudomonas aeruginosa is the opportunistic bacterium causing recalcitrant infections in immunocompromised patients. It exerts its pathogenicity upon the releasing of

virulence factors which lead to chronic infections, biofilm formation, and antibiotic resistance. *P. aeruginosa* has three major intertwined quorum sensing (QS) systems namely LasR, RhIR and PqsR. LasR plays at the top of the hierarchy and regulates other transcriptional regulators. In addition to this, under stress conditions PqsR plays the vital role (under IQS activation) in modulating the virulence factors. It has been established that strategies to disarm the bacterial pathogenesis-known as the virulence program allow host immune systems, antibiotics, and microflora to prevent or eradicate bacterial infections. Therefore, attenuating LasR and PqsR with dual-acting inhibitors will substantially reduce the virulence program, biofilm formation, pyocyanin and rhamnolipid production, of *P. aeruginosa*, both in normal and stressed conditions. Using structure-based and fragment-based approaches, a series of novel inhibitors have been designed containing pharmacophore capable of LasR or PqsR antagonism. The analogs were docked into the ligand-binding domain of PqsR (PDB ID: 4JVC) and LasR (PDB ID: 2UV0), and ligand-binding interactions were evaluated using StarDrop™. The top scored compounds were synthesized and evaluated against *P. aeruginosa* PAO1 as an inhibitor of the virulence program. The dual-acting inhibitors were shown to not interfere with the bacterial growth in concentrations up to 100 µM. The static biofilm assay using crystal violet staining showed a reduction of biofilm formation 36.10±2.712% to 74.73±3.13% (Mean±SEM) at a concentration range of 1 to 10 µM. The spectrometric-based quantification showed up to 24.11±0.45% reduction of pyocyanin and 17.11±2.534% reduction of rhamnolipid in dual-acting inhibitors treated group at 1 to 5µM. Altogether, this approach identified novel classes of quorum sensing inhibitors with the ability to disrupt the quorum sensing network, which was shown as the reduction of biofilm formation (*in-vitro*), pyocyanin, and rhamnolipid production. The structure-activity relationship studies will lead to making the potent quorum sensing inhibitors to fight *P. aeruginosa* associated virulence programs.

MEDI 42

TAT-functionalized pH-sensitive liposomes for the treatment of bacterial meningitis

Caterina Bartomeu Garcia, bartomeugarcia.c@husky.neu.edu, Di Shi, Thomas Webster. Chemical Engineering, Northeastern University, Boston, Massachusetts, United States

Brain inflammatory diseases have become a global concern in clinical care due to the emergence of antibiotic-resistant bacteria, making it increasingly difficult to treat these infections. Broad-spectrum antibiotics face difficulties penetrating the outer bacterial cell wall and the biofilms that bacteria form. Therefore, there is a growing need to develop alternative means for treating bacterial infections such as bacterial meningitis. To address this need, we report the use of pH-sensitive liposomes, which present a more fluid lipid bilayer and promote the destabilization of biological membranes, to deliver targeted antibiotics at the site of infection, notably inside the bacterial cell. The functionalization of the liposomes with cell-penetrating peptides (TAT 47-57) allows them to cross the blood brain barrier (BBB). To this end, we investigated the effect of

TAT-functionalized liposomes loaded with antibiotics to inhibit the growth of bacteria commonly associated with bacterial meningitis, including *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Escherichia coli*. The results from this study demonstrated excellent growth inhibitory effects of TAT-functionalized liposomes loaded with methicillin for treating MRSA, with a reported minimum inhibitory concentration of 1.7 µg/mL, well below the free antibiotic dosage needed (5 µg/mL). Cytotoxicity tests with astrocytes and endothelial cells showed a significant reduction of antibiotic cytotoxicity by encapsulating them inside the liposomes. All results obtained for TAT-functionalized liposomes provide evidence that this liposomal system can be a safe, alternative means for treating bacterial meningitis.

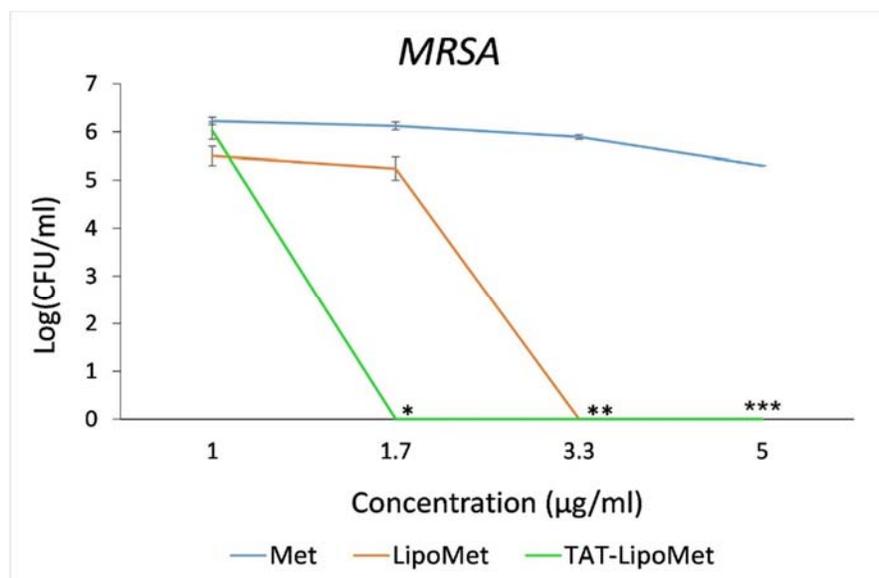


Figure 1. Colony-forming units (CFU) of methicillin resistant *Staphylococcus aureus* (MRSA) after treatment with free methicillin (Met), liposomes loaded with methicillin (LipoMet) and TAT-functionalized liposomes loaded with methicillin (TAT-LipoMet) for 8 hours.

*P>0.05 versus free Met and LipoMet (1.7 µg/mL); **P>0.05 versus free Met (3.3 µg/mL); ***P>0.05 versus free Met (5 µg/mL).

MEDI 43

Strategies for restoring β-lactam activity against antibiotic resistant bacteria

Marc A. Boudreau, marc.boudreau@unh.edu. Department of Chemistry, University of New Hampshire, Durham, New Hampshire, United States

Antibiotic resistant bacteria have emerged in response to the widespread and uncontrolled use of antibiotics. This global public health threat has spurred renewed research efforts into discovering new antibacterial agents, however, this has been insufficient to keep pace with the emergence of new resistant strains. Alternatively, significant efforts have also been devoted to bringing forth small molecules that do not possess inherent antibacterial activity but that enhance the activity of known antibiotics

by inhibiting a resistance or virulence mechanism in bacteria. These compounds are known as adjuvants, and their success in the clinic has been borne out for decades by the use of β -lactamase inhibitors in combination with β -lactam antibiotics. However, resistance toward β -lactamase inhibitors has also emerged and threatens their utility. Historically, β -lactams have been the safest and most widely prescribed antibiotics, thus extending the life span of these crucial drugs is of paramount importance. Our research group is interested in developing new small molecules for restoring β -lactam activity against bacteria that have become resistant to them, with a focus on harnessing underexplored mechanisms of inhibition. Our research efforts are divided among two main areas: 1) synthetic and biochemical studies of natural products that restore β -lactam activity against methicillin-resistant *Staphylococcus aureus* (MRSA), and 2) synthesis and evaluation of inhibitors of β -lactamases expressed by Gram-negative bacteria. Recent results will be presented.

MEDI 44

Bio-orthogonal chemistry-based approach for targeted treatment of bacterial infections

*Nathan Yee*², nathan@shasqi.com, *Jose Mejia Oneto*², *Maksim Royzen*¹, *Kui Wu*¹. (1) University at Albany, Albany, New York, United States (2) Shasqi, Inc, San Francisco, California, United States

It is estimated that 2 million patients suffer each year from antibiotic-resistant infections in the U.S. At least 23,000 die as a result of the infections according to the CDC. A bio-orthogonal chemistry-based strategy to address this problem will be presented. The strategy is termed 'catch and release' and it involves an inverse-electron demand Diels-Alder (IEDDA) reaction between tetrazine and *trans*-cyclooctene (TCO). A reloadable biocompatible hydrogel, modified with tetrazine is injected in the vicinity of an infected site. Prodrugs with attenuated activity and minimal side effects, containing a releasable TCO moiety are systemically injected. When the prodrug and the hydrogel come in contact, the bio-orthogonal agents react with each other through IEDDA reaction 'catching' the payload. Finally, the resulting intermediate isomerizes spontaneously releasing the active antibiotic from the hydrogel to perform its therapeutic function locally. *In vitro* data will be presented to show that the tetrazine-modified hydrogel is stable under simulated physiological conditions and capable of activating multiple doses of model prodrugs of vancomycin and daptomycin. Meanwhile, *in vivo* testing proved that the 'catch and release' strategy is capable of local activation of therapeutically meaningful quantities of vancomycin to treat methicillin-resistant *Staphylococcus aureus*. Multivalency of HMT allows for the process to be repeated with multiple doses of the systemically administered prodrugs.

MEDI 45

Development of aminoglycoside resistance enzyme inhibitors as a means to rescue antibiotic activity

Madelaine R. Leung^{1,2}, madelaineleung@rogers.com, Kyle C. Leckett¹, Xiaomeng Li¹, Aawista Chaudhry¹, Mehdi Keramane³, Alfredo Capretta^{1,4}. (1) Chemistry & Chemical Biology, McMaster University, Hamilton, Ontario, Canada (2) Michael G. Degroote School of Medicine, Hamilton, Ontario, Canada (3) Biointerfaces Institute, Hamilton, Ontario, Canada (4) Michael G. Degroote Institute of Infectious Disease Research, Hamilton, Ontario, Canada

Aminoglycosides are a class of antibiotics that are used primarily to treat Gram-negative infections, as well as some Gram-positive and Mycobacterium infections. High-level resistance is conferred by the actions of aminoglycoside-modifying enzymes such as aminoglycoside N-acetyltransferases (AACs), aminoglycoside nucleotidyltransferases (ANTs), and aminoglycoside phosphotransferases (APHs). It is therefore hypothesized that if these enzymes are inhibited, that resistance will be lost, and bacteria will once again be susceptible to these antimicrobials.

Preliminary screening identified three leads with inhibitory activity against ANT (2'')-Ia and/or AAC(3)-Ia. Parallel synthetic strategies were developed to build chemical libraries around these scaffolds (containing biphenyl, oxindole, and quinazoline cores), and the compounds were assayed against their respective targets. Results will be discussed.

MEDI 46

Specific structure variations of chimera ligand molecules for controlling bacterial drug-tolerance and persister formation

Felicia Burns, fnburns@syr.edu, Yan Y. Luk. Chemistry, Syracuse University, Syracuse, New York, United States

The use of antibiotics can inadvertently promote bacteria to develop drug-tolerant and persister populations. As these populations function as precursors to drug-resistant strains, there is a growing urgency for the development of new methods to control their formation. Here we describe a set of synthetic small organic molecules that enable antibiotics to kill drug-tolerant strains and prevent them from inducing persister formation and which also inhibit two antibiotic-promoted bacterial activities - swarming motility and biofilm formation. We also describe here the organic synthesis that enables us to optimize the structure of activity-validated leads. Based on a structure-activity hypothesis, we synthesised systematically branched hydrocarbons to explore the positional effect and steric contribution of substituent groups on the biological potency of these molecules. This work provides opportunity to discover new lead compounds with potential to eliminate drug tolerance and persistence and promote the effectiveness of antibiotics while defining a rigorous structure-activity correlation.

MEDI 47

Non-traditional antibiotic strategies targeting siderophore utilization in human pathogenic *Acinetobacter baumannii*

Tabbatha Bohac¹, tbohac@wustl.edu, **Justin A. Shapiro**², **Timothy A. Wencewicz**². (1) Chemistry, Washington University StL, Saint Louis, Missouri, United States (2) Chemistry, Washington University in St. Louis, Saint Louis, Missouri, United States

The rise of antibiotic resistance is driving exploration of non-canonical antibiotic approaches, including neutralization of virulence factors. Multi-drug resistant (MDR) Gram-negative pathogens, including *Acinetobacter baumannii*, are of particular concern because of the small number of clinically useful antibiotics available for use. Here we report a new method for blocking iron acquisition in MDR *A. baumannii* as an antivirulence strategy using rigid oxazole analogs of the siderophore acinetobactin. All genome sequenced clinical isolates of MDR *A. baumannii* to date possess the capacity for acinetobactin biosynthesis and utilization. Acinetobactin is a primary iron scavenging molecule for *A. baumannii* that is found in two isomeric forms composed of either an oxazoline or isooxazolidinone core. By oxidizing the oxazoline to an oxazole we stabilized this isomeric form providing a molecule that is still capable of forming high affinity 2:1 siderophore:iron(III) complexes and gains cell entry via the acinetobactin uptake pathway. Here we report a comprehensive investigation of acinetobactin structure-function relationships for the oxazoline, oxazole, and isooxazolidinone isomeric forms and show that iron chelation and receptor binding are critical for biological activity. The oxazole acinetobactin analog is a potent growth inhibitor (MIC values as low as 1 micromolar) of the CDC panel of MDR *A. baumannii* clinical isolates and represents a new lead antivirulence molecule for disrupting siderophore-mediated iron acquisition in this deadly pathogen.

MEDI 48

Semisynthetic analogues of anhydrotetracycline as potential inhibitors of tetracycline destructase enzymes

Jana L. Markley¹, jmarkley@wustl.edu, **Luting Fang**¹, **Andrew J. Gasparrini**², **Chanez T. Symister**³, **Hirdesh Kumar**⁴, **Gautam Dantas**², **Niraj Tolia**⁴, **Timothy A. Wencewicz**¹. (1) Chemistry, Washington University in St. Louis, St Louis, Missouri, United States (2) Pathology and Immunology, Washington University School of Medicine, St Louis, Missouri, United States (4) Molecular Microbiology, Washington University School of Medicine, St Louis, Missouri, United States

The preemptive understanding of the factors that affect newly emerging antibiotic resistance mechanisms is central to the development of efficient treatments of infectious diseases. In particular, those resistance mechanisms that proceed via enzymatic inactivation of “essential medicines”—through substrate modification and degradation pathways—pose a dangerous threat to the global population. While the clinical presentation of resistance via enzymatic degradation is prevalent and well established for beta-lactam, amphenicol, and aminoglycoside antibiotics, the appearance of such resistance pathways for the tetracyclines, a widely used family of polyketide natural product and natural product-derived broad-spectrum antibiotics, was only recently observed in a clinically relevant setting. However, though ribosomal protection and

substrate efflux are the main mechanisms of tetracycline resistance observed in human infection, *enzymatic inactivation is the most important mechanism to elucidate and combat*, as pathways that improve antibiotic clearance often dominate resistance landscapes. In this regard, we herein report the synthesis and biological evaluation of a small panel of anhydrotetracycline (aTc) analogues as potential inhibitors of tetracycline-inactivating enzymes. Studies focus on: (1) the formation of semisynthetic aTc analogues via acid-catalyzed dehydration or electrophilic aromatic substitution; (2) the *in vitro* evaluation of each aTc analog as a potential inhibitor of 3 representative tetracycline-inactivating enzymes using a sampling of tetracycline substrates; (3) the ability of the aTc panel to enhance tetracycline activity in corresponding whole cell assays.

MEDI 49

Potentiating penicillins, carbapenems, and cephalosporins to kill MRSA

Charles V. Rice, rice@ou.edu, Melissa Foxley, Anh K. Lam, Anita Ly, Madeline Harney, Erika Moen, Beatrice A. Wilson. Chemistry and Biochemistry, University of Oklahoma, Norman, Oklahoma, United States

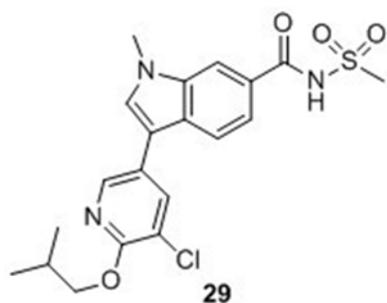
Compared to glycopeptides and linezolid, beta-lactams are superior anti-staphylococcal agents. Generally considered safe, beta-lactams are the #1 option for methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia. This advantage disappears for methicillin-resistant *Staphylococcus aureus* (MRSA) infections. In these cases, doctors turn to other antibiotics whose increased toxicity, requirement of PICC line use, and weeks of hospitalization are severe drawbacks. Survival is determined by patient age, comorbidities, severity of the acute infection, timely treatment, and effective treatment. While the first two factors are beyond the control of pharmaceutical therapy, anti-staphylococcal penicillins can be used effectively against mild and severe MSSA infections without delay. Clinical infectious disease experts would prefer to use beta-lactams against MRSA, but this approach requires a way to disable resistance mechanisms. As described in this presentation, beta-lactam antibiotics that target cell-wall synthesis penicillin binding proteins (PBPs) are potentiated against MRSA in a formulation that retains potency in serum while having minimal cytotoxicity. Antimicrobial resistance due to PBP2a and PBP4 requires wall teichoic acid (WTA) as an essential co-factor for proper location and orientation. Instead of targeting the PBP2a directly, we have created a library of cationic polymer potentiators that target WTA to prevent PBP2a and PBP4 from functioning properly; restoring susceptibility of MRSA to beta-lactams. We demonstrate anti-MRSA efficacy for numerous penicillins, carbapenems, and cephalosporins. Data demonstrate the mechanism of action and the mode of action. We report *in vivo* maximum tolerable dose (MTD or LD₀) of compounds in the potentiator library. Our approach allows treatment of MSSA, MRSA, and other drug-resistant bacteria using prescription antibiotics without the need for hospitalization. Likewise, our approach allows timely and effective treatment before the infection progresses to cause significant patient morbidity.

MEDI 50

Discovery of indole- and indazole-acylsulfonamides as potent and selective Nav1.7 inhibitors for the treatment of pain

Guanglin Luo, guanglin.luo@bms.com, Ling Chen, Amy Easton, Amy Newton, Clotilde Bourin, Eric Shields, Kathleen Mosure, Matthew Soar, Ronald Knox, Michele Matchett, Rick Pieschl, Debra Post-Munson, Shuya Wang, James Herrington, John Graef, Kimberly Newberry, Linda Bristow, Nicholas Meanwell, Lorin A. Thompson, Carolyn D. Dzierba. Research and Development, Bristol-Myers Squibb, Princeton, New Jersey, United States

Novel 3-aryl indole and indazole derivatives were found to be potent and selective Nav1.7 inhibitors and extensive SAR was carried out around these cores. Among all the analogs prepared, compound **29** was shown to be efficacious in not only the mouse formalin test model but also thermal hyperalgesia CFA mouse model as well as the cold hyperalgesia CCI mouse neuropathic pain model at 30 mpk IP. The efficacy correlated well with the mouse dorsal root ganglion (DRG) exposure. The SAR, synthesis and in vivo data for this series will be described.



Nav1.7 IC₅₀ = 108 nM
Nav1.7 EP IC₅₀ = 8 nM

MEDI 51

Discovery of new indole-based acylsulfonamide Nav1.7 inhibitors

Yong-Jin Wu, yong-jin.wu@bms.com, Brian Venables, Jason Guernon, Jie Chen, S.Y. Sit, Ramkumar Rajamani, Ronald Knox, Michele Matchett, Rick Pieschl, James Herrington, Linda Bristow, Nicholas Meanwell, Lorin Thompson, Carolyn D. Dzierba. Research and Development, Bristol-Myers Squibb, Wallingford, Connecticut, United States

Screening of 100 acylsulfonamides from the Bristol-Myers Squibb compound collection identified the indole acylsulfonamide **1** as a potent Nav1.7 inhibitor. Replacement of the C2 furanyl ring with a heteroaryl moiety or truncation of this group provided 4 analogs with hNav1.7 IC₅₀ values under 50 nM. Fluorine substitution of the C2-truncated compound led to **2** with improved potency and isoform selectivity. The inverted

indole **3** also maintained good activity. Both **2** and **3** exhibited favorable CYP inhibition profiles, good membrane permeability and a low efflux ratio, and therefore represent new leads in the search for potent and selective Na_v1.7 inhibitors to treat pain.

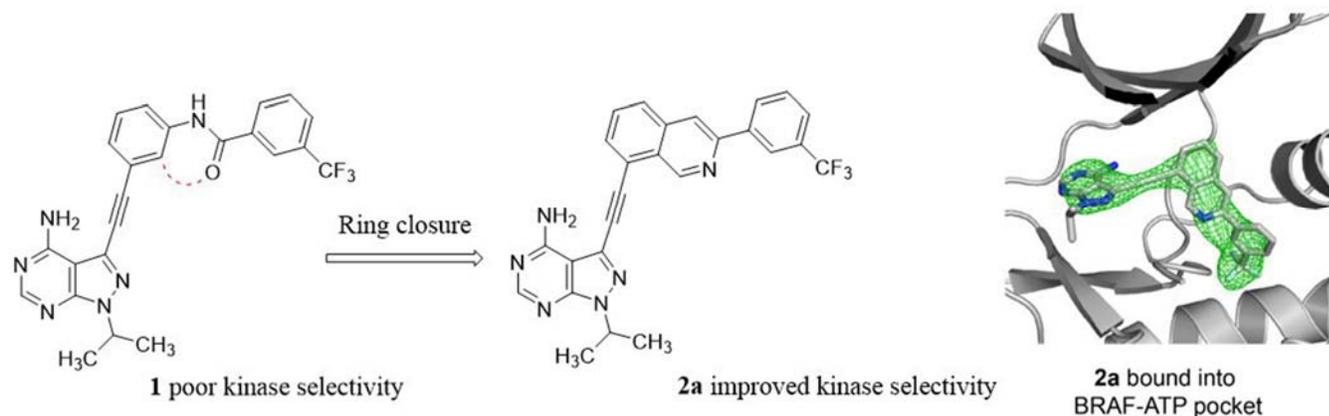
MEDI 52

Structure-based design to improve the selectivity of kinase inhibitors in cancer therapy

Amir Assadieskandar¹, assadies@usc.edu, Caiyun Yu¹, Chao Zhang². (1) University of Southern California, Los Angeles, California, United States (2) Department of Chemistry, University of Southern California, Los Angeles, California, United States

Receptor kinases have an important role in several cellular functions including cell division, cell communication, and regulation of signaling pathways. Though several mechanisms have been elucidated for receptor kinases in cellular processes, their roles and exact mechanism in the initiation and progression of uncontrolled cell division are not yet clear. Thus, drug design and development efforts are greatly focused on protein kinases to provide a more in depth knowledge about them as one of the most successful targets for the treatment of different diseases and particularly in cancer. However, development of highly selective inhibitors is still one of the major challenges in medicinal chemistry. Unfortunately, implementations of all rational design strategies into selective and potent binders do not always lead to predict the desired biological effects *in vitro* and/or *in vivo*.

Here in this project, we have designed and synthesized a series of alkyne-containing pyrazolo [3,4-*d*] pyrimidine analogues. Furthermore, the effect of these analogues on downstream signals were evaluated *in vitro* and *in vivo*. The result showed that desired compounds improved potency and selectivity for inhibition of Braf which is important in cell growth and proliferation. Additionally, selectivity of the optimized molecules compared to the reference compound was evaluated by kinome profiling analysis. Finally, co-crystal of one compound has been prepared that demonstrated the interaction of compound in the active site of protein. The result of this research introduces a novel approach for improving the selectivity of cancer chemotherapy.



MEDI 53

Design and synthesis of selective imidazo[1,2-*b*]pyridazine and pyrazolo[1,5-*a*]pyrimidine inhibitors of leucine-rich repeat kinase 2 (LRRK2) using a checkpoint kinase 1 (CHK1)-derived crystallographic surrogate

Stuart C. Ray, *s.ray@vernalis.com*. Chemistry, Vernalis, Cambridge, Great Abington, United Kingdom

Mutations in leucine-rich repeat kinase 2 (LRRK2), such as G2019S, are associated with an increased risk of developing Parkinson's disease. Using a surrogate of the LRRK2 kinase domain based on a 10-point mutant of checkpoint kinase 1 (CHK1 10-pt mut), X-ray structures were obtained for a number of hits obtained from fragment and kinase-focussed library screening.

This work covers how structure-based drug design (SBDD) was used to quickly improve on-target affinity of imidazopyridazine hits, chosen as they have only one polar interaction with the "hinge" region of the kinase ATP binding site. This is appealing, as LRRK2 inhibitors have to be CNS penetrant to treat Parkinson's disease. X-ray structures of ligands from earlier series and of literature molecules within our CHK1 10-pt mutant crystallographic surrogate allowed us to identify 'hot spots' within the protein, key for affinity and selectivity. This allowed us to rapidly improve on target affinity for this series against LRRK2 G2019S.

Use was also made of early DMPK data and in silico modelling of physicochemical properties to help guide early compound evolution. Selectivity against a number of closely-related kinases was subsequently added, further utilising SBDD. This led to highly ligand efficient, potent and selective inhibitors of LRRK2.

MEDI 54

Quantitative characterization of bivalent probes for the dual bromodomain protein transcription initiation factor TFIIID subunit 1, TAF1

Junghyun L. Suh¹, *jhlee229@email.unc.edu*, **Brian Watts**², **Jacob I. Stuckey**^{1,3}, **Jacqueline L. Norris-Drouin**¹, **Stephanie H. Cholensky**¹, **Bradley M. Dickson**^{1,4}, **Yi An**¹, **Sebastian Mathea**^{5,6}, **Eidarus Salah**⁵, **Stefan Knapp**^{5,7}, **Abid Khan**⁸, **Alexander T. Adams**⁸, **Brian D. Strahl**⁸, **Cari A. Sagum**⁹, **Mark T. Bedford**⁹, **Lindsey I. James**¹, **Dmitri Kireev**¹, **Stephen V. Frye**¹. (1) Center for Integrative Chemical Biology and Drug Discovery, Division of Chemical Biology and Medicinal Chemistry, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States (2) Duke Human Vaccine Institute, Duke University School of Medicine, Duke University, Durham, North Carolina, United States (3) Constellation Pharmaceuticals, Cambridge, Massachusetts, United States (4) Center for Epigenetics, Van Andel Research Institute, Grand Rapids, Michigan, United States (5) Nuffield Department of Medicine, Structural Genomics Consortium, Oxford University, Oxford, United Kingdom (6) German Cancer Centre, Frankfurt, Germany (7) Institute of Pharmaceutical Chemistry and Buchmann Institute for Life Sciences, Goethe-University

Frankfurt, Frankfurt, Germany (8) Department of Biochemistry and Biophysics and Lineberger Comprehensive Cancer Center, UNC at Chapel Hill School of Medicine, Chapel Hill, North Carolina, United States (9) Department of Epigenetics and Molecular Carcinogenesis, University of Texas MD Anderson Cancer Center, Smithville, Texas, United States

A multivalent ligand-protein complex features multiple simultaneous, independent, noncovalent interactions. In general, a bivalent ligand shows an enhanced affinity compared to the affinity of the corresponding monovalent ligands. In chemical biology, multivalent binding can be used to enhance both the affinity and specificity of chemical probes, which are useful tools applied to the study of the function of proteins and their roles in disease. Indeed, various post-translational modifications (PTMs) on histones are often specifically recognized by chromatin reader proteins in a multivalent manner. Thus, multivalent interactions between reader proteins and PTMs are a hallmark of chromatin regulation.

While the effect of binding enhancement for bivalent ligands has been theoretically characterized, the practical, physical, and structural characterization of bivalent binding encounters multiple technical difficulties. In particular, both the bivalent ligand and protein have flexible linkers that makes them difficult to study by X-ray crystallography and NMR. Moreover, multiple possible types of binding events, especially at high protein concentrations required for experimental techniques such as isothermal titration calorimetry (ITC), may confound the analysis. Here, we present a case study utilizing a combination of experimental techniques and explicit computational simulations to study the dual bromodomain protein, TAF1, which was chosen based on the availability of structural information, prior characterization of multivalent engagement, TAF1's known role in transcription initiation, and the availability of functionalizable small molecule bromodomain ligands.

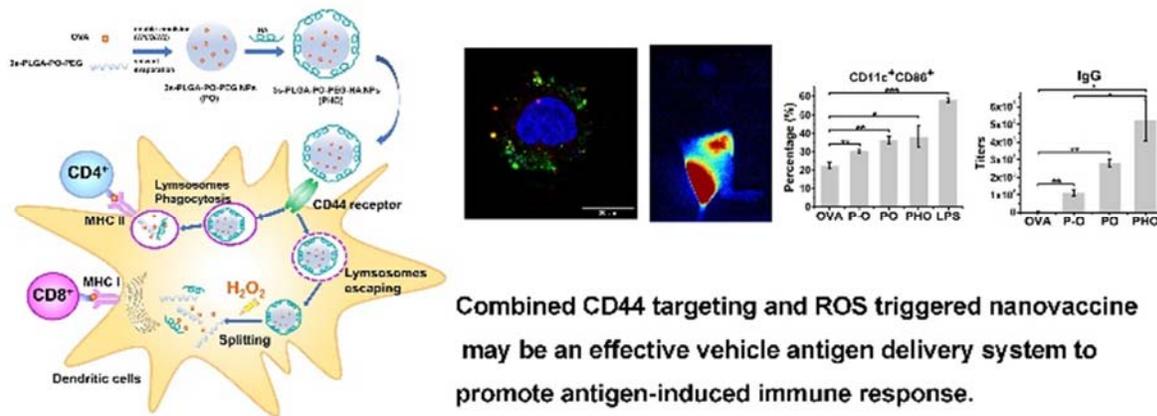
We report our efforts to investigate the dynamics of TAF1 recognition using multivalent ligands. Several experimental techniques including ITC, X-ray crystallography and surface plasmon resonance were used to comprehensively characterize both the binding of monomeric ligands, as well as to assess apparent affinities for bivalent ligands with varying linker lengths. The experimental data for the monomeric ligands were fed into explicit computational simulations, in which ligand and protein species were represented in a broad range of concentrations. The simulations provided accurate estimates for both apparent affinities and individual binding constants for each type of ligand-protein complex. Finally, we hope to apply this approach to other dual-domain chromatin reader proteins.

MEDI 55

Nanoparticles with targeting and ROS triggering properties as an antigen delivery system

*Xiaoyu Liang, Jianwei Duan, Youlu Chen, Huiyang Li, Chen Li, **Jing Yang**, yangjing37@hotmail.com. Tianjin Key Laboratory of Biomaterial Research, Institute of*

Currently, subunit vaccine based on recombinant antigens or peptides has become an important alternative option for vaccine. However, induction of potent immune response with desired efficacy remains a major challenge. The nanoparticle-based antigen delivery system has been considered a potential carrier system to improve the efficacy of subunit vaccine. In the present study, we have designed an immune-stimulatory delivery system by conjugating three-armed PLGA to PEG via the peroxalate ester bond which is sensitive to hydrogen peroxide (H_2O_2), a major reactive oxygen species (ROS). Hyaluronic acid (HA), a ligand for CD44 receptors was also modified onto the outer shell of the 3s-PLGA-PEG nanoparticles to promote immune cell uptake. For in vitro and in vivo immune response assessment, a model antigen ovalbumin (OVA) was enclosed within the core of the 3s-PLGA-PEG nanoparticles to form 3s-PLGA-PO-PEG/HA nanoparticles (PHO NPs). Our results showed that the PHO NPs enhanced dendritic cell maturation, antigen uptake and antigen presentation in vitro, likely due to enhanced lysosomal escape. In vivo experiments further revealed that the PHO nanovaccine robustly promoted OVA-specific antibody production and T cell response accompanied by modest stimulation of memory T cells. In summary, the ROS-responsive PHO NPs with modified HA may be an effective vehicle antigen delivery system to promote antigen-induced immune response.



MEDI 56

Identification of receptor interacting protein kinase 3 (RIPK3) type II inhibitors using high-throughput mechanistic studies in hit triage

Amy C. Hart, amy.hart@bms.com, Lynn M. Abell, Carolyn Weigelt, Junqing Guo, Michael Mertzman, Charu Chaudhry, Hao Lu, Ramesh Padmanabha, Matthew Pokross, Kevin Kish, Andrew Douglas, Deepa Columbar, Ping Zhang, Brian Carpenter, John E. Macor, William J. Pitts. Bristol-Myers Squibb, Princeton, New Jersey, United States

Receptor interacting protein kinase 3 (RIPK3) is a critical kinase in the necroptotic cell death signaling pathway. Necroptosis has been associated with a variety of diseases, and as a result, there is a high interest in selectively targeting the kinases and pseudokinase which participate in this cell death pathway. As a means to identify non-Type I inhibitors for RIPK3, mechanistic studies were incorporated into the hit triage phase of high throughput screening (HTS). Relying on high throughput time dependency (TD) and mode of inhibition (MOI) studies, a putative Type II inhibitor was identified. Protein crystallography confirmed that the inhibitor was binding in a DFG-out conformation in RIPK3. This represents the first non-Type I RIPK3 inhibitor reported.

MEDI 57

Application of organocatalysis in bioorganometallic chemistry: Asymmetric synthesis of multifunctionalized spirocyclic pyrazolone-ferrocene hybrids as novel RalA inhibitors

Bo Han^{1,2}, hanbo@cdutcm.edu.cn, **Wei Huang**¹, huangwei@cdutcm.edu.cn, **Cheng Peng**¹. (1) Chengdu University of Traditional Chinese Medicine, Chengdu, China (2) Department of Chemistry, University at Albany, SUNY, Albany, New York, United States

The Ras-like GTPase RalA is an important driver of tumor growth and metastasis, and development of small-molecule inhibitors of RalA has become a potential therapeutic strategy for tumor inhibition. We have designed and synthesized a collection of chiral spirocyclic pyrazolone-ferrocene organometallic hybrids bearing multiple stereocenters and functional groups. Compound **5b** in this library displayed the most potent RalA inhibition, and it led to accumulation of reactive oxygen species and inhibited proliferation of pancreatic cancer cells. Molecular docking studies of **5b** onto RalA suggest that it binds similarly as a C3 exoenzyme substrate peptide. To our knowledge, this is the first report of asymmetric organo-catalysis in organometallic medicinal chemistry.

MEDI 58

Organocatalytic cascade reaction for asymmetric synthesis of novel chromane-fused spirooxindoles that potently inhibit cancer cell proliferation by inhibiting MDM2-p53 interaction

Wei Huang, 2128830@qq.com, **Bo Han**, **Cheng Peng**. Chengdu University of Traditional Chinese Medicine, Chengdu, China

Asymmetric organocatalytic cascade reactions has grown rapidly to become a fascinating and efficient tool in total synthesis, natural product synthesis and chiral molecular library construction. Despite these advances, the additional applications of organocatalytic cascade reaction to access optically active molecules for medicinal chemistry and drug candidates purposes are also in high demand. Chiral chromane and spirooxindole scaffolds have been referred to as 'privileged

structures' because such frameworks occur widely among biologically active natural products and pharmaceuticals. Recent years have seen intense efforts to develop organocatalytic multicomponent cascade reactions to form highly optically active chromane derivatives or spirooxindole derivatives, respectively. Interestingly, we wonder whether the intriguing combination of pharmacologically important chromane and spirooxindole motifs could provide potential anticancer candidates bearing a novel drug-like skeleton.

We have developed a flexible and simple organocatalytic cascade reaction involving an oxa-Michael-Michael-Michael-Aldol relay, and we have used it to assemble a functionalized chiral chromane-fused spirooxindole scaffold. Starting from 2-nitrovinyl phenol, β,β -disubstituted enal and olefinic oxindole, we obtained a library of bioactive products in moderate to good yield with high stereoselectivity. Within these compounds, **7e** showed the best cell proliferation inhibition potency, molecular mechanism studies suggested that **7e** could activate p53 via interfering p53-MDM2 interactions, and subsequently induced caspase-independent apoptosis.

Moreover, **7e** could also induce G2/S cell cycle arrest by p53 and p21 activation. These findings indicated that chiral chromane-fused spirooxindole could serve as a novel scaffold of small molecular p53-MDM2 interaction inhibitor for chemotherapy of malignancies.

MEDI 59

Discovery of EOS789: A novel inhibitor of NaPi-IIb, Pit-1 and Pit-2 for hyperphosphatemia

Nobuyuki Hori¹, horinbyk@chugai-pharm.co.jp, **Atsushi Kimbara**², **Naoki Okamoto**¹, **Yoshihisa Murata**¹, **Yoshihito Ohtake**¹, **Yoshiyuki Ono**¹, **Shota Tanaka**², **Eisaku Mizuguchi**¹, **Takeo Harada**¹, **Kazutaka Tachibana**², **Mitsuaki Ide**¹, **Kenichi Nomura**¹, **Hiroataka Kashiwagi**¹, **Rie Hirokane**², **Kenji Morikami**¹, **Shuichi Ohtomo**¹, **Yasuhiro Ichida**¹, **Yoshinori Tsuboi**¹, **Naoshi Horiba**¹, **Koji Yamaguchi**¹, **Tadakatsu Takahashi**². (1) Research Division, Chugai Pharmaceutical, Gotemba, Shizuoka, Japan (2) Research Division, Chugai Pharmaceutical, Kamakura, Kanagawa, Japan

Phosphate concentration in blood is strictly regulated by being absorbed in the small intestine and excreted from the kidney. However, in patients with impaired renal function, e.g. chronic kidney disease or dialysis patients, the amount of phosphorus excreted from the kidney is decreased, which in turn elevates the phosphate concentration in blood, resulting in hyperphosphatemia. Hyperphosphatemia causes secondary hyperparathyroidism and vascular calcification, which are known as risk factors for death and as causing a decline in the quality of life. Phosphate is absorbed mainly in the upper small intestine, and sodium-dependent phosphate transporters NaPi-IIb, Pit-1 and Pit-2 are reported to play central roles in phosphate uptake. EOS789 is a novel inhibitor of NaPi-IIb, Pit-1 and Pit-2. A phase 1 clinical study of EOS789 is currently ongoing in the US. This presentation will describe the optimization process of the lead compound and the *in vivo* pharmacology of EOS789. EOS789 showed potent *in vivo* activity in an adenine-induced nephritis model.

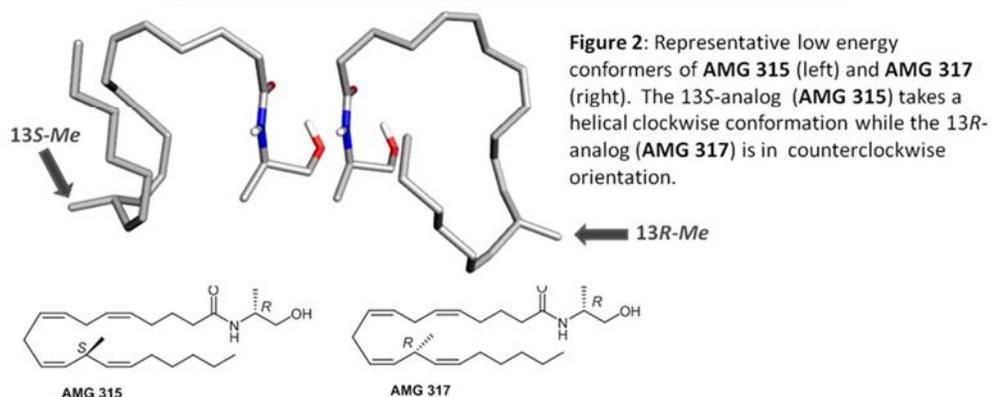
MEDI 60

Novel conformational-restricted endocannabinoid probes with improved metabolic stability

Lipin Ji¹, l.ji@husky.neu.edu, Spyros Nikas¹, Yingpeng Liu¹, Marsha DSouza¹, Shalley N. Kudalkar², Othman Benchama¹, Anisha Korde¹, Chandrashekhar Honrao¹, Srikrishnan Mallipeddi¹, Simiao Wu¹, Shu Xu³, Nikolai Zvonok¹, Lawrence J. Marnett², Alexandros Makriyannis¹. (1) Dept. of Pharmaceutical Science/Center for drug discovery, Northeastern University, Malden, Massachusetts, United States (2) Vanderbilt University, Nashville, Tennessee, United States (3) Biochemistry, Vanderbilt University, Nashville, Tennessee, United States

CB1 and CB2 cannabinoid receptors belong to class-A G-protein coupled receptors (GPCRs). They are currently being targeted for a number of conditions including pain, inflammation, CNS disorders and cancer. *N*-arachidonylethanolamine (AEA) and 2-arachidonoyl glycerol (2-AG) are the two well recognized endogenous ligands (endocannabinoids, eCBs) for the CB receptors. However, they are rapidly inactivated by enzymes throughout the body. AEA is mainly metabolized hydrolytically by fatty acid amide hydrolase (FAAH), and 2-AG is primarily metabolized by monoacylglycerol lipase (MGL). Among the oxidative metabolizing enzymes for eCBs, cyclooxygenase-2 (COX-2) plays the major role. The metabolic instability of eCBs hampers the understanding of the biological role(s) of these lipids. Despite around twenty years of extensive studies, there has been no success in developing 2-AG analogs with potent agonist properties and enhanced metabolic stabilities. Here, we present the development of novel conformational-restricted eCBs analogues with high affinities for CB receptors, agonist properties, and increased stabilities to the actions of hydrolytic and/or oxidative enzymes. Currently we are exploring the enzymatically vulnerable positions of the eCBs focusing on the head group, bis-allylic carbons and the omega position of the arachidonoyl template. Our approach incorporates chiral centers and steric hindrance at strategic positions within the eCBs prototype. These novel endocannabinoid probes along with the recent determination of the crystal structures of the CB1 receptor will inspire the design of improved analogs for *in vitro*, *in vivo*, as well as computational studies aimed at exploring the physiological roles of AEA and 2-AG in cannabinoid receptor function. A detailed SAR study along with a full biological evaluation of the novel analogues reported here is underway.

compound	rCB1 (Ki, nM) without PMSF	rCB1 (Ki, nM) with PMSF	mCB2 (Ki, nM)
anandamide	-	61	1930 ± 345
AMG 315	7.8 ± 3.2	8.9 ± 2.1	653 ± 135
AMG 317	~1,000	~1,000	>1,000



Chiral AEA analogues with distinct biological properties

MEDI 61

Mono and bifunctional cannabinoid receptor probes

Shan Jiang, jiang.shan@husky.neu.edu, **Spyros Nikas**, **Christos Iliopoulos Tsoutsouvas**, **Wen Zhang**, **Simiao Wu**, **jimit raghav**, **Joseph Anderson**, **Alexandros Makriyannis**. Center for Drug Discovery, Northeastern University, Boston, Massachusetts, United States

We report the design, synthesis and biochemical characterization of novel cannabinergic ligands with remarkably high binding affinities for cannabinoid receptors and tight/irreversible binding characteristics. These molecular probes are currently being used in studies aimed at uncovering the binding motifs of classical cannabinoids with the CB1 and CB2 receptors by using two approaches, receptor crystallography, and the Ligand Assisted Protein Structure (LAPS) approach which combines the use of receptor mutants and mass spectrometric proteomic analysis. Our ligand design relies on the incorporation of reactive groups at judiciously chosen positions within the classical cannabinoid structure including the aliphatic chain at C3 and the substituents at C11. Reactive groups included the electrophilic isothiocyanate, nitrate ester, and cyano groups, as well as the photoactivatable azido moiety all of which are capable of tight/irreversible interactions with the target protein. Incorporation of one reactive group results in mono functional probes, while incorporation of two reactive groups leads to bifunctional ligands which can carry either a single reactive group (homo-bifunctional) or two different reactive groups (hetero-bifunctional). The novel probes behave as potent CB1 agonists as evidenced by functional data while a representative nitrate ester probe is a potent analgesic in mice.

MEDI 62

Discovery of small-molecule Bax activators for the treatment of triple-negative breast cancer

Gang Liu¹, Dengfeng Li², Haiying Chen¹, Ye Ding¹, Qiang Shen², **Jia Zhou**¹, jizhou@utmb.edu. (1) Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, Texas, United States (2) Department of Clinical Cancer Prevention, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, United States

Bax, a central cell death regulator, is a requisite gateway to mitochondrial dysfunction and a major pro-apoptotic member of the Bcl-2 family of proteins that control apoptosis in normal and cancer cells. Several lines of evidence suggest that Bax is a promising target for treatment of human cancers by direct activation of this protein. Accumulating studies support that serine 184 (Ser184) is a critical switch to functionally regulate Bax's proapoptotic activity. Therefore, manipulation of the phosphorylation status at Ser184 with small molecules represents a novel strategy for treatment of human cancers including triple-negative breast cancer (TNBC) by altering the activity of Bax in tumors. Herein, we report the preclinical development of Bax activators based on our identified lead compounds with the aid of molecular docking around Ser184 site. Several novel direct Bax activators have been identified as chemical leads with low nanomolar binding affinity to Bax protein. More importantly, these compounds not only exhibited potent antiproliferative activity against human cancer cells with low micromolar to nanomolar IC₅₀ values, but also displayed remarkable *in vivo* inhibitory effects against TNBC xenograft tumor growth with potential to overcome drug resistance.

MEDI 63

Design, synthesis, and structure-activity relationships (SARs) of novel series of irreversible LSD1 inhibitors with improved hematological liability

Yasushi Hattori, yasushi.hattori@takeda.com, Shinji Morimoto, Masashi Toyofuku, Shigemitsu Matsumoto, Satoru Matsuda, Rina Baba, Yusuke Tominari, Misa Iwatani, Hideyuki Oki, Shinji Iwasaki, Mitsuhiro Ito. Takeda Pharmaceutical Company Ltd., Fujisawa, Kanagawa, Japan

Lysine-specific demethylase 1 (LSD1) is an enzyme which demethylates methylated histone H3 lysine 4 (H3K4). The inhibition of LSD1 enzymatic activity could therefore increase H3K4 methylation levels and be used to treat CNS disorders caused by epigenetic dysregulation. However, currently known LSD1 inhibitors have potential hematological side effects, such as thrombocytopenia, resulting from the dissociation of LSD1 and GFI1B, one of the cofactors of LSD1, during the course of enzyme inhibition. Based on an X-ray analysis of the co-crystal structure of LSD1 and **1c**, a known LSD1 inhibitor, we hypothesized that the structure around the central benzene ring of **1c** plays an important role in avoiding this disruption. We therefore designed and synthesized

phenylcyclopropylamine derivatives, and discovered a novel series of 3-(*trans*-2-aminocyclopropyl)benzamide derivatives that prevented the increase of *GF11* mRNA expression, an *in vitro* surrogate marker of LSD1-GFI1B disruption. Subsequent optimization of the side chains led to the identification of 3-((1*S*,2*R*)-2-(cyclopropylamino)cyclopropyl)-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)benzamide (**11b**) (LSD1 K_{inact}/K_i 4.5E+03 M⁻¹sec⁻¹) with good oral absorption and blood brain barrier penetration in mice and rats. The oral administration of **11b** at 10 mg/kg significantly reduced the enzyme activity of LSD1 in the mouse brain. Furthermore, **11b** did not cause hematological side effects after oral administration of 100 mg/kg.

MEDI 64

Folic acid derived-P5779 mimetics regulate DAMP-mediated inflammation through disruption of HMGB1:TLR4:MD-2 axis

Shan Sun, ssun1@northwell.edu, Mingzhu He, Yongjun Wang, Huan Yang, Yousef Al-Abed. Feinstein Institute for Medical Research, Manhasset, New York, United States

High mobility group box 1 (HMGB1) is a damage-associated molecular pattern (DAMP) protein that mediates inflammatory responses after infection or injury through toll-like receptor 4 (TLR4). Recently, our group has (1) shown that TLR4/myeloid differentiation factor 2 (MD-2)/HMGB1 complex formation is required for HMGB1 to induce cytokine production, and (2) identified a peptide inhibitor of HMGB1 (P5779) that acts by directly interrupting HMGB1/MD-2 binding. To understand the mechanism of HMGB1-triggered TLR4 activation, we explored the protein-protein interactions by modeling and simulating HMGB1:TLR4:MD-2 complex formation. In addition, using fingerprint similarity searches and docking and molecular dynamic (MD) simulation studies, we identified several folic acid derived-drugs as P5779 mimetopes. In surface plasmon resonance (SPR) binding studies, these drugs showed direct interaction with TLR4/MD-2 but not HMGB1. They also inhibited HMGB1 and MD-2 binding and suppressed HMGB1-induced TNF release in human macrophages in the nanomolar range. We assert from our findings that the anti-inflammatory effects of these folic acid analogue drugs are mediated at least partially through inhibition of TLR4-dependent signaling.

MEDI 65

Design, synthesis, and evaluation of functionalized 5-(phenoxyethyl)-1,3-dioxane analogs as potential treatments for metabolic syndrome

Benjamin E. Blass^{1,3}, blasse@verizon.net, Pravin Iyer², Magid Abou-Gharbia^{1,3}, Wayne E. Childers^{1,3}, John C. Gordon^{1,3}, Mercy Ramanjulu^{1,3}, George C. Morton^{1,3}, Premkumar Arumugam², Joshodeep Boruwa², John W. Ellingboe², Sayan Mitra², Rajashekar Nimmareddy², Shalini Paliwal², Jamallamudi Rajasekhar², Savithiri Shivakumar², Pratima Srivastava², Raghuram S. Tangirala², Konda Venkataramanaiah², Mahesh Yanaandra², Ramreddy Bobbala², Krishnakanth R. Leleti². (1) Pharmaceutical Sciences, Temple University School of Pharmacy, Eagleville,

Pennsylvania, United States (2) 2GVK Biosciences Private Limited, Hyderabad, India (3) Moulder Center for Drug Discovery, Collegeville, Pennsylvania, United States

Metabolic syndrome, also referred to as Syndrome X” or “Insulin Resistance Syndrome,” remains a major, unmet medical need despite over 30 years of intense effort. Recent research suggests that there may be a causal link between this condition and abnormal glucocorticoid processing. Specifically, dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis leads to increased systemic cortisol concentrations. Cushing’ syndrome, a disorder that is also typified by a marked elevation in levels of cortisol, produces clinical symptomology that is similar to those observed in MetS, and they can be alleviated by decreasing circulating cortisol concentrations. As a result, it has been suggested that decreasing systemic cortisol concentration might have a positive impact on the progression of MetS. This could be accomplished through inhibition of enzymes in the cortisol synthetic pathway, 11 β -hydroxylase (Cyp11B1), 17 α -hydroxylase-C17,20-lyase (Cyp17), and 21-hydroxylase (Cyp21). We have identified a series of novel 5-(phenoxymethyl)-1,3-dioxanes that are potent inhibitors of these enzymes. In addition, our lead compound has pharmacokinetic properties consistent with orally delivered drugs, making it well suited to further investigation as a potential therapy for MetS.

MEDI 66

New class of mononuclear ruthenium complexes as antimicrobial agents

Biyun Sun¹, *biyun.sun@student.adfa.edu.au*, **Richard Keene**^{2,3}, **Grant Collins**¹. (1) *PEMS, University of New South Wales, Australian Defence Force Academy, Canberra, Australian Capital Territory, Australia* (2) *School of Physical Sciences, University of Adelaide, Adelaide, South Australia, Australia* (3) *Australian Institute of Tropical Health & Medicine/BMDT, James Cook University, Townsville, Queensland, Australia*

We synthesized and fully characterized a series of mononuclear ruthenium(II) complexes containing the tetradentate ligand bis[4(4'-methyl-2,2'-bipyridyl)]-1,7-heptane ligand and examined their biological properties. In the synthesis of the [Ru(phen')(bb₇)]²⁺ complexes (where phen' = 1,10-phenanthroline and its 5-nitro, 4,7-dimethyl and 3,4,7,8-tetramethyl derivatives), both the symmetric *cis*- α and non-symmetric *cis*- β isomers were formed. However, the highly strained *cis*- β isomers were unstable and converted to the more thermodynamically stable *cis*- α isomer. The incorporation of particular substituents on the ligand did affect the antimicrobial activities. The antimicrobial activity of the [Ru(phen')(bb₇)]²⁺ complexes could be potentially improved through an increase of the lipophilicity. However, increased lipophilicity could also increase the toxicity to eukaryotic cells. An alternative approach is to increase the electron density at the ruthenium center through the incorporation of electron-donating groups on the 1,10-phenanthroline ligand. The minimum inhibitory concentrations (MIC) and the minimum bactericidal concentrations (MBC) of the ruthenium(II) complexes were determined against two Gram-positive strains and four Gram-negative strains of bacteria. The results suggested that the antimicrobial activity

is strongly related to the electron density on the 1,10-phenanthroline ligand. The *cis-α*-[Ru(Me₄phen)(bb₇)]²⁺ complex with four electron donating groups on the 1,10-phenanthroline ligand exhibited good cellular accumulation while the *cis-α*-[Ru(5-NO₂phen)(bb₇)]²⁺ complex had little or no activity against any of the bacterial strains. In order to gain an understanding of the relative antimicrobial activities, the DNA binding affinity, cellular accumulation and water-octanol partition coefficients (log P) of the ruthenium complexes were determined. Interestingly, all the [Ru(phen')(bb₇)]²⁺ complexes exhibited stronger DNA binding affinity ($K_a \approx 1 \times 10^7 \text{ M}^{-1}$) than the well known DNA intercalating complex [Ru(phen)₂(dppz)]²⁺ (where dppz = dipyrido[3,2-a:2',3'-c]phenazine).

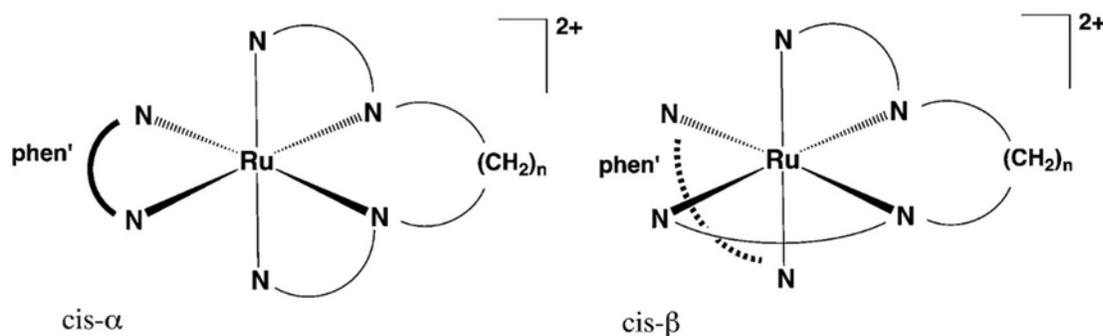


Figure 1. Structures of *cis-α*- and *cis-β*-[Ru(phen')(bb_n)]²⁺

MEDI 67

Suitable chemical library for academic researchers in Japan

Hirotsu Kojima, kojima@mol.f.u-tokyo.ac.jp. Drug Discovery Initiative, Univ of Tokyo, Tokyo, Japan

Drug Discovery Initiative (DDI) of the University of Tokyo was launched to promote academic drug discovery. DDI is maintaining the largest public chemical library in Japan, which consists of about 280,000 compounds including non-commercial unique samples from universities and deposited samples from pharmaceutical companies. The chemical samples are provided to any researchers in Japan who can confidentially disclose their themes and report the assay results to DDI. The general samples themselves are free of charge, but payment for microplates and shipping is needed. DDI does not claim any right to them without our intellectual collaboration. Short training courses on chemical screening are held several times a year. The researchers may also access HTS facilities in DDI. DDI has provided more than 22 million samples to more than 500 users so far.

The samples of the chemical library have been chosen mainly based on druggability and structural diversity, and added every year since 2007. Druggable unique compounds synthesized in some universities were accepted. It is difficult for many academic researchers to carry out random screening of more than 10,000 samples. In such cases, DDI can provide "core library," which is a diverse 9,600-sample set. In addition, "advanced core library" has been recently prepared in order to encourage

larger-scale assays, which is another diverse 22,400-sample set. DDI has been making improvements of the chemical library such as exclusion of promiscuous hitters based on reported data, while taking into consideration the users' circumstances.

MEDI 68

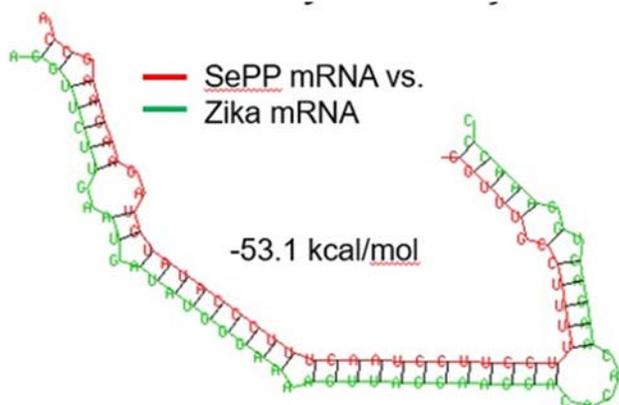
Antisense-mediated knockdown of host selenoprotein expression in ZIKV infected cells via targeting of cellular mRNA by viral RNA

Gabrielle P. Dailey, *gpdailey@uncg.edu*. Chemistry and Biochemistry, University of North Carolina at Greensboro, Greensboro, North Carolina, United States

Zika (ZIKV) viral infection continues to be a growing concern for inhabitants of the southern United States, Puerto Rico, and the Caribbean. Infection in pregnant women can often lead to microcephaly in the resulting children. According to the CDC, 2,364 pregnant women in the United States had lab evidence of ZIKV infection in 2017. The possibility of ZIKV being spread to the rest of the southern United States is a threat to many pregnant individuals and a concern for those looking to conceive; making the need to understand how ZIKV causes microcephaly critically important.

The ZIKV congenital microcephaly mimics a rare genetic disorder, Progressive Cerebello-Cerebral Atrophy (PCCA). This disorder is characterized by a knockdown of the expression of selenoproteins, resulting in a lack of micronutrient selenium to the brain; which is essential for neuronal development. Our preliminary data has already identified a segment of ZIKV RNA which has the potential for antisense interaction with host cellular mRNAs of selenoproteins Thioredoxin Reductase (TR1) and Selenoprotein P (SePP1). Our results suggest that this interaction is possible through computer modeling and gel shift assays. Our group ***hypothesizes*** that ZIKV RNA has an affinity for host cellular mRNAs coding for the expression of selenoproteins, and that an antisense-mediated interaction between these two species is occurring. This resulting interference with selenium-host biochemistry may mimic the loss of selenoproteins due to the genetic defect of PCCA, giving insight into why ZIKV infection in pregnant women can cause microcephaly in the resulting children.

The ***goal*** of this study is to address the gap in knowledge surrounding how ZIKV causes microcephaly. With information gathered from this study, possible avenues to circumvent the mechanism and prevent the onset of microcephaly could be opened up to further study.



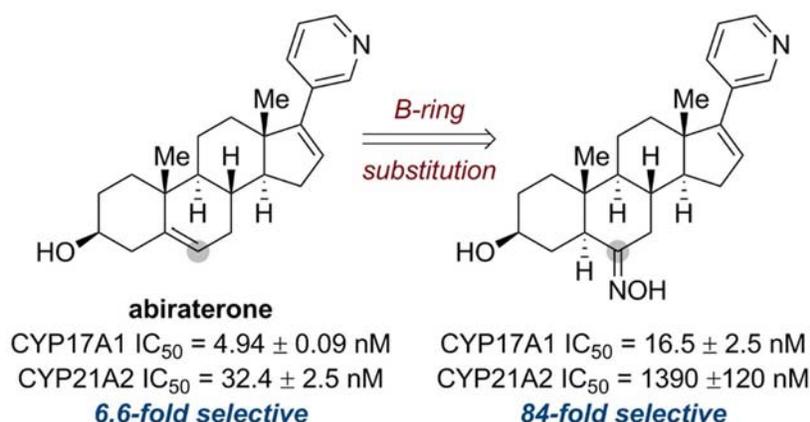
Shown through RNA hybridization software, free energy associated with the antisense interaction between SePP1 mRNA and ZIKV RNA suggests a strong interaction is possible *in vivo*.

MEDI 69

Inhibitors of cytochrome P450 17A1 that spare 21-hydroxylase activity

Caleb D. Vogt³, cdvogt@unc.edu, **Charlie Fehl**¹, **Rahul Yadav**², **Kelin Li**³, **Emily E. Scott**^{2,4}, **Jeffrey Aube**³. (1) Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas, United States (2) Department of Medicinal Chemistry, University of Michigan, Ann Arbor, Michigan, United States (3) Division of Medicinal Chemistry and Chemical Biology, UNC Eshelman School of Pharmacy, Chapel Hill, North Carolina, United States (4) Department of Pharmacology, University of Michigan, Ann Arbor, Michigan, United States

Abiraterone is the only approved inhibitor of cytochrome P450 17A1 (CYP17A1) for the treatment of metastatic castration-resistant prostate cancer, the most aggressive form of the disease. Despite its ability to improve survival rates, abiraterone commonly causes hypertension, hypokalemia, and peripheral edema in patients. One possible cause of these adverse effects is overlapping, off-target inhibition of cytochrome P450 21A2 (CYP21A2), which catalyzes the 21-hydroxylase reaction necessary for corticosteroid biosynthesis. Herein, we report that abiraterone suppresses 21-hydroxylase activity with similar potency to CYP17A1 (6.6-fold selective), and we employ a structure-based approach in order to develop a series of analogues that spare inhibition of CYP21A2. Using available crystal structures, we identify a non-conserved polar pocket in the CYP17A1 active site, which we leverage through B-ring modifications of abiraterone to enhance the selectivity of an analogue by more than 80-fold. Based on computational docking studies, substituents at this position introduce steric clashes with residues in the CYP21A2 active site, accounting for the observed selectivity. Overall, this design strategy could lead to new inhibitors of CYP17A1 that possess fewer adverse side effects and a higher safety profile for the treatment of metastatic castration-resistant prostate cancer.



MEDI 70

Highly selective purine based covalent CDK12 inhibitors

Jeffrey W. Johannes¹, jeffrey.johannes@astrazeneca.com, **Christopher Denz**¹, **Nancy Su**¹, **Allan Wu**¹, **Anna Impastato**¹, **Scott Mlynarski**¹, **Jeffrey Varnes**¹, **Bryan Prince**¹, **Justin Cidado**¹, **Ning Gao**¹, **Malcolm Haddrick**², **Natalie Jones**¹, **Shaobin Li**³, **Xiuwei Li**³, **Yang Liu**³, **Toan Nguyen**¹, **Nichole O'Connell**¹, **Emma Rivers**⁴, **Daniel Robbins**¹, **Ronald Tomlinson**¹, **Tieguang Yao**³, **Xiahui Zhu**¹, **Andrew Ferguson**¹, **Michelle L. Lamb**¹, **John Manchester**¹, **Sylvie Guichard**¹. (1) AstraZeneca R D Boston, Waltham, Massachusetts, United States (2) AstraZeneca Alderley Park, Macclesfield, United Kingdom (3) Pharmaron Beijing, Beijing, China (4) AstraZeneca Cambridge, Cambridge, United Kingdom

Cyclin dependent kinase 12 (CDK12) has emerged as a target of interest in DNA damage response (DDR) biology. CDK12 plays a role in transcription due to its ability to modify the phosphorylation state of the C-terminal domain (CTD) of RNA polymerase II (RNA pol II). It has been shown that siRNA knockdown or small molecule inhibition of CDK12 (with covalent inhibitor THZ531) results in preferential reduction of expression of DDR associated genes. Furthermore, siRNA knockdown of CDK12 has been shown to sensitize cells to olaparib in vitro, and combination treatment using the covalent CDK12 inhibitor THZ1 with olaparib showed an enhanced effect on tumor growth inhibition. However, since THZ1 is known to inhibit CDK7, we sought to deliver a highly selective, covalent CDK12 inhibitor. Starting with a highly potent purine based scaffold, we were able generate selective covalent CDK12 inhibitors, putatively by engaging Cys1039 on CDK12. Broad kinase panel binding and inhibition assay, along with kinase affinity proteomics data and secondary pharmacology on these purine derived covalent CDK12 inhibitors demonstrate a high degree of selectivity for CDK12. Protein mass spectrometry data supports the hypothesis that our compounds covalently modify CDK12. Furthermore, these compounds are able to inhibit the phosphorylation of serine 2 on the CTD of RNA pol II and show potent growth inhibition of OV90 cells at levels similar to THZ1 and THZ531 with improved selectivity for CDK12.

MEDI 71

Discovery, characterization and anti-Parkinsonian effect of a novel mGluR4 PAM chemical series

*Anne-Laure Blayo*¹, ablayo@domaintherapeutics.com, *Baptiste Manteau*², *Stanislas Mayer*³, *Stephan Schann*⁴, *Mélanie Frauli*¹, *Delphine Charvin*⁵. (1) Domain Therapeutics, Illkirch, France (2) Bioparc, DOMAIN Therapeutics, Illkirch, France (4) BIOPARC, Domain Therapeutics, Illkirch, France (5) Prexton Therapeutics, Geneve, Switzerland

The glutamate receptor mGluR4 is an emerging target for the treatment of Parkinson's disease (PD). However, since the discovery of its therapeutics potential, no ligand was successfully developed to be tested in the clinic. In the present poster, we are reporting the medicinal chemistry development conducted around the pharmacological tool PHCCC. These efforts led to the identification of a potent and selective mGluR4PAM with good water solubility and demonstrating consistent activity, after intraperitoneal administration, across validated preclinical rodent models of PD motor symptoms. Moreover, we described the identification of a close analog with improved PK profile after oral administration. Based on its favorable and unique profile, compound PXT002331 or foliglurax could be a good candidate for clinical development.

MEDI 72

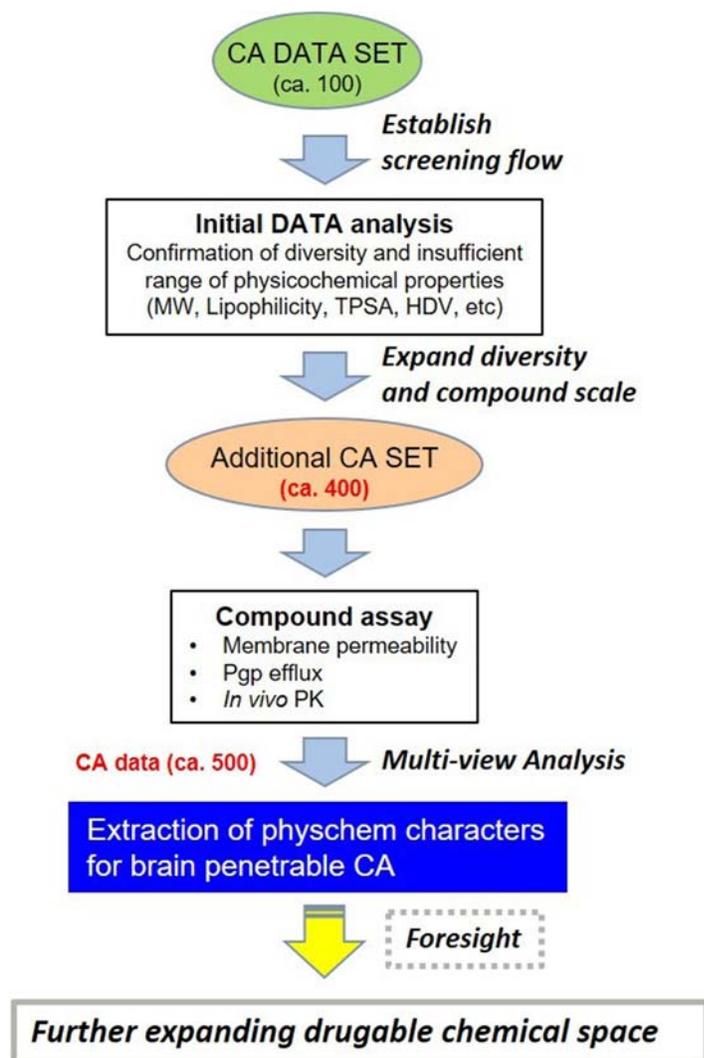
Investigation of the chemical space for brain penetrable, carboxylic acid-containing compounds: Expanding the area available for CNS drug discovery

*Yoshiaki Ohashi*¹, y2-ohashi@hhc.eisai.co.jp, *Daiju Hasegawa*¹, *Makoto Kotake*¹, *Toshiki Kurokawa*¹, *Tomoki Nishioka*², *Ikuo Kushida*³, *Takako Yoshida*³, *Toshiki Mochizuki*³, *Masae Yamamoto*³, *Takafumi Komori*³, *Yu Yoshida*¹, *Kunitoshi Takeda*¹, *Taro Terauchi*¹. (1) Neurology business group, Eisai Co., Ltd., Ibaraki, Japan (2) hhc data creation center, Eisai Co., Ltd., Ibaraki, Japan (3) Medicine development center, Eisai Co., Ltd., Ibaraki, Japan

Drug discovery trends are shifting towards emerging drug targets which are related to human biology and the root causes of diseases, but have classically been deemed to be “poorly ligandable” or “difficult”. In order to increase the possibility of finding clinical candidate compounds for such emerging drug targets, expansion of our tractable chemical space would seem to be essential.

Carboxylic acid (CA) is one very important functionality that can be built into a pharmacophore, and to date a lot of CA-containing compounds have been developed for peripheral targets. However, historically this functional group has very often been neglected in the field of CNS drug discovery due to its reputation for poor brain penetrability. Therefore, if we could find appropriate chemical space for CNS-like CA, the scope for finding clinical candidates in CNS drug discovery would be widened significantly, improving productivity.

The CNS-likeness of our CA library (ca. 500 compounds) was investigated through the screening flow we established (see image), then the data was analyzed from several aspects. As a result, some signs and trends in physicochemical properties to secure CNS-likeness were extracted. In this presentation, our approach, our results and the remaining issues will be presented.



MEDI 73

Discovery of the clinical candidate OWL833 as an orally active non-peptide GLP-1R agonist

Hitoshi Yoshino, yoshinohts@chugai-pharm.co.jp, Satoshi Tsuchiya, Atsushi Matsuo, Masahiro Nishimoto, Kyoko Takami, Kataoka Hiroko, Yoshikazu Nishimura, Yoshiyuki Furuta, Takuma Kamon, Nobuyuki Hori, Takuya Shiraishi, Hiroataka Kashiwagi, Akemi Mizutani, Fumiki Kawagishi, Mitsuaki Ide, Tsuyoshi Haneishi, SangYong Yeu, Manabu Sugiyama, Takashi Emura, Satoshi Niizuma, Manabu Wadamoto, Takahiro Kawai,

Shoshin Yoshida, Yoshiyuki Suzuki, Kotaro Ogawa, Shunsuke Nagao, Satoshi Tanida, Masahide Aoki, Tsutomu Sato, Haruhiko Sato. Research Division, Chugai Pharmaceutical Co., LTD., Gotemba, Shizuoka, Japan

No orally active glucagon-like peptide-1 receptor (GLP-1R) agonist has yet been introduced in clinic, although injectable peptide analogs of GLP-1 are clinically used to treat type 2 diabetes mellitus. We successfully identified OWL833 as an orally active non-peptide GLP-1R agonist. OWL833 showed cAMP accumulation in cells expressing human GLP-1R ($EC_{50} = 1.1$ nM) and oral bioavailability in both rats (30%) and cynomolgus monkeys (25%). OWL833 also decreased the blood glucose level and the food intake in in vivo animal models. Here we will mainly describe the key structural optimization of the weak hit compound that improved the cAMP activity by more than 10,000 times and also dramatically improved its oral absorption.

MEDI 74

Fluorinated (*R*)-(-)-aporphines as potential agonist positron emission tomography ligands for serotonergic 5-HT_{1A} receptor

Yulong Xu, yxu27@mclean.harvard.edu, Anna W. Sromek, John L. Neumeyer. Harvard Medical School, McLean Hospital, Belmont, Massachusetts, United States

1. Background

Accumulating evidence indicates that the 5-HT_{1A} receptor is closely implicated in the pathophysiology of major neuropsychiatric disorders, including depression, pain, neuroprotection, schizophrenia, Parkinson's disease and Alzheimer's disease. Because of this psychopharmacological involvement of the 5-HT_{1A} receptor, tools to image the 5-HT_{1A} receptor in the human brain are urgently needed. Positron emission tomography (PET) is regarded as a key molecular imaging tool, allowing for the study of the function and neurochemistry of the human brain. Until now, the development of 5-HT_{1A} antagonist PET ligands has achieved great success. However, compared to the extensive research interests in 5-HT_{1A} antagonist PET ligands, the development of 5-HT_{1A} agonist PET ligands has been much less explored, and only a few examples have been reported. Thus, further exploration of even more highly potent 5-HT_{1A} agonist PET ligands with high affinity and selectivity is therefore still a significant goal in the field.

2. Methods

Numerous reports in the literature revealed that introducing a more lipophilic group at the C11 position of the aporphine structure affords analogs with high affinity and selectivity for the 5-HT_{1A} receptor. Therefore, a series of aporphines with fluorinated alkyl or benzyl groups attached to C11 through an oxygen-linkage were synthesized and evaluated for their neuropharmacological properties.

3. Results

These novel fluorinated aporphines exhibited potent and selective affinity for 5-HT_{1A} receptor but moderate or low affinity for other brain receptors and transporter. Among them, MCL-587 displayed high affinity at the 5-HT_{1A} receptor with an inhibitory constant (K_i) value of 21 nM. Meanwhile, the lowest K_i value for other brain receptors

and transporter was about 8-fold higher than that for the 5-HT_{1A} receptor.

4. Conclusions

According to these highly promising results, such novel fluorinated aporphines could potentially prove to be valuable as 5-HT_{1A} agonist PET ligands for detecting disease processes or therapeutic effects involving the 5-HT_{1A} receptor. Results will be presented in detail.

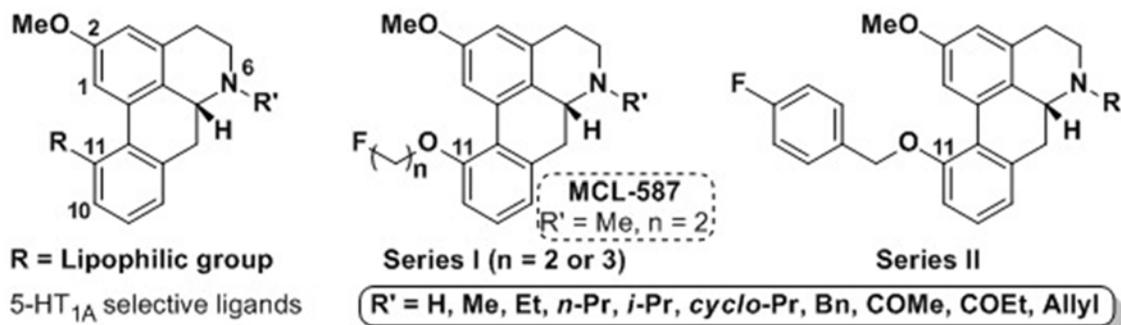


Figure 1. Structures of proposed aporphines

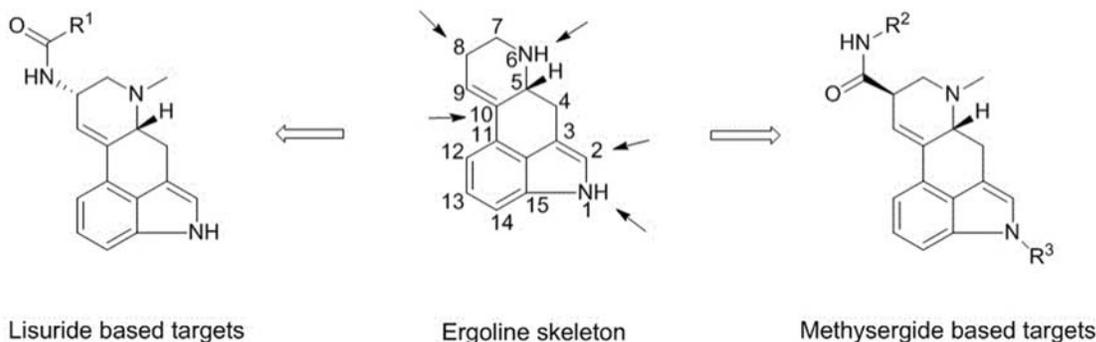
MEDI 75

Synthesis of ergoline-based analogs

Ármin Szabolcs¹, armin.szabolcs@cominnex.com, **Viktória Ujj**¹, **János Gerencsér**², **Miguel Guzman**³, **Thomas Armer**³, **Scott Borland**³. (1) ComInnex, Inc., Budapest, Hungary (2) BioBlocks, Inc., Budapest, Hungary (3) Xoc Pharmaceuticals, Inc., Los Gatos, California, United States

Many naturally occurring and synthetic ergoline compounds are known to bind to neurotransmitter receptors, including the dopamine, noradrenaline and serotonin receptors. Compounds that are selective or specific for certain receptors, either as agonists or antagonists, may lead to desirable therapeutic actions while eliminating or reducing unwanted side effects. For example, selective serotonin antagonists and dopamine agonists have previously been developed for the treatment of migraine and the treatment of Parkinson's disease and hyperprolactinemia, respectively. Our group's research attempted to identify and synthesize ergoline analogs with specific agonist/antagonist behaviors at particular receptors, showing absence of other undesirable behaviors, and also yielding metabolites with no undesirable receptor characteristics. For example, particular compounds of interest might be antagonists at the 5-HT_{2B} receptor that also yield metabolites lacking agonistic behavior at the 5-HT_{2A} and 5-HT_{2B} receptors. Forty two unique compounds were prepared by modifying the ergoline skeleton at ergoline ring positions 1, 2, 6, 8 and 10 by various methods, including trifluoromethylation, Suzuki coupling after bromination at position 2, selective hydrogenation, amidation of lysergic

acid and 8-aminoergoline, and radical addition of methoxy or hydroxy groups at position 10.



MEDI 76

Syntheses of 2-substituted oxetan-3-amines

Leiliang Zhang, zhang_leiliang@4ringchem.com, **GuiHua Liu**, **Hui Li**, **Xihan Wu**, **Minmin Yang**. PharmaBlock Sciences, Nanjing, China

Oxetan-3-amines are privileged structure motif which has found ever increasing application in medicinal chemistry. Herein we are reporting a convenient method of preparation from ethyl 2-(dibenzylamino)acetate and aldehydes or ketones. Our protocol features inexpensive starting materials, benign reaction conditions, as well as broad substrate scopes. With this method, a series of 2-substituted, 2,2-disubstituted and spiro oxetan-3-amines are obtained in good to excellent yields [**Figure1**].

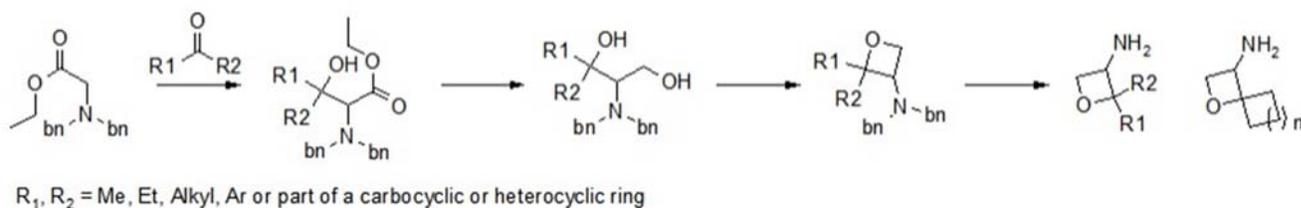


Figure 1. Syntheses of 2-substituted oxetan-3-amines

MEDI 77

Exploration of strained saturated heterocycles as isosteres in medicinal chemistry

Chulho Choi¹, chulho.choi@pfizer.com, **James Mousseau**^{2,1}, **James A. Bull**³. (1) Medicine Design, Pfizer, Groton, Connecticut, United States (2) Pfizer, Old Lyme, Connecticut, United States (3) Department of Chemistry, Imperial College London, London, United Kingdom

To improve drug-like properties and introduce the novel vectors to access new design space, the design of new pharmaceutically relevant molecules with the increased sp³ characters presents the interesting challenges to synthetic organic chemistry. Herein we presented our efforts in collaboration with the Bull group at the Imperial College London to develop new synthetic methods to the facile access novel 3,3-disubstituted oxetanes and other related rings. These methods have been applied towards the synthesis of complex molecules with drug-like properties whose physicochemical properties have been studied to determine their feasibility as ketone, amide, and thioester isosteres.

MEDI 78

Synthesis and evaluation of novel BACE1 inhibitors based on the *N*-amidino nitrogen-containing ring structure

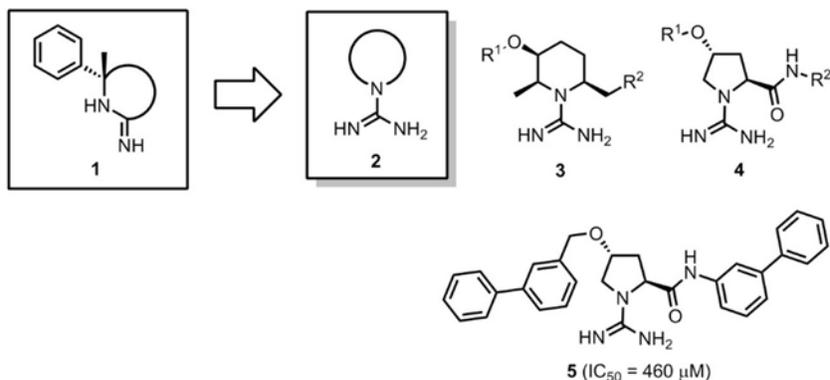
Kazuya Kobayashi¹, *kkoba@mb.kyoto-phu.ac.jp*, **Daiki Joho**¹, **Chinami Taniguchi**¹, **Misaki Tanaka**¹, **Rani Kimura**¹, **Kaho Komurasaki**¹, **Yuki Kawasaki**¹, **Yasunao Hattori**², **Kenichi Akaji**¹. (1) Department of Medicinal Chemistry, Kyoto Pharmaceutical University, Kyoto, Japan (2) Center for Instrumental Analysis, Kyoto Pharmaceutical University, Kyoto, Japan

β -Secretase (BACE1: β -site Amyloid precursor protein Cleaving Enzyme 1) is an important therapeutic target for Alzheimer's disease, because it concerns initial step in the production of amyloid β protein, which has been considered to be one of the causal agents for the disease. Recently, many small molecule BACE1 inhibitors containing a non-planar cyclic amidine structure **1** has been reported, and the structure is expected as a promising pharmacophore. Based on the amidine structure, we devised *N*-amidino nitrogen-containing ring structure **2**. In this work, we designed and synthesized *N*-amidino piperidine- and *N*-amidino pyrrolidine-type BACE1 inhibitors **3** and **4**.

In the synthesis of *N*-amidino piperidine-type inhibitors, 3,6-*cis*-2,3,6-trisubstituted piperidine was constructed from alanine using the reported procedure and various substituents were introduced at its 3 and/or 6 position. Evaluation of their inhibitory activity suggested that bulky hydrophobic substituent was appropriate for their activity, although the activity value was not sufficient.

In the synthesis of *N*-amidino pyrrolidine-type inhibitors, hydroxyproline was used as a starting material, and hydrophobic substituents were connected with the hydroxyl group and carboxyl group. As with *N*-amidino piperidine-type inhibitors, bulky substituent was appropriate, and we found out the derivative **5** with weak but clear inhibitory activity for BACE1.

This presentation will describe synthesis and evaluation of these BACE1 inhibitors.



MEDI 79

Design of potent and selective inhibitors for human b-secretase 1 (memapsin 2), a target for Alzheimer's disease

Arun K. Ghosh, **Emilio L. Cardenas**, *cardenae@purdue.edu*. Chemistry, Purdue University, West Lafayette, Indiana, United States

We report the design, synthesis and biological evaluation of BACE1 inhibitors based off previous success of GRL-8234. The promising "drug-like" profile of GRL-8234 exhibited excellent enzymatic and cellular activity with 1.8 nM and 1 nM, respectively. GRL-8234 has been shown to rescue age-related cognitive decline in Tg2576 mice. X-ray crystal structure of inhibitor-bound BACE1 has shown that hydrophobic interactions within the cleft region of the catalytic domain can be further optimized. We further investigated the hydrophobic pocket as well as incorporated a less peptidic scaffold as P2 ligands to improve "drug-like" properties.

MEDI 80

Design, synthesis and validation of small molecules that sensitize HIV-1 infected cells to antibody dependent cellular cytotoxicity (ADCC)

Melissa C. Grenier¹, *grenier@sas.upenn.edu*, **Shilei Ding**^{2,3}, **Andrés Finzi**^{3,4,2}, **Amos B. Smith**¹. (1) Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania, United States (2) Department of Microbiology, Infectiology and Immunology, Université de Montréal, Montreal, Quebec, Canada (3) Centre de Recherche du CHUM, Montreal, Quebec, Canada (4) Department of Microbiology and Immunology, McGill University, Montreal, Quebec, Canada

With over 37 million people living with HIV worldwide and an additional 1.5 million new infections reported each year, the need to derive novel strategies to prevent transmission and suppress viral reservoirs remains of critical importance. One potential strategy for diminishing the latent viral reservoir involves eliminating infected cells via antibody dependent cellular cytotoxicity (ADCC). HIV-1 has evolved a sophisticated mechanism to conceal epitopes from ADCC-mediating antibodies present in sera from

most HIV-1 infected individuals. Our program aims to circumvent this evasion via the development of potent small molecules that expose CD4i epitopes and sensitize HIV-1 infected cells to ADCC. Towards this objective, rapid structure-based optimization of an initial screening hit via high-throughput parallel synthesis and purification has led to the development of more potent small molecules that elicit this cell-mediated immune response. Continued synthetic efforts look to further increase the therapeutic potential of these small molecules.

MEDI 81

Porphyrins - A gift of nature to eradicate cancer? (Photodynamic therapy)

Zemen S. Berhe, *zberhe@umassd.edu*, Emmanuel C. Ojadi. University of Massachusetts Dartmouth, Dartmouth, Massachusetts, United States

The porphyrins are an important class of naturally occurring macrocyclic compounds found in biological systems that play a very significant role in the metabolism of living organisms. They have a universal biological distribution and were involved in the oldest metabolic phenomena on earth. Some of the best examples are the iron-containing porphyrins found as heme and the magnesium-containing reduced porphyrin found in chlorophyll. Without porphyrins, aerobic life on planet earth would be impossible and therefore the knowledge of these systems and their excited states are essential in understanding a wide variety of biological processes. The progress of porphyrin polymers and their derivatives provide the potential for diverse applications in life and industry. Most known are the formulation of artificial blood, and the development of photocatalysts for solar energy conversion, development of electronic conductors and semiconductors, energy storage and photodynamic therapy. In this work, we attempt the synthesis of water-soluble free-base (Tetra-p-trimethyl-ammonium-phenyl-porphyrin-tetraiodide) and metallo (Tetra-(p-trimethyl-ammonium-phenyl) zinc(II)-porphyrin-tetraiodide) porphyrins which are to be used to test phototoxic effects in vitro using human cancer cells. The full potential of these applications are yet to be realized. This work includes various analytical techniques UV-Vis absorption, Emission Spectroscopy, GC-MS, LC-MS, NMR and element analysis for the characterization of reactions products and intermediates.

MEDI 82

Discovery of novel phosphonate prodrugs by *de novo* rational design

Manuel De Lera Ruiz¹, *manuel.ruiz@merck.com*, Izzat T. Raheem², Michael T. Rudd³, John McCauley⁴, John Schreier⁵, Timothy J. Hartingh⁶, Bennett Ma⁷, Herve Aloysius⁸, Steve Carroll⁹, Ming-Tain Lai¹⁰, Jaume Balsells-Padros¹¹, Amrith Bennet¹². (1) Discovery Chemistry, Merck Research Laboratories, West Point, Pennsylvania, United States (2) WP14-2315, Merck Research Laboratory, West Point, Pennsylvania, United States (3) WP14-3, Merck Co Inc, West Point, Pennsylvania, United States (5) WP14-2, Merck Research Laboratories, West Point, Pennsylvania, United States (6) Chemistry,

Merck , Richlandtown, Pennsylvania, United States (7) Pharmacokinetics, Pharmacodynamics, and Drug Metabolism, Merck Research Laboratories, West Point, Pennsylvania, United States (8) Merck Co., Inc., Kenilworth, New Jersey, United States (9) *In vitro* pharmacology, Merck Research Laboratories, West Point, Pennsylvania, United States (10) Discovery Biology, Merck Research Laboratories, West Point, Pennsylvania, United States (11) Discovery Process Chemistry, Merck Reserach Laboratories, West Point, Pennsylvania, United States (12) Safety Assessment Laboratory Animal Resources, Merck Research Laboratories, West Point, Pennsylvania, United States

Nucleosides represent a well-established and extremely important class of drugs in the treatment of infectious diseases, including HIV and HCV. All of these nucleosides require kinase-mediated phosphorylation in target cells to form their active triphosphate (or phosphonate diphosphate) anabolites to inhibit viral replication. The initial phosphorylation step is often rate limiting, therefore one effective method commonly employed to bypass this step is to prepare the monophosphate or phosphonate forms of the nucleoside. However, monophosphates and phosphonates are highly polar anionic functional groups that do not readily cross biological membranes. Prodrug approaches that mask the charge overcome this limitation and have proven to improve the permeability of these molecules and subsequently their intracellular delivery. While early interest in prodrugs was focused on developing molecules with improved oral bioavailability, attention has shifted in recent years to the design of prodrugs that target intracellular enzymes to liberate the parent molecule inside target cells. Herein we describe the de novo rational design and discovery of two structurally novel phosphonate prodrug classes using tenofovir as a prototype parent molecule. A thiolactone/lactone phosphoramidate series was identified in which a carboxylate group derived from the intracellular hydrolysis of the thiolactone or lactone moiety potentially triggers the conversion to the parent drug. This series exhibits double-digit nanomolar potency in a viral replication inhibition cell-based assay. A novel phosphinic amide prodrug class displaying single-digit nanomolar potency *in vitro* was also discovered. This class was found to be very stable in relevant biological and simulated media, likely as a result of the unique P-C bond in the promoiety. In addition to these two classes, other structurally novel phosphonate prodrugs were also identified. Prodrug SAR, synthesis, and *in vitro* and *in vivo* data will be presented.

MEDI 83

Design, synthesis and *in vitro* evaluation of dual inhibitors of phosphatidylinositol-3-kinase delta (PI3Kd) and histone deacetylase 6 (HDAC6)

Ashish Thakur¹, ashish.thakur@nih.gov, Gurmit Grewal², Gregory J. Tawa², Mark Henderson², Carina Danchik², Tobie D. Lee³, Anton Simeonov⁴. (1) Medicinal Chemistry, National Center for Advancing Translational Sciences, Rockville, Maryland, United States (2) National Center for Advancing Translational Sciences, Lexington, Massachusetts, United States (3) National Center for Advancing Translational Sciences, Rockville, Maryland, United States

Dysregulation of both Histone Deacetylase (HDAC) and Phosphatidylinositol-3-kinase (PI3K) is often involved in over-expression of oncogenes c-Myc and Cyclin D1, thereby promoting cell growth and proliferation. Dual inhibition of HDAC and PI3K is an emerging therapeutic approach for cancer as it offers the advantages of better efficacy resulting from synergy and overcoming the developed resistance. A series of pyrimidine-amine/purine based hydroxamic acids were designed and synthesized as dual inhibitors of Histone Deacetylase (HDAC) and phosphatidylinositol-3-kinase (PI3K) enzymes. Structure Activity Relationships (SAR) were explored to develop highly potent PI3Kd and HDAC6 selective inhibitors ($IC_{50} < 10$ nM against both enzymes) with good ADME profile. *In vitro* screening against a panel of 60 different cancer cell lines at National Cancer Institute (NCI) revealed several hit molecules with potent cell-kill activity against various cancer cell lines including Leukemia, Melanoma, Renal, Non-small cell lung cancer, Central Nervous System (CNS) cancer and Breast cancer.

MEDI 84

Development of chemical probes targeting ASH1L histone methyltransferase

Hao Li^{1,2}, *hlumich@umich.edu*, *Jing Deng*², *David Rogawski*², *Szymon Klossowski*², *Trupta Purohit*², *Katarzyna Kempinska*², *EunGi Kim*², *Marta Szewczyk*², *Zhuang Jin*², *Dmitry Borkin*², *Deanna Montgomery*³, *Juliano Ndoj*², *Hyo Je Cho*², *Hongzhi Miao*², *Jolanta Grembecka*^{2,1}, *Tomasz Cierpicki*^{2,1}. (1) Program in Chemical Biology, University of Michigan, Ann Arbor, Michigan, United States (2) Department of Pathology, University of Michigan, Ann Arbor, Michigan, United States (3) Department of Medicinal Chemistry, University of Michigan, Ann Arbor, Michigan, United States

ASH1L (absent, small, or homeotic-like 1) is a SET domain-containing histone lysine methyltransferase. It is shown to mono- and di-methylate lysine 36 on histone H3 (H3K36), which is associated with transcriptional activation. Emerging data link ASH1L to multiple cancers. *ASH1L* gene is amplified in 27% of aggressive, basal-like breast cancers, and high levels of ASH1L mRNA are associated with shorter survival in breast cancer patients. ASH1L activates clusters of *HOX* genes, including *HOXA9*, which is overexpressed in acute myeloid leukemias (AML) and leukemias with *Mixed Lineage Leukemia (MLL)* rearrangements. Recent study demonstrates that ASH1L knockdown compromises growth and clonogenic activity of MLL leukemia cells and abolishes development of leukemia in mice. Therefore, well-characterized chemical probes with inhibitory activity against ASH1L would be extremely valuable for elucidating the biological functions of ASH1L in cancers.

To develop ASH1L inhibitors, we performed an NMR-based fragment screening using ¹⁵N-labelled ASH1L SET domain. We identified compounds that bind to ASH1L with millimolar binding affinity and performed extensive optimization by medicinal chemistry to improve their binding affinity. Through these efforts, we developed a series of compounds that bind to ASH1L with nanomolar binding affinity and 1:1 stoichiometry. Biochemical analyses demonstrated that these compounds effectively inhibit ASH1L histone methyltransferase activity through a noncompetitive inhibition mechanism with

nucleosome substrate. We also obtained high resolution crystal structures of ASH1L-SET in complex with inhibitors, which revealed that compounds bind to a well-defined pocket formed in the post-SET region of ASH1L. The activity of ASH1L inhibitors was further tested in MLL leukemia cells, resulting in selective inhibition of cell proliferation and differentiation in these cells. ASH1L inhibitor treatment also led to the downregulation of *HOXA9*, which is an important gene required for leukemic transformation by MLL fusion proteins. Our study demonstrates that development of ASH1L inhibitors is feasible, resulting in compounds with potent activity in leukemia cells. To our knowledge, these compounds represent the first-in-class chemical probes targeting ASH1L to investigate its role in leukemia and other diseases.

MEDI 85

Discovery of leniolisib (CDZ173), a potent and selective new generation PI3Kdelta inhibitor for autoimmune and inflammatory diseases

Nicolas G. Soldermann, *nicolas.soldermann@novartis.com*. NIBR, Novartis, Basel, Switzerland

The discovery and characterization of leniolisib (CDZ173), a potent and selective inhibitor of Phosphoinositide 3-kinase delta (PI3Kd) will be presented. We report how innovative medicinal chemistry efforts led to the identification of a novel and promising tetrahydro-pyrido-pyrimidine lead series that could be rapidly further optimized into a favorable physicochemical space and resulted in the identification of leniolisib, currently in clinical development as an anti-inflammatory therapeutic agent.

In vitro, leniolisib shows the capacity to inhibit a large spectrum of immune cell functions and *in vivo*, leniolisib inhibits B cell activation in rats and monkeys in a concentration- and time-dependent manner. In preclinical animal models, leniolisib potently inhibited the antibody production in response to immunization and reduced clinical symptoms in rat collagen-induced arthritis models. Structurally, leniolisib differs significantly from the first generation of PI3Kd and/or PI3Kgd-selective clinical compounds and, therefore, could differentiate favorably in its safety profile.

First-in-human study indicated an excellent tolerability, favorable pharmacokinetic properties and a direct PK/PD relationship. A first clinical trial in patients suffering from APDS/PASLI, a rare disease caused by gain-of-function mutation of PI3Kd demonstrated that leniolisib was well tolerated and significantly improved laboratory and clinical parameters in APDS patients.

MEDI 86

Efficacy of compounds derived from a native medicinal plant against common wound-colonising bacteria

Vajira A. Agampodi, *vajiraasela.agampodi@hdr.qut.edu.au*, Trudi Collet. Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia

Herbal remedies for the treatment of wound infections have been used for millennia across a multitude of cultures. As such, there is an increased interest in plant-derived compounds which have the potential to inhibit wound-colonising bacteria, thereby modulating the healing process. This study aimed to investigate the antibacterial properties of compounds present in plant species denoted 8481.

Dried and ground plant leaves were extracted with methanol and tested against 14 of the most common wound-colonising microflora using the well diffusion assay. The dry extract was fractionated with preparative normal phase silica gel column using a solvent gradient consisting of hexane, ethyl acetate, chloroform and methanol successively. Active primary fractions were further fractionated in a preparative reverse phase silica gel column using a gradient of acetonitrile in water. Primary and secondary fractions were evaluated for their antibacterial activity. Compounds in active fractions were isolated with gradient elution by reverse phase high performance liquid chromatography on an analytical C18 column. The mobile phase consisted of 0.05% formic acid in water and methanol. Structures of the isolated compounds were elucidated with nuclear magnetic resonance and mass spectroscopy data.

Plant extract and methanolic fractions were shown to be bactericidal against Gram-positive bacteria including *Staphylococcus aureus*, two clinical isolates of MRSA and *Staphylococcus epidermidis*. Verbascoside, a phenylpropanoid glycoside isolated from the plant, demonstrated significant antibacterial activity against a range of *Staphylococcus* spp. Investigations are underway to identify the remaining compounds and examine their antibacterial activity against various multi-drug resistant pathogens.

Since plant species 8481 contain bioactive compounds which have been shown to elicit bactericidal activity against several common wound-colonising bacteria, the reduction in microbial load may augment the wound healing process. The real world implication of this research is expected to produce novel plant-based therapeutics which can significantly enhance the healing of chronic wounds.

MEDI 87

Novel 2-arachidonoyl glycerol analogs with enhanced bio-activities and stabilities: Design, synthesis and *in vitro* biochemical evaluation

Yingpeng Liu¹, chrislyp1987@gmail.com, Spyros P. Nikas¹, Lipin Ji¹, Anisha Korde¹, Alex Ciesielski³, Alex Straker³, Othman Benchama¹, Amey S. Dhopeswarkar³, Chandrashekhar Honrao¹, Ken Mackie³, Alexandros Makriyannis². (1) Dept. of Pharmaceutical Sciences, Center for Drug Discovery, Northeastern University, Boston, Massachusetts, United States (2) Center for Drug Discovery, Northeastern University, Boston, Massachusetts, United States (3) Dept. of Psychological&Brain Sciences, Indiana University Bloomington, Bloomington, Indiana, United States

The endogenous 2-arachidonoyl glycerol (2-AG) acts at the CB1 and CB2 receptors, two Gi/o-protein-coupled cannabinoid receptors (CBs) that are currently being targeted for a number of conditions including pain, inflammation, CNS disorders and cancer. However, it is fairly difficult to use 2-AG directly to probe its biological role and to explore the bioactivities of distinct receptors and enzymes because of its intrinsically chemical and biochemical instability. The biological actions of 2-AG are terminated by a transport mechanism and enzymatic deactivation. In most tissues, 2-AG is metabolized by monoacylglycerol lipase (MAGL). In addition, fatty acid amide hydrolase (FAAH) and a brain hydrolase (ABHD6) can inactivate 2-AG. Moreover, recent studies have demonstrated that oxidative enzymes including cyclooxygenase-2 (COX-2), cytochrome P450, and lipoxygenases (LOXs) can transform 2-AG into eicosanoid related bioactive products. In an effort to explore the pleiotropic biological role of the endocannabinoid 2-AG we are developing novel analogs with enhanced bio-activities at CB receptors and increased stabilities to the actions of hydrolytic and/or oxidative enzymes. Towards this end, currently we are exploring the head group of 2-AG with special emphasis on the ester moiety and the methylene linker. Our design focuses on the reverse ester design approach and the incorporation of steric features at the methylene linker of the endogenous prototype.

MEDI 88

Indole-based positive allosteric modulators for targeting CB₁ receptor to overcome neuropathic pain

Angel Resendez¹, aresende@ucsc.edu, **Kaavya Kumar³**, **Vineet Kumar²**, **Brian K. Kobilka³**, **Sanjay Malhotra^{1,4}**. (1) Radiation Oncology, Stanford University, Stanford, California, United States (3) Molecular and Cellular Physiology, Stanford University, Stanford, California, United States (4) Radiology, Stanford University, Stanford, California, United States

Cannabinoid CB₁ receptor is one the most abundantly expressed G protein coupled receptors (GPCRs) in the central nervous system (CNS) and has been demonstrated to be a viable target for variety of diseases including neuropathic pain. Through the stimulation of CB₁, its agonists can inhibit pain transmission at central, spinal, and peripheral synapses. However, direct activation of CB₁ at the orthosteric site can induce a cannabis-mimetic side effect profile, which includes abuse, addiction, and memory impairment. These side effects limit agonist for therapeutic use and further development. An alternative approach to target the CB₁-mediated signaling pathway has been taken to develop positive allosteric modulators (PAMs) that bind to distinct sites from the orthosteric site. Recently discovered indole derivative, ZCZ-011, targeted the allosteric site on CB₁ receptor and demonstrated effective neuropathic pain reduction without psychoactive or hypothermic effects in-vivo. Based on this precedence, a library of 1- and 2-aryl and alkyl substituted indole analogues were synthesized and screened for G protein (i.e. Gs, Gi and Gq) activation when bound to CB₁ receptor using a Luciferase-based Glo assay to study their structure activity relationship. As proof of principle, our preliminary data show that by using the

Luciferase-based Glo assay we can differentiate biased ligands for CB₁ towards Gs, Gi and Gq. Additionally, the potential of these derivatives for biased β -arrestin recruitment was also examined using a bioluminescence resonance energy transfer (BRET) assay. These novel ZCZ-011 analogues have potential to be used as tool compounds to understand CB₁ receptor signaling bias and eventually as therapeutic agents for neuropathic pain.

MEDI 89

Synthesis of new benzodiazepines that function as α_5 -GABA_A receptor ligands to target group 3 medulloblastomas

Farjana Rashid¹, *frashid@uwm.edu*, **Guanguan Li**¹, **Taukir Ahmed**¹, **Oliver Jonas**³, **Soma Sengupta**², **James M. Cook**¹. (1) *Chemistry & Biochemistry, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin, United States* (2) *Neurology, Emory University School of Medicine, Atlanta, Georgia, United States* (3) *David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States*

Medulloblastoma is a form of malignant brain tumor which is most common in children. Contemporary genetic research has been used to classify this malignant tumor into four subtypes. Among these subtypes, subgroup-3 was identified as the most lethal one. This particular subtype was characterized with the exhibition of a high expression of the GABA_AR α_5 subunit gene (GABA5), as well as amplification of MYC regulator gene. New α_5 subtype selective benzodiazepines have been synthesized to study medulloblastoma cell survival and also the Structure-Activity Relationship (SAR) on the GABA_AR binding efficacy. The lead ligand for this study, QH-II-066, had shown promising results as an α_5 -GABA_AR subtype selective agonist (HEK293 cell lines), and it displayed marked membrane depolarization and a significantly lower medulloblastoma cancer cell survival rate. But, when tested in *Xenopus laevis* oocytes to observe the efficacy at GABA_AR subunits (α_1 - α_3 , $\beta_3\gamma_2$), data indicated that QH-II-066 also exhibited α_2/α_3 subtype efficacy as well. In order to improve α_5 efficacy the 2'-H atom in QH-II-066 was replaced with fluorine and also chlorine atom. Ligands KRM-II-08, TA-01-12, KRM-III-77, and FR-01-43 are representative examples. The most potent ligand in the series with activity against tumors was KRM-II-08. Benzodiazepine derivatives have proven to be promising in targeting subgroup 3 medulloblastomas. Recent synthesis, pharmacology, and cytotoxicity are presented herein.

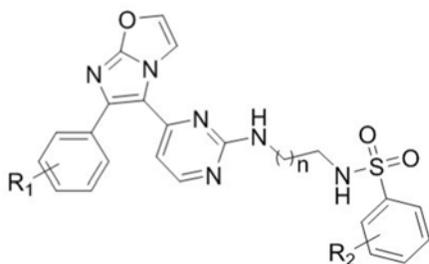
MEDI 90

Synthesis and biological evaluation of novel imidazo[2,1-b]oxazole derivatives as V600E BRAF inhibitors for treatment of melanoma

Mohammed S. Abdel-Maksoud¹, *ph_ss@hotmail.com*, **Mohammed I. El-Gamal**^{2,3}, **Usama M. Ammar**^{4,5}, **Eslam M. Ali**^{4,5}, **Karim I. Mersal**^{4,5}, **Hong S. Choi**⁶, **Chang H. Oh**^{4,5}. (1) *Medicinal & Pharmaceutical Chemistry, National Research Centre, Cairo,*

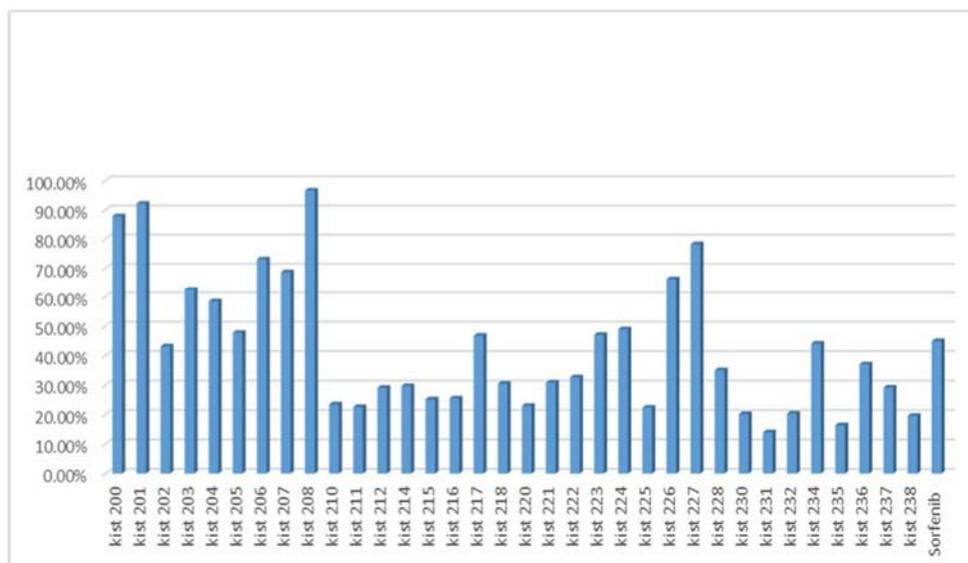
Egypt (2) Department of Medicinal Chemistry, University of Sharjah, Sharjah, United Arab Emirates (3) Department of Medicinal Chemistry, University of Mansoura, Mansoura, Egypt (4) Center for Biomaterials, Korea Institute of Science & Technology, Seoul, Korea (the Republic of) (5) Department of Biomolecular Science, University of Science & Technology (UST),, Daejeong, Korea (the Republic of) (6) College of Pharmacy, University Gwangju, Gwangju, Korea (the Republic of)

In this study, a new series of imidazo[2,1-*b*]oxazol derivatives was synthesized and evaluated for their anticancer activity over NCI 60 cell lines and A375 melanoma cell line; in order to investigate and increase the selectivity of compounds belong to imidazo[2,1-*b*]oxazol scaffold toward melanoma. **Kist 210, kist 211, kist 225, kist 230, kist 231, kist 232 and Kist 235** showed higher potency compared to sorafenib. Compounds containing *m*-OH phenyl at position 6 and 2-substituted pyrimidine at position 5 with propyl bridge between pyrimidine and sulfonamide moiety showed the highest activity. In addition, ten compounds exhibited 100% inhibition for BRAF, V600E BRAF and RAF1 at single dose 10 μ M. The new series provides a good candidate for preclinical investigations in treatment melanoma.



R1= *m*-OMe, and *m*-OH
R2= H, *p*-f, *p*-OMe, *p*-Me, *p*-OH
n=1 and 2

General structures of the target compounds



Inhibitory effect of the new compounds represented as growth % of A375 melanoma cell line compared to sorafenib .

MEDI 91

Using bacterial cytological profiling to determine the mechanism of action of antimicrobial peptides

Sam A. Juliano, *samuel.juliano@uconn.edu*, Searle S. Duay, Alfredo M. Angeles Boza. Department of Chemistry, University of Connecticut, Storrs Mansfield, Connecticut, United States

Bacterial cytological profiling (BCP) is a technique that was developed to rapidly identify not only the bacterial synthesis pathway affected by a given antibiotic, but also the specific target within that pathway. This is accomplished through the use of confocal fluorescence microscopy along with membrane and DNA active fluorescent dyes. It has been proven to work as a method to identify the mechanism of action for novel small molecule antibiotics, reducing the time and number of experiments required to determine how an antibiotic is inhibiting bacterial growth. While this technique has proven effective for small molecule antibiotics, which usually affect only one cellular pathway, it has yet to be determined whether BCP is effective for determining the mechanism of action for antimicrobial peptides. Antimicrobial peptides are capable of affecting more than one area of a cell, and in some cases their mechanisms of action are different from those observed for small molecules. Here we attempt to use BCP to determine the mechanism of action of several antimicrobial peptides. In this work we will perform BCP on several known classes of small molecule antibiotics and well-studied antimicrobial peptides including Magainin 2, Buforin 2, Ixosin, and Piscidins 1 and 3. This work will allow for rapid determination of the mechanism of action for antimicrobial peptides, either eliminating or supplementing the battery of tests currently required to make this determination.

MEDI 92

Novel CMKLR1 inhibitors and structure activity relationship studies for application in demyelinating disease

*Vineet Kumar¹, Melissa LaJevic³, Brian A. Zabel³, **Sanjay V. Malhotra^{1,2}**, smalhotra@stanford.edu. (1) Dept of Radiation Oncology, Stanford University, Palo Alto, California, United States (2) Department of Radiology, Stanford University, Palo Alto, California, United States (3) Palo Alto Veterans Institute for Research, Palo Alto Health Care System, Palo Alto, California, United States*

Multiple sclerosis (MS) is a devastating demyelinating disease of the central nervous system (CNS) that affects approximately 2.5 million people worldwide. Although a number of MS treatments are available, there remains a substantial unmet need for improved therapeutics. Therapies that target white blood cells can reduce disease activity and improve clinical outcomes in MS. Earlier we identified a small molecule inhibitor of a white blood cell receptor important in guiding inflammatory cell migration into the CNS. This compound, 2-(α -naphthoyl) ethyltrimethylammonium iodide (α -NETA), significantly suppresses MS-like symptoms in preclinical mouse models. Despite having multiple favorable features, α -NETA possesses certain liabilities that limit its potential for clinical development. To study preliminary structure-activity-relationship (SAR), we generated several analogs of α -NETA by modifying its key structural features and measuring IC₅₀ values for inhibition of chemerin-stimulated CMKLR1 signaling in vitro. Improved α -NETA analogs have the potential to impact the clinical management of MS and potentially other autoimmune or inflammatory disorders.

MEDI 93

Small molecules facilitating DNA repair in breast cancer cells

*Mallesha Pandrala¹, Kedar Hastak³, Vineet Kumar⁵, Makelle Gardiner³, James M. Ford^{3,4}, **Sanjay V. Malhotra^{4,2}**, smalhotra@stanford.edu. (1) Dept of Radiation Oncology, Stanford University, Palo Alto, California, United States (2) Department of Radiology, Stanford University, Palo Alto, California, United States (3) Medicine, Stanford University, Palo Alto, California, United States (4) Stanford Cancer Institute, Stanford University, Palo Alto, California, United States (5) Department of Radiation Oncology, Stanford University, Palo Alto, California, United States*

Breast cancers with germline mutations in the BRCA1 and triple negative breast cancers (TNBC) are known to respond to drugs that target DNA repair pathways. Earlier study from our group has shown that chemo preventive agents that target base-excision DNA repair activity potentially enhance the DNA repair abilities of mutant BRCA1 and TNBC tumors, thereby, reducing tumor onset and delaying metastasis. More recently, we have developed novel small molecules and investigated their potential to protect BRCA1 mutant and TNBC cells from oxidative DNA damage by enhancing the DNA repair function. Our study shows that these small molecules are well tolerated and have

negligible toxicity. Furthermore, we found that the 'hit' compound protects breast cancer cells from hydrogen peroxide mediated oxidative DNA damage. Modified analogs of the 'hit' enhance DNA repair in TNBC cells. Thus, this study offers a new approach to chemoprevention by enhancing DNA repair and protecting cells from oxidative DNA damage.

MEDI 94

Novel chalcone derivatives as potential therapeutic agents for triple negative breast cancer

Vineet Kumar², kumarvin@stanford.edu, Catherine C. Going³, Dhanir Tailor¹, Mallesh Pandrala⁵, Alisha M. Birk³, Sharon Pitteri^{3,4}, **Sanjay V. Malhotra**^{1,4}, smalhotra@stanford.edu. (1) Dept of Radiation Oncology, Stanford University, Palo Alto, California, United States (2) Department of Radiation Oncology, Stanford University, Palo Alto, California, United States (3) Radiology, Stanford University School of Medicine, Palo Alto, California, United States (4) Canary Center at Stanford for Cancer Early Detection, Stanford University School of Medicine, Palo Alto, California, United States (5) Department of Radiation Oncology, Stanford University School of Medicine, Palo Alto, California, United States

Chalcones are a,b-unsaturated ketone bearing natural products found in variety of plants. Also, chalcones are key intermediates in the biosynthesis of flavonoids and isoflavonoids, and historically known to exhibit anti-cancer, anti-oxidant, anti-inflammatory, anti-viral, anti-bacterial, anti-malarial, and radical scavenger activities. We report synthesis of a study of 25 synthetic chalcone derivatives and their anti-proliferative activities in the sixty human tumor cell lines. The phenotypic screening identified three 'hit' chalcones which showed potent anti-cancer activity in various cancer cell lines, including the triple negative breast cancer (TNBC) cell lines MDA-MB-231 and MDA-MB-468. Quantitative proteomics experiments were performed using mass spectrometry to identify key pathways affected by these 'hit' compounds in these TNBC cell lines. Results showed an increase in the abundances of proteins involved in the G2/M and S phases of the cell cycle and a decrease in the abundances of tubulins, which form the microtubule spindle essential for cell division. This data suggests that the compounds act by induction of cell cycle arrest, leading to apoptosis. Details on the synthesis, anti-cancer screening, proteomics, and validation will be presented.

MEDI 95

Prevention of trigeminal neuropathic pain development in rats using novel deuterated GABA_AR- α 6 subtype selective ligands

Daniel E. Knutson¹, knutsond@uwm.edu, Dina Vasovic⁴, Branka Divovic³, Marco Treven², Friederike Steudle², Petra Scholze², Bozidar Brković⁴, Werner Sieghart², Margot Ernst², James M. Cook¹, Miroslav M. Savic³. (1) Department of Chemistry & Biochemistry, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin, United States

(2) *Department of Molecular Neurosciences, Center for Brain Research, Medical University of Vienna, Vienna, Austria* (3) *Department of Pharmacology, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia* (4) *School of Dentistry, University of Belgrade, Belgrade, Serbia*

GABA_A receptors (GABA_ARs) which contain the $\alpha 6$ subunit are found primarily in the granule cells of the cerebellum and the olfactory bulb, but also in the trigeminal ganglia. Reduction of $\alpha 6$ subunit expression in trigeminal ganglia by small interfering RNA increased inflammatory pain in rats. Thus, we hypothesized that enhancing the activity of $\alpha 6$ -GABA_ARs may be effective in the treatment of painful neuropathic syndromes originating from the trigeminal system. Herein, the results of electrophysiological, pharmacokinetic and behavioral studies of two deuterated, structurally similar pyrazoloquinolinones (**DK-I-56-1** and **DK-I-87-1**) are reported. While both ligands act at the Bz site ($\alpha + \gamma$ - interface) of GABA_ARs as null modulators, only the functionally selective ligand, **DK-I-56-1**, exerts an effect at the $\alpha 6 + \beta 3$ - interface (PQ Site) of $\alpha 6$ -GABA_ARs as a positive allosteric modulator. Results obtained in two protocols of chronic constriction injury of infraorbital nerve in rats dosed IP with **DK-I-56-1** during 14 days after surgery, or with **DK-I-56-1** or **DK-I-87-1** during 14 days after trigeminal neuropathy displayed that **DK-I-56-1** but not **DK-I-87-1** significantly reduced the allodynia scores of hypersensitivity to von Frey filaments. Therefore, ligands which positively modulate $\alpha 6$ -GABA_ARs are candidates for novel treatment options against the development of trigeminal neuropathic pain.

MEDI 96

Design and synthesis of proanthocyanidin derivatives as an inhibitor of amyloid β aggregation

Mirei Mizuno¹, mizuno@pharm.showa-u.ac.jp, **Kazunori Mori**¹, **Ikuo Nakanishi**³, **Ken-ichiro Matsumoto**², **Motoko Shibamura**¹, **Kiyoshi Fukuhara**¹. (1) *School of Pharmacy, Showa University, Shinagawa, Tokyo, Japan* (2) *NIRS, QST, Inage, Chiba, Japan* (3) *Res Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan*

Alzheimer's disease is an intractable disease; one of the pathological characteristics is the amyloid deposition in hippocampus. Reactive oxygen species (ROS) is known to be generated in the aggregation process of amyloid beta ($A\beta$), to injured nerve cells. In general, it is reported that polyphenol have the ability to inhibit aggregation of $A\beta$. Previously, a catechin analogue, called "planar catechin (PCat)", in which the geometry of (+)-catechin was constrained to be planar, was synthesized. Comparing with catechin, it exhibited potent radical scavenging activity, several novel biological activities and enhanced inhibitory activity against $A\beta$ aggregation. Proanthocyanidin, oligomers of catechin, has received attention largely due to their biochemical and physiological functions. Especially, procyanidin B3 (Cat-Cat), the dimer of (+)-catechin, is characterized to be able to cross the blood brain barrier easily. In this study, we designed novel two derivatives Cat-PCat and PCat-PCat by constraining the geometry

of one or both catechin molecules to be planar, based on the structure of procyanidin B3 (Cat-Cat), aimed at the protection of A β induced neurotoxicity by way of both potent inhibition of A β aggregation and antioxidation toward A β -induced intracellular ROS generation. These derivatives were synthesized according to a procedure for the synthesis of procyanidin B3. Assessed radical scavenging activity, Cat-PCat was increased to 1.9 times than that of Cat-Cat. Furthermore, PCat-PCat was increased to 1.5 times than that of Cat-PCat. These results are expected that constrained the geometry of catechin molecules to be planar is effective for scavenging ROS, generated in the aggregation process of A β . In addition to antioxidative activities, strong protective effects of A β induced neurotoxicity and potent inhibitory activities against A β aggregation were observed, and their activities increased with the number of planar catechin in catechin dimers. These results indicate that PCat-PCat has potent inhibitory activity for either neurotoxicity or A β aggregation. In this presentation, the details of these results will be reported.

MEDI 97

Efficient synthetic methodology for the construction of dihydronaphthalene and benzosuberene molecular scaffolds with application as potent inhibitors of tubulin polymerization

Haichan Niu¹, haichan_niu@baylor.edu, Deboprosad Mondal¹, Tracy E. Strecker¹, Jeni Gerberich³, James W. Campbell III³, Debabrata Saha², David J. Chaplin^{1,4}, Ernest Hamel⁵, Ralph P. Mason³, Mary L. Trawick⁷, Kevin G. Pinney⁶. (1) Department of Chemistry and Biochemistry, Baylor University, Waco, Texas, United States (2) Department of Radiology Oncology, University of Texas Southwestern Medical Center, Dallas, Texas, United States (3) Department of Radiology, University of Texas Southwestern Medical Center, Dallas, Texas, United States (4) Mateon Therapeutics, Inc., South San Francisco, California, United States (5) Cancer Treatment and Diagnosis, National Cancer Institute, Frederick, Maryland, United States (6) Dept of Chemistry Biochemistry, Baylor University, Waco, Texas, United States (7) Baylor Univ, Waco, Texas, United States

A promising design paradigm for the discovery of potent small-molecule inhibitors of tubulin polymerization that bind to the colchicine site draws structural inspiration from the natural products colchicine and combretastatin A-4 (CA4). Our previous studies with benzocycloalkenyl and heteroaromatic ring systems, that incorporate pendant aryl ring functionality, led to the discovery of a variety of promising small-molecule inhibitors. In one subset, dihydronaphthalene and benzosuberene molecular scaffolds featuring phenolic (KGP03 and KGP18) and aniline (KGP05 and KGP156) congeners emerged as lead agents. Water-soluble phosphate prodrug (and related) salts of several of these compounds demonstrated dual mechanism of action, functioning as both potent vascular disrupting agents (VDAs) and as highly cytotoxic anticancer agents. In each case the mechanism was attributed to inhibition of tubulin polymerization. A further series of benzosuberene and dihydronaphthalene analogues was designed and synthesized in an effort to extend functional group diversity and probe regioisomeric

tolerance for structural and functional group modification while maintaining biological potency. An efficient synthetic route was utilized that proved suitable for the accommodation of functional group diversity. Synthetic methodology was also introduced to convert phenolic-based compounds directly to their corresponding aniline congeners. Ten molecules from this series of seventeen analogues were identified as promising inhibitors of tubulin polymerization ($IC_{50} < 5 \mu M$, cell free assay), while seven were highly potent and comparable in activity ($IC_{50} \approx 1 \mu M$) to CA4 and our lead compounds (KGP18, KGP03). Details regarding molecular design, synthesis, and biological evaluation (inhibition of tubulin polymerization and cytotoxicity against human cancer cell lines) will be presented.

MEDI 98

Design, synthesis, and structure-activity relationships of pyrido[3,2-*d*]pyrimidines as microtubule targeting agents that are effective against Pgp and β III-tubulin overexpressing cancer cells

Aleem Gangjee¹, Arpit B. Doshi¹, arp.1311@gmail.com, Ernest Hamel², Susan Mooberry³. (1) Grad Sch Pharm Sciences, Duquesne University, Pittsburgh, Pennsylvania, United States (2) Screening Technologies Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, Frederick National Laboratory for Cancer Research, National Institutes of Health, Frederick, Maryland, United States (3) Science Center- Dept of Pharmacology, University of Texas Health, San Antonio, Texas, United States

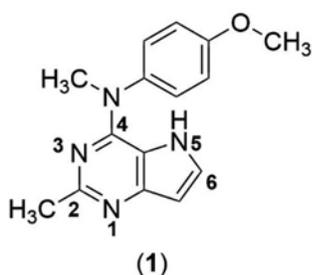
Dynamic microtubules are involved in essential cellular processes, including mitosis, the trafficking of proteins, organelles, and RNA, cellular signaling and migration. Microtubule targeting agents (MTAs) disturb microtubule dynamics by altering $\alpha\beta$ -tubulin heterodimer addition and loss from the microtubule, which disrupts microtubule-dependent cellular processes. The MTAs are divided into two classes: microtubule depolymerizing agents binding to either the vinca domain, the maytansine site or the colchicine site and microtubule polymerizing agents binding to the taxol site or the laulimalide/peloruside A site on the microtubule. The clinical efficacy of MTAs is limited by multidrug resistance due to expression of the P-glycoprotein drug efflux pump or increased expression of the β III-isotype of tubulin. The development of MTAs that are effective against cell lines representative of these forms of drug resistance could have advantages in patients who fail to respond to current MTAs, such as paclitaxel. In general, MTAs that bind within the colchicine site circumvent Pgp and β III-tubulin mediated resistance. However, no MTA that binds to this site is approved for the treatment of cancer. We have designed water soluble, colchicine site binding agents with different substitutions at the C2 and N4-positions of the pyrido[3,2-*d*]pyrimidine scaffold. The most potent compound inhibited tubulin assembly and had antiproliferative potency in the nanomolar range against the MDA-MD-435 melanoma cell lines. This compound retained efficacy in β III-tubulin expressing HeLa cells (WT β III), as well as Pgp-overexpressing SK-OV-3 MDR-1-M6/6 (M6/6) cells. The design, synthesis and biological activities of these analogs will be presented and discussed.

MEDI 99

Pyrazolo[4,3-*d*]pyrimidines: A novel scaffold for microtubule-targeting agents (MTAs)

Farhana Islam¹, farhanap40@gmail.com, **Tasdiq M. Quadery**¹, **Ruoli Bai**², **Ernest Hamel**², **Aleem Gangjee**¹. (1) Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, Pennsylvania, United States (2) Screening Technologies Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute at Frederick, National Institutes of Health, Frederick, Maryland, United States

Microtubules are involved in a wide variety of cellular functions, including cellular transport, protein trafficking, and mitosis. Microtubule-targeting agents (MTAs) have gained significant interest as important targets for cancer therapy. Paclitaxel, podophyllotoxin, vinca alkaloids, and the epothilones are some examples of natural products which interfere with microtubule dynamics. Combretastatin A-4 phosphate (CA-4P, fosbretabulin) and A-1 diphosphate (CA-1P, OXi4503), 2-methoxyestradiol, and verubulin are a few of the colchicine site binding agents that have been evaluated in phase 1 and 2 clinical trials as anticancer agents alone and in combination with other drugs. Thus far, no colchicine site agent has been approved as an anticancer agent. Hence, this site provides new opportunities for drug discovery. The success of tubulin binding agents is limited by the emergence of multi-drug resistance mechanisms including the overexpression of P-glycoprotein and /or β III-tubulin. We previously reported the design, synthesis, and antitumor activity of pyrrolo[3,2-*d*]pyrimidine (**1**), which inhibits tubulin assembly. Compound **1** also circumvented P-glycoprotein and β III-tubulin mediated resistance. On the basis of the anti-tubulin activity of **1**, we designed pyrazolo[4,3-*d*]pyrimidine analogs and their derivatives. Regioselectivity of pyrazolo compounds was determined by means of NOESY experiments, which showed a spatial closeness of the pyrazole hydrogen atom to the adjacent protons on appropriate substituents. The design, synthesis, structure-activity relationship, and biological evaluations of these agents will be presented and discussed.



MEDI 100

Investigating the binding modes and structure-activity relationships of small molecule FPR2 agonists using receptor homology modelling

Monika Maciuszek^{1,2}, monika.maciuszek@lifearc.org, **Tim Chapman**¹, **Gerry Nicoales**³, **Kristian Birchall**¹, **Chris Reutelingsperger**³, **Mauro Perretti**², **Andy Merritt**¹. (1) LifeArc, Stevenage, United Kingdom (2) The William Harvey Research Institute, Barts and The London School of Medicine, Queen Mary University of London, London, United Kingdom (3) Department of Biochemistry, CARIM – School for Cardiovascular Sciences, Maastricht University, Maastricht, Netherlands

The resolution of inflammation (RoI) represents a novel approach to treat cardiovascular inflammatory pathologies. Formyl peptide receptor type 2 (FPR2) is a G-protein coupled receptor situated on the surface of many cell types e.g.: neutrophils, monocytes or T-cells and plays a key role in the RoI process with implications in a number of cardiovascular inflammation processes e.g.: atherosclerosis and the vascular complications of diabetes, hence there has been significant interest in developing agonists of FPR2 as effectors of resolution towards potential new therapeutics. The FPR2 agonists can be divided into three groups: natural molecules, synthetic peptides and small molecule agonists. In these studies, small molecule agonists of diverse origins were investigated. Due to the lack of a high resolution experimental structure, two homology models were used, an agonist bound μ -opioid based structure and a dual template model based on the antagonist-bound μ -opioid receptor and antagonist-bound chemokine receptor crystal structure. The studies have shown the importance of amino residues confirmed by site-directed mutagenesis Arg26, Asp106, Arg205, Asp281 and the crucial role of aromatic stacking mainly Phe257, Phe180, and His102 in most of the binding modes. Comparison of docking binding poses based on two the different homology models assisted the rationalization of the structure-activity relationships and allowed novel ligand structures to be proposed.

MEDI 101

Synthesis and characterization of imidazopyrazine derivatives as VAV1 inhibitors

Marc Gerspacher¹, marc.gerspacher@novartis.com, **Philip Skaanderup**¹, **Patricia Imbach-Weese**¹, **Lionel Doumampouom Metoul**¹, **Esther Roehn-Carnemolla**¹, **Dorothee Arz**¹, **Audrey-Laure Garlot**¹, **Anne-Catherine Remond**¹, **Vangrevelinghe Eric**¹, **Mark Knapp**², **Andreas Lingel**¹, **Volker Stucke**¹, **Patrick Chene**¹, **Francesco Hofmann**¹. (1) Novartis Institutes for BioMedical Research Basel, Novartis Pharma AG, Basel, Switzerland (2) Novartis Institutes for BioMedical Research Emeryville, Emeryville, California, United States

Guanine nucleotide exchange factors (GEFs) act as activators of GTPases and based on the fact that aberrant GTPase signaling is well known to be involved in a number of diseases, GEFs are viewed as potential drug targets. However, the highly dynamic character of these multi-domain proteins has made them difficult to target with small molecular weight inhibitors. We have reported recently on the discovery, co-crystal structure and detailed mode of interaction of an imidazopyrazine derivative as a selective VAV1 guanine nucleotide exchange factor (GEF) inhibitors. Now in this disclosure we will focus on the synthetic aspects of the imidazopyrazine derivatives and

we will discuss key aspects of the structure activity relationship & properties of this series of compounds as VAV1 guanine nucleotide exchange factor (GEF) inhibitors: We have identified derivatives with potent and selective VAV1-inhibitory activity capable of exhibiting activity in cellular assays. A correlation between the GNE-inhibitory activity and the degree of protein stabilization from thermal shift experiments has been established. The discovery of this unique series of compounds illustrates that it is indeed possible to identify specific small molecular weight guanine nucleotide exchange factor inhibitors that have the potential to exhibit suitable drug-like properties.

MEDI 102

Synthesis of novel chloramphenicol derivatives as ribosome-targeting antibiotics

Payagala Udawattage Ashvin I. Fernando¹, afernando@chm.uri.edu, Steven T. Gregory², Samantha Donhue², Brenton L. DeBoef³, Paul Cesana¹, Jogi Gerwald⁴. (1) Chemistry, University of Rhode Island, Kingston, Rhode Island, United States (2) Cell and molecular biology, University of Rhode Island, Kingston, Rhode Island, United States (3) University of Rhode Island, Kingston, Rhode Island, United States (4) Molecular Biology, Cell Biology and Biochemistry, Brown University, Providence, Rhode Island, United States

Chloramphenicol (CAM) binds to the bacterial 50S ribosomal subunit and inhibits the peptide bond forming reaction catalyzed by the peptidyltransferase active site. High-resolution crystal structures of the ribosome have revealed that the CAM binding site is deep within the 50S subunit in a structure composed almost exclusively of rRNA. Computational docking leads us to predict that binding can be further improved with changes to certain CAM functional groups. Individual modifications can potentially either enhance or impair binding, and both can be informative with regard to the nature of drug-ribosome interactions. Here we describe derivatives of CAM and their inhibitory activity against the bacterium *Thermus thermophilus*, a model system for ribosome structural studies. We also report their activity against a number of CAM-resistant mutants of *T. thermophilus* with base substitutions in the CAM binding site.

MEDI 103

Synthesis and evaluation of α,β -unsaturated phosphonate esters as DXR inhibitors

Kenneth Heidel¹, kennyheidel@gwu.edu, Rachel Edwards², Stacy Arnett⁴, Helena I. Boshoff³, Marvin J. Meyers⁴, Audrey R. Odom², Cynthia S. Dowd¹. (1) Chemistry, The George Washington University, Washington, District of Columbia, United States (2) School of Medicine, Washington University, St. Louis, Missouri, United States (3) Tuberculosis Research Section, NIAID, NIH, Bethesda, Maryland, United States (4) Center for World Health & Medicine, Saint Louis University, Saint Louis, Missouri, United States

Each year, millions succumb to infections caused by *Plasmodium falciparum* (*Pf*) and *Mycobacterium tuberculosis* (*Mtb*). Not only do these diseases cause severe discomfort, but pose a risk of death if left untreated. Furthermore, drug resistant strains of both *Pf* and *Mtb* continue to spread across the globe. Thus, there remains a considerable need for development of novel, next-generation therapies to combat these organisms. The methyl erythritol phosphate (MEP) pathway of isoprenoid biosynthesis, common to both organisms, is not found in humans, making it an attractive set of drug targets. For several years, our lab has developed inhibitors of the first committed step of the MEP pathway, 1-deoxy-D-xylulose-5-phosphate reductoisomerase (Dxr). This work showed that an α,β -unsaturated lipophilic phosphonate prodrug, RCB-185, has potent activity against *Mtb* and *Pf*, but an unfavorable half-life. Attempts to improve the pharmacokinetic profile of RCB-185 have resulted in the synthesis of other prodrugs. The goal of this work is to develop analogs with increased stability and retained whole cell activity.

MEDI 104

Design, synthesis and evaluation of novel antimalarials targeting apicoplast DNA polymerase (apPOL) from *P. falciparum*

Pratik Rajesh Chheda, pratikrajesh-chheda@uiowa.edu, Robert J. Kerns. Medicinal and Natural Products Chemistry, University of Iowa, Iowa City, Iowa, United States

Plasmodium spp. are the causative agents of malaria, killing nearly 600,000 people each year. Resistance of *Plasmodium* to chloroquine and artemisinin-based therapies accentuates the need for new drugs that target novel aspects of the parasite's biology. Nearly all parasites in the phylum *Apicomplexa* have an unusual organelle called the apicoplast, acquired through a secondary endosymbiotic event with algae. It participates in the biosynthesis of fatty acids, heme, iron-sulfur clusters, and isoprenoids and any defect in apicoplast metabolism or failure of the apicoplast to replicate and divide leads to the death of the organism. Additionally, lack of a human counterpart to the apicoplast makes apicoplast promising drug target. The 35-kb genome of apicoplast is replicated by select DNA replication enzymes of which the apicoplast DNA polymerase (apPOL) is unique to the parasite. The apPOLs from *P. falciparum* and *P. vivax* have 84% homology, while the most similar human DNA polymerases are the lesion bypass polymerases theta and nu (23 and 22% identity, respectively). This suggests that drugs targeted against the *Pf*-apPOL would also be effective in treating *P. vivax* infections with low human toxicity. Towards identifying inhibitors of apPOL, a high throughput screen of 400 compounds from the Open Malaria Box provided by MMV identified an inhibitor of apPOL with an IC_{50} of $0.8 \pm 0.3 \mu\text{M}$. Preliminary studies indicate that MMV666123 is specific for apPOL, with no inhibition of human DNA Pol or *E. coli* DNA Pol I. Also, MMV666123 inhibits the polymerase activity of apPOL but not its exonuclease activity, suggesting binding to the C-terminal polymerase domain of apPOL. Additionally, being from the malaria box substantiates anti-malarial activity of MMV666123. Presented here are initial design, synthesis and *in-vitro* evaluation efforts toward understanding the

structural requirements of MMV666123 for inhibition of apPOL and identifying more potent and drug-like apPOL inhibitors.

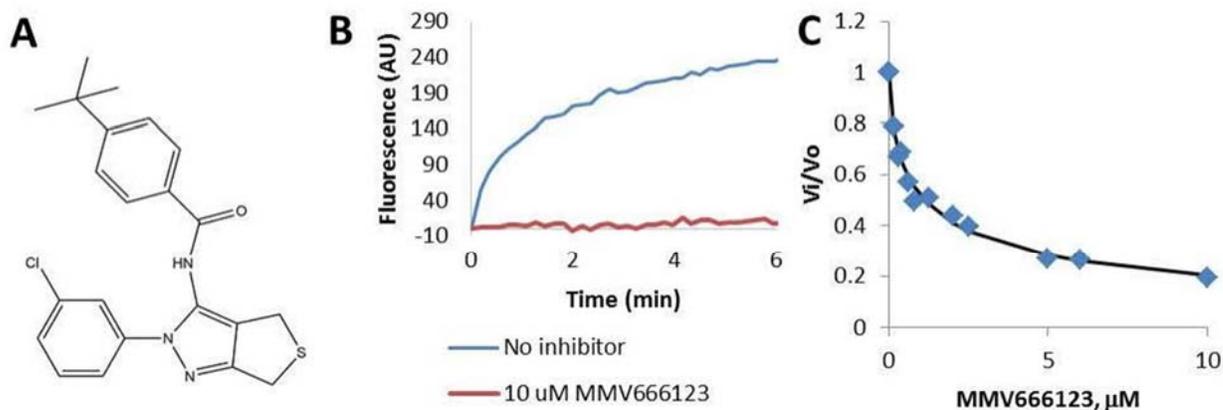


Figure 1. A) Structure of MMV666123. B) Effect of MMV666123 on apPOL activity as measured with the HT substrate. C) Dose/Response curve showing IC₅₀ of 0.8 µM.

MEDI 105

Microwave assisted synthesis and characterization of 4-aminopyridine (ampyra) derivatives and their applications

Mohammed A. Abusultan, ma1402954@qu.edu.qa, **Yousef M. Hijji**. Department of Chemistry and Earth Sciences, Qatar University, Doha, Qatar

4-Aminopyridine is an organic compound, and a drug as well called Ampyra, used to help patients with multiple sclerosis to walk. In order to versatile its use and applicability we have designed and synthesis and characterized few derivatives using microwave assisted synthesis. The derivatives were investigated as chemical sensors for detection of anions such as cyanide. The study have shown that some of these derivatives are selective and sensitive cyanide optical sensors. The selectivity, selectivity and binding constants as well as the stoichiometry have been determined and will be presented. Bioactivity of these compounds have been screened and evaluated against a number of microorganisms as well.

MEDI 106

Preliminary evaluation of novel serotonin antagonists as potential antidepressant agents

Haidy Giratallah³, haidy.giratallah@temple.edu, **Kevin M. Blattner**¹, **John C. Gordon**³, **Douglas A. Pippin**², **Benjamin E. Blass**¹, **Daniel J. Canney**³. (2) Praeventix, LLC, Exton, Pennsylvania, United States (3) Moulder Center for Drug Discovery Research, Department of Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, Pennsylvania, United States

Depression is a serious and prevalent mood disorder that can dramatically affect the quality of life of patients suffering from the disease. In recent years, effective pharmacological treatments have been developed that are effective in many patients and have good safety profiles. For example, Selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs), for example, are widely used and have improved the quality of life of many patients. However, it has been estimated that as many as 30% of patients do not respond adequately to these marketed antidepressant agents. In addition, adverse effects experienced by some patients limit the use of currently available drugs. Therefore, while advances have been made, there is a significant population of patients who require novel treatment options. It is well known that the majority of antidepressants affect parameters of the sleep-wake cycle and circadian rhythms by increasing the latency of and suppressing REMS. This overlap in pharmacology led investigators to evaluate the impact of antagonizing 5-HT₇ receptors in *in vivo* models of depression. The forced swim test (FST) and the tail suspension test (TST) are behavioral models that are routinely used to evaluate potential antidepressant agents. Interestingly, 5-HT₇^{-/-} mice exhibit reduced immobility times in both the FST and the TST. These findings stimulated further research into the impact of pharmacological blockade of 5-HT₇ in these assays. Specifically, the selective 5-HT₇ antagonists SB-269970 and JNJ-18038683 have been shown to induce antidepressant-like activity. SB-269970 induced a reduction in immobility time in both the FST and the TST in mice and rats. Similar results were observed in the TST model when mice were treated with JNJ-18038683. In addition, SB-269970 demonstrated a significantly faster antidepressant response in olfactory bulbectomized rats when compared to fluoxetine. These data suggest that the 5-HT₇ receptor is a promising target for the development of antidepressant agents. We recently identified a novel series of highly selective 5-HT₇ antagonists possessing drug-like properties. The binding data, physicochemical properties, and *in vitro* ADME data for this series of novel 5-HT₇ selective ligands will be discussed. The pharmacokinetic data for compound(s) selected to undergo animal models of depression will also be presented.

MEDI 107

Design, synthesis and bioactivity testing of *azotochelin* analogs as potential antibiotics

Nishant M. Karadkhelkar, nikks.nishant@gmail.com. Department of Pharmacy, St. John's University, Fresh Meadows, New York, United States

Siderophores (Greek: *iron* carrier) are biosynthesized by bacteria and fungi for ferric ion uptake through chelation in *iron* deficient environments. These organisms require *iron* as an essential element in variety of their cellular pathways. It has been proved that brominated analogues of *enterobactin*, a well-studied siderophore, exhibit antibacterial property. Another siderophore, called *azotochelin* is also a catechol-based siderophore like *enterobactin*, and has potential to be an antibacterial lead. Our focus is to synthesize *azotochelin* analogues through structural modification, which will be potential antibacterial agents. We have synthesized a library of first generation

analogues by modifying the aryl-ring component of this siderophore. This modification is expected to not interfere with iron binding. As the second phase, we will be studying the iron binding and antibacterial effect. Based on the results, we plan to synthesize a library of second generation analogues. Finally, we will test these analogues for their iron-binding properties and antibacterial activity as well.

MEDI 108

Discovery of AM-2995, a potent, selective and orally bioavailable APJ agonist for the treatment of heart disease

Zhihua "Max" Ma¹, maxwellmzh@gmail.com, Xiaodong Wang², Malgorzata Wanska², Lars Heumann², Richard Connors², Frank Kayser², Julio C. Medina², Qi Guo³, yinhong chen³, Rhonda Chen³, Ying Zhang³, Ji Ma⁴, Jianxia Shi⁴, Jamie Wong⁴, gayathri swaminath³, Jonathan B. Houze¹. (1) Department of Therapeutic Discovery, Amgen Discovery Research, Cambridge, Massachusetts, United States (2) Department of Therapeutic Discovery, Amgen Research Discovery, South San Francisco, California, United States (3) Department of Metabolic Disorders, Amgen Research Discovery, South San Francisco, California, United States (4) Department of Pharmacokinetics & Drug Metabolism, Amgen Inc., South San Francisco, California, United States

Heart failure (HF) and related complications constitute a major health burden in developed countries. Despite considerable advances in recent decades, a clear unmet medical need for the development of novel treatment options for HF still exists. APJ receptor (APLNR) and its endogenous peptidic ligand (apelin) have been implicated as important modulators of cardiovascular function. However, the use of apelin peptides as therapeutic reagents is very challenging due to their short in vivo half-lives. Herein we report the discovery of a novel series of potent, selective, orally bioavailable small molecule agonists of APJ, exemplified by **AM-2995**, which improved cardiovascular function in rodent models.

MEDI 109

Chemical modification and structure activity relationship (SAR) evaluation of Fellutamide B

Nikita Acharekar¹, nikita.190492@gmail.com, **Sabesan Yoganathan**², yoganats@stjohns.edu. (1) Pharmaceutical Sciences, St. John's University, Jamaica, New York, United States (2) Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, St. Johns University, Jamaica, New York, United States

Fellutamides (A-F) belong to a unique class of lipopeptide drug leads. Fellutamide A and B were isolated from a marine fungus *Penicillium fellutanum*. Fellutamide B consists of a C-terminal aldehyde and an N-terminal acyl chain. These structural features are conserved among other members as well. Fellutamide B exhibits a broad

spectrum of activity, including antibiotic, antifungal and anticancer activities. More specifically, it has been shown that fellutamide B binds inhibits the proteasome, and causes cytotoxicity. To date, very limited SAR is known for this unique class of natural product. Hence we decided to investigate the SAR of various groups within this natural product, and test the analogs for anticancer and antibacterial properties. Our studies involved substitution of the N-terminus with three different simple unfunctionalized lipid chains (C10-C14), and substitution of the aldehyde moiety with different bioisosteres. The initial bioactivity evaluation indicates that three of the analogs containing C-14 lipid chain are active against Gram-positive bacteria (*S. aureus* and *S. epidermidis*). Current efforts are focused on derivatizing the C-terminal end and the N-terminal with various structural motifs to improve activity. We are also evaluating the anticancer activity of analogs generated.

MEDI 110

Tantalum oxide nanoparticles for use in contrast enhanced computed tomography

Taylor Lawson^{1,4}, tlawson@bu.edu, **Amit Patwa**², **Jonathan Freedman**¹, **Brian D. Snyder**^{3,2}, **Mark W. Grinstaff**². (1) Boston University, Boston, Massachusetts, United States (2) Boston Univ Dept of Chem, Boston, Massachusetts, United States (3) Orthopedic Surgery, Boston Children's Hospital, Boston, Massachusetts, United States (4) Center for Advanced Orthopedic Studies, Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States

Contrast enhanced computed tomography (CECT) is a widely used medical imaging technique that relies on the use of a contrast agent to provide enhanced visualization of tissues. We are evaluating a new positively charged tantalum-oxide nanoparticle (NP) based contrast agent for CECT assessment of cartilage health and integrity. Articular cartilage is a biphasic material comprised of a poroelastic collagen network coupled with a hydrated matrix of negatively charged sulfated and carboxylated glycosaminoglycans (GAGs). A decline in GAG content is an early sign of osteoarthritis (OA). To date, early diagnosis of OA remains nearly impossible. Tantalum oxide was incorporated into the core-shell of nanoparticles, with positively charged tetra-ammonium ligands to bind the anionic GAGs and a short polyethylene glycol shell layer to concur biocompatibility. The tantalum oxide (Ta_2O_5) core was formed by hydrolysis of tantalum (V) ethoxide, $Ta(OEt)_5$ and the size of the NPs was controlled by the amount of deuterated water and isobutyric acid added to n-propanol (Figure 1). We have successfully imaged naturally occurring osteoarthritic defects in *ex vivo* human metacarpal phalangeal joints using CECT and our nanoparticles. We will be presenting the use of these NPs to predict the biochemical and biomechanical state of cartilage, as GAG content correlates with mechanical performance of the tissue.

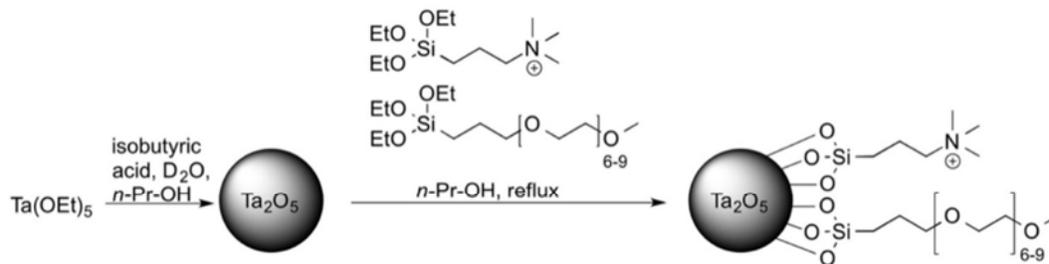


Figure 1. Synthesis of tantalum oxide nanoparticles with polyethylene glycol and tetra-ammonium ligands.

MEDI 111

Small molecule quinolinone derivatives that increase survival motor neuron protein via an SMN2 gene transcription enhancing mechanism

Dawid K. Fiejtek¹, fiejtek.d@husky.neu.edu, Jung-Eun Ahn¹, Anne Rietz², Hongxia Li², Elliot J. Androphy², Kevin J. Hodgetts¹. (1) Laboratory for Drug Discovery in Neurodegeneration, Brigham and Women's Hospital and Harvard Medical school, Boston, Massachusetts, United States (2) Dermatology, Indiana University School of Medicine, Indianapolis, Indiana, United States

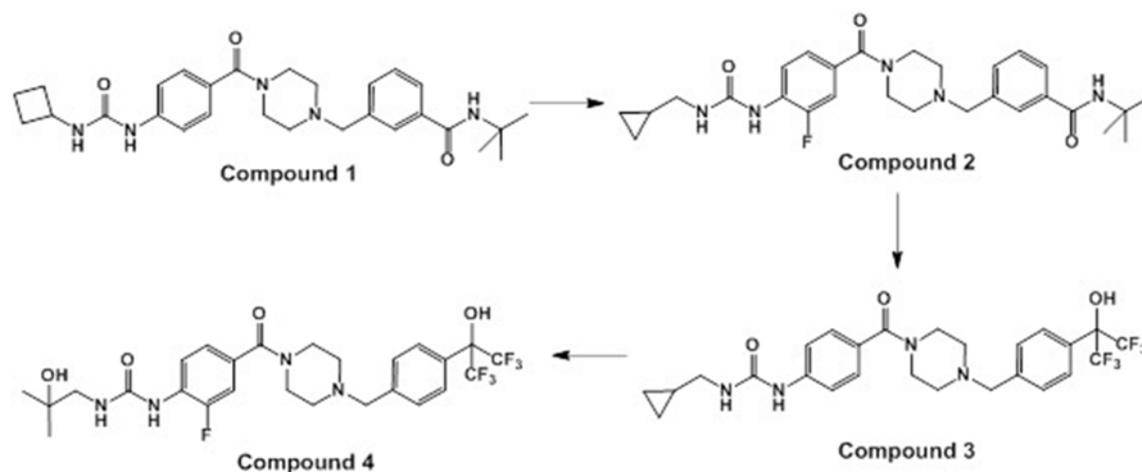
Spinal Muscular Atrophy (SMA) is a neurodegenerative disease that is the leading cause of infant mortality worldwide. SMA results from low levels of survival motor neuron (SMN) protein due to a mutation or deletion of the SMN1 gene. The SMN2 gene does not produce sufficient amounts of SMN protein to prevent SMA. In an effort to identify compounds that target the SMN2 gene during transcription or stabilize the SMN protein, a large library of small molecules was tested in an SMN2-luciferase assay. As a result, a 3,4-dihydro-4-phenyl-2(1H)-quinolinone derivative ($EC_{50} = 8.3 \mu\text{M}$) was identified as a hit compound that increased SMN protein *in vitro* and *in vivo*. A structure-analysis relationship (SAR) study was started to improve the activity of the hit compound. The most active analog from the SAR study (LDN-2391, $EC_{50} = 4.1 \mu\text{M}$) was racemic. Both enantiomers of LDN-2391 were separated by chiral column chromatography. One of the enantiomers (LDN-4301, $EC_{50} = 1.4 \mu\text{M}$) held all of the activity in the SMN2-luciferase assay, and the other enantiomer (LDN-4300) was inactive. The stereocenter of LDN-4301 was R, and this was determined via x-ray crystallography. The SAR study, to improve the activity and solubility of the new analogs, is in progress and will be reported here.

MEDI 112

Biostructural optimisation of a piperazine amide based series of Liver X Receptor (LXR) agonists

Andrew Cooke¹, andrew.cooke@merck.com, **Xavier Fradera**², **David J. Bennett**¹. (1) Merck, West Point, Pennsylvania, United States (2) Structural Chemistry, Merck, Boston, Massachusetts, United States

The Liver X Receptor (LXR)- α and - β isoforms are nuclear transcription factors that regulate a number of genes involved in lipid metabolism e.g. the ATP-binding cassette transporter A1 (ABCA1). ABCA1 is involved in the process of reverse cholesterol transport, where cholesterol is removed from plaques in the arterial wall, to form high density lipoproteins (HDL), which are transported to the liver for metabolism. As such, LXR agonists may offer therapeutic potential in the treatment of atherosclerosis. Our research program, aimed to use biostructural information to optimize a series of piperazine amide based LXR agonists. Compound 1 had low permeability (and low F%) and attempts were made to reduce the number of H-bond donors. Both the NH's of the urea H-bonded to Glu103 of LXR α and replacing either with a CH₂ led to ≥ 10 fold decrease in activity (and improved permeability). An alternative strategy was to introduce a halogen atom ortho to the aromatic NH (e.g. F in compound 2) which gave a >20 fold improvement in PAMPA permeability with comparable activity. Compound 2 was found to have an off target human acetylcholinesterase (hAChE) effect and SAR studies showed this was related to the t-butyl amide region. Attempts were made to alter this region and one approach was to hybridize with the literature LXR agonist T1317, which led to the potent LXR agonist 3, which was inactive at hAChE. Compound 3 suffered from poor solubility, and an isopropyl solvent molecule from a GW3965 structure, was inspiration to incorporate polar functionalities onto the alkyl group of the urea to give compounds like 4.



MEDI 113

Synthesis and evaluation of the metabolites of GLS362E, an anti-*Clostridium difficile* lead compound

Antonia Marashio, amarashio@worchester.edu, Bryan Urbina, Weichu Xu, Renata Lima. Chemistry, Worcester State University, Worcester, Massachusetts, United States

Clostridium difficile is a Gram-positive pathogenic anaerobe that has become a prime health concern worldwide in recent years. GLS362E, a compound that has shown highly selective anti-bacterial activity against *C. diff*, is a N7-substituted guanine derivative. This project focused on the synthesis, activity and the toxicity profile of the metabolite of GLS362E to enrich the preclinical package.

MEDI 114

Comparing and validating machine learning models for *Mycobacterium tuberculosis* drug discovery

Thomas Lane^{1,4}, tom@collaborationspharma.com, Daniel P. Russo^{1,2}, Kimberley M. Zorn¹, Alex Clark³, Alexandru Korotcov⁵, Valery Tkachenko⁵, Robert Reynolds⁶, Alexander L. Perryman⁷, Joel S. Freundlich⁸, Sean Ekins⁹. (1) Collaborations Pharmaceuticals, Inc, Raleigh, North Carolina, United States (2) The Rutgers Center for Computational and Integrative Biology, Rutgers University, Camden, New Jersey, United States (3) Molecular Materials Informatics, Inc, Montreal, Quebec, Canada (4) Biochemistry and Biophysics, University of North Carolina Chapel Hill, Chapel Hill, North Carolina, United States (5) Science Data Software, LLC, Rockville, Maryland, United States (6) Department of Medicine, Division of Hematology and Oncology, University of Alabama at Birmingham, Birmingham, Alabama, United States (7) Department of Pharmacology, Physiology and Neuroscience, Rutgers University-New Jersey Medical School, Newark, New Jersey, United States (8) Pharmacology & Physiology/Medicine, Rutgers University - NJMS, Princeton, New Jersey, United States (9) Collaborations Pharmaceuticals, Fuquay Varina, North Carolina, United States

Tuberculosis is a global health dilemma. In 2016, the WHO reported 10.4 million incidences and 1.7 million deaths. The need to develop new treatments for those infected with the causative bacterium *Mycobacterium tuberculosis* (*Mtb*) has led to many large-scale phenotypic screens and many thousands of new active compounds identified *in vitro*, with only a select few transitioning into clinical trials. With the emergence of multi-drug resistant (MDR) and extensively-drug resistant (XDR) strains, the need for new pharmacological intervention has become even more important. However, with limited funding, efforts to discover new active molecules against *Mtb* need to be more efficient. Several computational machine learning approaches have been shown to have improved enrichment and hit rates as compared to HTS. We have now curated small molecule *Mtb* data and developed new models using ECFP6 molecular descriptors with a total of 18,886 molecules with various activity cutoffs. These datasets were used to evaluate different machine learning methods and metrics, as well as to generate predictions for additional novel datasets curated post model development. A *Mtb* Bayesian model, containing combined *in vitro* and *in vivo* data, with a 100 nM activity cutoff, yielded the following metrics for five-fold cross validation: Accuracy = 0.88, Precision = 0.22, Recall = 0.91, Specificity = 0.88, Kappa =

0.31, and MCC = 0.41. We have also curated an evaluation set (n = 153 compounds), comprised of data from ten 2017 publications, and when used to validate our model it showed comparable statistics (Accuracy = 0.83, Precision = 0.27, Recall = 1.00, Specificity = 0.81, Kappa = 0.36, and MCC = 0.47). We have also compared these models with additional machine learning algorithms, showing Bayesian machine learning models constructed with literature *Mtb* data generated across labs were generally equivalent to or outperformed Deep Neural Networks with our external test sets. Finally, we have also compared our training and test sets to show they were suitably internally diverse and externally dissimilar using ECFP6 molecular fingerprints, demonstrating their usefulness as evaluation sets. Such *Mtb* machine learning models could help prioritize novel compounds for testing *in vitro* and *in vivo*.

MEDI 115

Selective sulfa drug acylations for antitubercular drug design

Michael J. Hearn¹, mhearn@wellesley.edu, Catherine Pugh¹, Michael H. Cynamon². (1) Wellesley Colg, Wellesley, Massachusetts, United States (2) Veterans Affairs Medical Center, Syracuse, New York, United States

Recent clinical reports on the unexpected effectiveness of sulfa drugs in combination therapy against *Mycobacterium tuberculosis* stimulated our interest in understanding better the potential relationships between sulfa structure and antimycobacterial activity. Sulfa drugs are susceptible to the deactivating action of arylamine N-acetyltransferases (NATs), enzymes endogenous within both patient and pathogen in tuberculosis. The metabolic products, N⁴-acetyl compounds, have lower antibacterial activities than their un-acetylated counterparts, compromising their role in effective chemotherapy. A potential strategy for the improvement of antimicrobial character emphasizes blocking the deactivating effects of NATs through changes in sulfa drug structure. In particular, Krebs had observed some time ago the unique behavior of sulfamethazine towards acetylating and de-acetylating enzymes. Using methods which we had previously developed for the chemical synthesis of NAT metabolites of sulfa drugs, we focused on the preparation of functionalized sulfamethazines as potential sources for drug discovery. In an example typical of the synthesis of our compounds, addition of valeric anhydride to a rapidly stirred slurry of sulfamethazine in valeric acid at 80°C, followed by further warming for an hour, readily led to the N⁴-valeroylated derivative (I, 78%), the structure of which was fully supported by spectrometric and elemental analysis data. Subsequent treatment of I with acetic anhydride in pyridine produced the N¹-acetyl-N⁴-valeroylsulfamethazine (II, 93%). The ability to strictly control the site and extent of acylation permits a considered study of the effects of blocking the action of NATs. Some of our materials have shown activity *in vitro* against the virulent experimental laboratory strain *M. tuberculosis Erdman*, with a representative minimum inhibitory concentration of 16 mg/mL for compound I. We conclude that further investigation will be warranted of the synthesis and antitubercular nature of these sulfa drug derivatives in combination therapy.

MEDI 116

Strained amine heterocycles as non-hydrolyzable β -lactam surrogates: Mechanistic probes for *Mycobacterium tuberculosis*

Sarah M. Scarry¹, sscarry@email.unc.edu, **Drew Cesta**¹, **Tigran Abramyan**¹, **Ben Gold**², **Landys Lopez Quezada**², **Kohta Saito**², **Dmitri Kireev**¹, **Selin Somersan Karakaya**², **Carl F. Nathan**², **Jeffrey Aube**¹. (1) *Chemical Biology and Medicinal Chemistry, University of North Carolina, Chapel Hill, North Carolina, United States* (2) *Microbiology Immunology, Weill Cornell Medicine, New York, New York, United States*

β -Lactam antibiotics are among the most valued drug classes and act via covalent inhibition of penicillin-binding proteins. Until recently, it was regarded that β -lactams were ineffective against *Mycobacterium tuberculosis* (*Mtb*), due to β -lactamase activity and the presence of transpeptidases in the cell wall. We have identified cephalosporin analogues active against *Mtb*; however, these compounds are unstable in mouse plasma. To probe this observation and develop structurally distinct analogues, we have prepared a library of benzazetidines containing features of our hit compounds. While benzazetidines and β -lactams both contain a highly strained four-membered nitrogen heterocycle, azetidines are not prone to covalent binding via the classic β -lactam ring-opening mechanism. A summary of our synthetic efforts and screening results against *Mtb* of this rare and underexploited heterocyclic scaffold will be presented.

MEDI 117

Synthesis of Pan-CMP mimics to inhibit CoaBC

Hailey Butman¹, haileybutman@gmail.com, **Xu Wang**¹, **Robert C. Brothers**¹, **Valerie Mizrahi**², **Joanna C. Evans**², **Erick Strauss**³, **Cynthia S. Dowd**¹. (1) *Chemistry, The George Washington University, Washington, District of Columbia, United States* (2) *MRC/NHLS/UCT Molecular Mycobacteriology Research Unit & DST/NRF Centre of Excellence for Biomedical TB Research, Institute of Infectious Disease and Molecular Medicine and Department of Pathology, Cape Town, South Africa* (3) *Dept of Biochem Stellenbosch U, Matieland, South Africa*

The increase in multidrug-resistant pathogens due to the overuse of antibiotics, as well as the lack of development of novel therapeutics, has presented an urgent need for the discovery of next-generation antibacterial agents. The enzyme cofactor CoA plays an essential role in the biosynthesis of fatty acids and the generation of energy. The significant differences between microbial and mammalian CoA biosynthesis pathways make it an attractive target for drug development. In *Mycobacterium tuberculosis* (*Mtb*), CoA precursor pantothenate (Pan) is synthesized by PanB, PanC, PanD, and PanE. In the second stage of biosynthesis, Pan is converted to CoA in five steps that are catalyzed by PanK, CoaBC, CoaD, and CoaE enzymes. It was recently shown that, of all the enzymes in the pathway, depletion of only CoaBC resulted in bactericidal activity, while the depletion of other enzymes was only bacteriostatic. The importance of CoaBC

in prokaryotic metabolism leads to the hypothesis that inhibitors of CoaBC will disrupt CoA synthesis and kill bacterial cells. Bacterial CoaBC is bifunctional and contains both phosphopantothienoylcysteine synthetase (PPCS) and phosphopantothienoylcysteine decarboxylase (PPCDC) activities. Together, these activities catalyze the transformation of 4'-phospho-pantothenic acid (P-Pan) into 4'-phospho-pantetheine (P-PantSH). This reaction proceeds through formation of the reactive 4'-phospho-pantothienoyl-CMP (Pan-CMP) intermediate. Mimics of Pan-CMP have been synthesized as inhibitors of CoaBC. This family of compounds has the potential to further validate CoaBC as a new antitubercular drug target.

MEDI 118

Synthesis and antimycobacterial activity of new *N*-oxide compounds active against multi-resistant tuberculosis

*Paula C. Souza*¹, *Guilherme F. Fernandes*¹, *Leonardo B. Marino*¹, *Camila M. Ribeiro*¹, *Patricia B. da Silva*¹, *Marlus Chorilli*¹, *Caio S. Siva*¹, *Debbie M. Hunt*², *Luis Pedro S. de Carvalho*², *Carlos Alberto d. Costa*³, *Sang H. Cho*⁴, *Yuehong Wang*⁴, *Scott G. Franzblau*⁴, *Chung ManChin*¹, *Fernando R. Pavan*¹, **Jean L. Dos Santos**¹, *santosjl@fcar.unesp.br*. (1) State University of São Paulo - School of Pharmaceutical Science, Araraquara, São Paulo, Brazil (2) Mycobacterial Metabolism and Antibiotic Research Laboratory, The Francis Crick Institute, London, United Kingdom (3) São Paulo State University (UNESP), School of Odontology, Araraquara, São Paulo, Brazil (4) Institute of Tuberculosis Research, University of Illinois at Chicago, Chicago, Illinois, United States

According to World Health Organization, the *Mycobacterium tuberculosis* (Mtb), the causative agent of tuberculosis (TB), caused 9.6 million of new cases and 2 million deaths worldwide in 2015. The current treatment for drug-sensitive TB recommends a combination of isoniazid (INH), rifampicin (RMP), ethambutol, and pyrazinamide for 6 months; however, this same treatment is not effective against multidrug-resistant TB (MDR-TB) and extensively drug resistant (XDR-TB). Therefore, the search for safe and effective new drugs against resistant strains is urgent. Here, the synthesis and evaluation of 1,2,5-oxadiazole 2-*N*-oxide using drug-sensitive Mtb and MDR-TB strains were characterized. The compounds exhibited MIC₉₀ values ranging from 0.40 - 0.43 µM against Mtb H37Rv strain in active state. Three compounds have shown activity against latency state with MIC₉₀ values ranging from 2.0 - 7.7 µM. The cytotoxicity assay against MRC-5 cell line have shown IC₅₀ values ranging from 854 - 1281 µM and selective index from 2033 - 3204, respectively. All these 3 compounds also demonstrated activity against Mtb mono-resistant strains for the main drugs available in the therapy. The most active compound (4c), exhibited bactericidal activity in time-kill experiments performed for up to 15 days. Specifically, this compound reduced the initial inoculum ($6.73 \pm 0.18 \text{ Log}_{10}\text{UFC.mL}^{-1}$) sharply until the seventh day and maintained $1 \text{ Log}_{10}\text{UFC.mL}^{-1}$ by the fifteenth day, being more active than the first line drugs INH and RMP. Bioavailability studies using Balb/c mice have shown that plasma containing compound 4c administered at 300 mg/Kg/body inhibited Mtb H37Rv strains in active

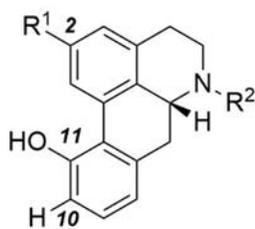
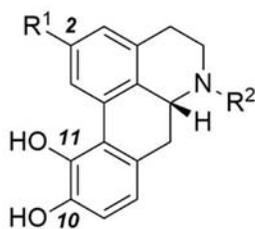
state. In the time 2h, it was observed a inhibition of 46% of Mtb load, while for RMP that value was found as being 76%. Animals infected with Mtb were treated during 20 days orally with compound 4c (200 mg / Kg/ body weight) by once-daily dosing. It was observed absence of Mtb in the lung of all animals treated with 4c. This effect was not observed for RMP. Preliminar toxicological analysis reveals that compound 4c is not mutagenic and genotoxic. In addition, biochemical parameters did not suggest liver and kidney toxicity for animals treated with this compound. All these data suggested that the *N*-oxide compound (4c) is a new compound active against MDR-TB and could be a new therapeutic alternative against resistant strains.

MEDI 119

Development of high affinity agonist ligands for the D2 receptor: Potential PET imaging agents

Aniq Nurani¹, nuraniqiq@gmail.com, **Yulong Xu²**, **Anna W. Sromek³**, **John L. Neumeyer¹**. (1) Medicinal Chemistry, McLean Hospital, Boston, Massachusetts, United States (2) Harvard Medical School, McLean Hospital, Belmont, Massachusetts, United States (3) McLean Hospital, Belmont, Massachusetts, United States

The dopaminergic system is one of the most important neurotransmitter systems in the brain. Among the different receptors and transporters, the D2 receptor is especially important: dysfunction of this receptor is involved in several neurological disorders, including Parkinson's disease, schizophrenia, drug abuse, and others. It is hypothesized that in these disorders, a higher proportion of D2 receptors are found in the active, or high-affinity state. Positron emission tomography (PET) is a valuable tool for noninvasive investigation of changes in the dopaminergic system *in vivo*. It is hypothesized that in contrast to antagonist ligands, **agonist** ligands would be more sensitive to changes in endogenous concentrations of dopamine *in vivo*. Thus, our goal is to develop high affinity, highly selective agonist ligands for the D2 receptor. Based on previous structure-activity relationship studies, the substituent at position 2 has a significant influence on the binding affinity and selectivity for the D2 receptor. Thus, a novel series of fluorinated catechol and 11-hydroxy aporphines, potential agonist ¹⁸F-radioligands for imaging the D2 receptor in the living brain, will be presented. Their synthesis, affinities for dopamine receptors, and structure-activity relationships will be discussed.



MEDI 120

Pharmacophore models for inhibitors of DNA methyltransferases

*Javier Ruiz-Rios, Fernanda I. Saldívar-González, **Jose L. Medina-Franco**, jose.medina.franco@gmail.com. Universidad Nacional Autonoma de Mexico, Scottsdale, Arizona, United States*

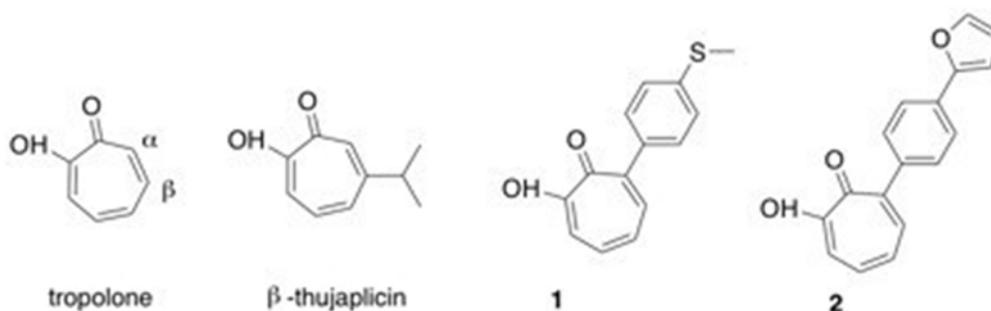
Methylation of DNA is an important mechanism in epigenetic regulation. There is a large body of evidence that dysregulation of DNA methylation is associated with cancer and other diseases. As such, identification and development of DNMT inhibitors (DNMTi) is increasingly attractive to develop epi-drugs. Several DNMTi have been identified and there are a number of studies aimed at exploring systematically their structure-activity relationships and explain the mode of action at the molecular level. In this work, we discuss advances in the computer-guided elucidation of pharmacophoric points of DNMTi. The models were build based on literature information and docking models for known inhibitors. The pharmacophores generated are valuable to advance the understanding of structure-activity relationships of DNMTi, and aid in the virtual screening of compound data sets.

MEDI 121

Alpha-substituted tropolones as potential anti-blood cancer therapeutics

Jin Li, jin.li@uconn.edu, Eric Falcone, Dennis Wright, Andrew J. Wiemer. Pharmaceutical Sciences, University of Connecticut, Storrs, Connecticut, United States

Tropolones are seven-membered non-benzenoid aromatic compounds with a propensity for metal binding. Naturally occurring tropolones, such as beta-thujaplicin (aka hinokitiol) are found to exhibit antiproliferative effects. We synthesized a library of alpha-tropolone derivatives, including alkyl chain series, para-substitutions on the phenyl ring, meta- substitutions on phenyl ring and non-phenyl based tropolone. We screened these alpha-tropolone derivatives towards a panel of blood cancer cell lines, including T cell, B-cell and myeloid malignancies based on cell viability assays. The tropolones appear to be a preference towards cancer cells of T-cell lineage, especially Molt-4 cells with a sub-micromolar GI₅₀. We further studied the potential cellular mechanism of the anti-proliferative effect of two potent alpha-tropolone derivatives. Both compound **1** and **2** upregulate p53. Caspase inhibition using a pan caspase inhibitor Z-VAD-FMK prevents the tropolone-induced anti-proliferative effect. Alpha-substituted tropolones can be potentially used for the development of novel anti-blood cancer agents.



MEDI 122

HIV protease as a target for novel antiretroviral therapies

Ian W. Windsor^{1,2}, iwindsor@mit.edu, **Brian Gold**^{1,3}, **Dawn M. Dudley**⁴, **Brian Graham**^{1,3}, **Michael J. Palte**⁵, **John C. Lukesh**³, **Thomas P. Smith**³, **Katrina T. Forest**⁶, **David H. O'Connor**⁴, **Ronald T. Raines**^{1,2}. (1) Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States (2) Biochemistry, University of Wisconsin-Madison, Madison, Wisconsin, United States (3) Chemistry, University of Wisconsin-Madison, Madison, Wisconsin, United States (4) Pathology and Laboratory Medicine, University of Wisconsin-Madison, Madison, Wisconsin, United States (5) Molecular & Cellular Pharmacology Graduate Training Program, University of Wisconsin-Madison, Madison, Wisconsin, United States (6) Bacteriology, University of Wisconsin-Madison, Madison, Wisconsin, United States

The treatment of HIV/AIDS remains a challenge. Despite 30 years of breakthroughs, a cure remains elusive. Integrating ideas and methods from structural biology, enzymology, medicinal chemistry, protein engineering, and virology has led us to several novel strategies directed at the HIV-1 protease.

We have solved the first crystal structure of the HIV-1 protease in a complex with a substrate optimized by phage display. Our structure reveals unprecedented side-chain hydrogen-bonding interactions. By analyzing this and other co-crystal structures, we have discovered an unappreciated stereoelectronic effect (namely, an n -to- π^* interaction) within the substrate that has important implications for both the enzymatic reaction mechanism and drug design.

We have also created a derivative of a clinical HIV-1 protease inhibitor with greatly enhanced potency. By considering co-crystal structures, we have enabled darunavir to form additional hydrogen bonds with the enzymic S2' subsite. The key is replacing the aniline moiety of darunavir with a phenylboronic acid. The new ligand has a 20-fold greater affinity for the wild-type protease than does darunavir and maintains high affinity for a protease variant with a drug-resistance substitution in the S2' subsite.

Even the best protease inhibitors are susceptible to drug resistance. We have developed an alternative strategy that relies on the *activity* of the protease rather than on its inhibition. To do so, we used an intein to form a cyclic zymogen of an otherwise

cytotoxic ribonuclease. Catalysis by HIV-1 protease restores wild-type activity, and emerging data suggest that our zymogen can be prophylactic for HIV-1 infection.

These approaches could advance the treatment of HIV/AIDS and, potentially, other retroviral infections.

MEDI 123

Structure-based design, synthesis, evaluation and x-ray crystal structure analysis of HIV-1 protease inhibitors with modified P1, P1' and P2' groups

Linah Rusere¹, linah.rusere@umassmed.edu, Akbar Ali¹, Gordon L. Lockbaum¹, Sook-Kyung Lee², Ronald Swanstrom², Celia A. Schiffer¹. (1) Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, Massachusetts, United States (2) Department of Biochemistry and Biophysics, and the UNC Center for AIDS Research, University of North Carolina, Chapel Hill, North Carolina, United States

Currently approved HIV-1 protease inhibitors are prone to drug resistance due to the rapid evolution of HIV. Darunavir (DRV) has shown great promise in the treatment of drug resistant HIV, but emerging resistance strains are challenging its efficacy. We have developed a substrate envelope guided strategy to rationally design HIV-1 protease inhibitors with improved potency and resistance profiles. This strategy together with insights from detailed structural analysis of protease-inhibitor complexes led to the design of new inhibitors with high potency against highly resistant strains of HIV. Here, we describe the substrate envelope guided design, synthesis, biological evaluation, and X-ray crystal structure analysis of a series of novel HIV-1 protease inhibitors. The inhibitors were designed by incorporating key features of DRV and other FDA approved HIV-1 protease inhibitors with variable P1, P1' and P2' moieties. The SAR data and molecular insights from X-ray crystal structures may allow further optimization of this novel series of HIV-1 protease inhibitors.

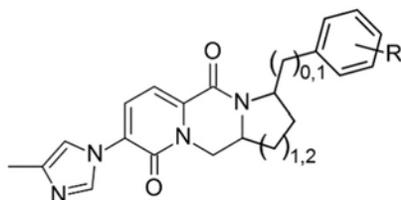
MEDI 124

Design and synthesis of novel tricyclic 3,4-dihydro-2H-pyrido[1,2-a]-pyrazine-1,6-dione derivatives as gamma-secretase modulators

François Bischoff², fbischof@its.jnj.com, Frans Van den Keybus³, Frederik Rombouts², Marc Mercken¹, Harrie Gijssen². (1) Neuroscience Biology, Janssen Research & Development, Janssen, Beerse, Belgium (2) Neuroscience Medicinal Chemistry, Janssen Research & Development, Turnhout, Belgium (3) Neuroscience Medicinal Chemistry/ Janssen research |Development, Janssen, Turnhout, Belgium

Alzheimer's disease (AD) is a devastating, progressive neurodegenerative disease, which remains one of the principal unmet medical needs, being the third highest cause of death after cancer and heart disease. Genetic mutations promoting the proteolytic

processing of the amyloid precursor protein (APP) by β - or γ -secretase (GS) are believed to be responsible for the rapid onset of the disease and their study has provided the genetic framework for the amyloid hypothesis. GS modulation has been proposed as a potential disease modifying anti-Alzheimer's approach. In contrast to γ -secretase inhibitors (GSIs), γ -secretase modulators (GSMs) cause a product shift from the longer amyloid isoforms to shorter, more soluble and less amyloidogenic isoforms, without inhibiting NOTCH proteolytic processing. Potent GSMs, from different chemicals classes, have been reported recently. Typically, these compounds are characterized by high lipophilicity and high molecular weight, properties that have been associated with low probability of success in clinical development. We have disclosed in the past series of pyridopyrazine-1,6-dione derived GSMs with improved properties such as a lower lipophilicity, higher solubility, higher sp^3 character, resulting in compounds with higher free fraction. We will report the design, the synthesis and some pharmacological properties of a novel series of tricyclic 3,4-dihydro-2H-pyrido[1,2-a]-pyrazine-1,6-dione derivatives, in which the active conformation has been locked through an extra cyclisation.



MEDI 125

Enterovirus inhibitory activity of substituted urea and thiourea derivatives of *p*-benzene sulfonamide

Prashant Chakrasali^{1,2}, prashant@kRICT.re.kr, Han Soo Bong^{1,2}, Young-Sik Jung^{1,2}. (1) Division of Bio and Drug Discovery, Korea Research Institute of Chemical Technology, Daejeon, Korea (the Republic of) (2) Department of Medicinal and Pharmaceutical Chemistry, University of science and Technology, Daejeon, Korea (the Republic of)

A series of substituted urea, thiourea and amide derivatives of *p*-Benzene sulfonamide were prepared with one or two methylene group/s as linker between them. These were tested for their inhibition property against hRV-A and hRV-B. Some of the compounds synthesized have sub-micro molar range of activity against hRV-14 and hRV-71 and moderate activity against hRV-21 with low cytotoxicity and high selectivity index values. Docking, initial time of addition experiment and replicon assay reveals that these are capsid binding inhibitors.

MEDI 126

Design and synthesis of some novel 6,7-dimethoxyquinazoline analogs as multi-target-directed ligands for the treatment of hypertension

Rahul B. Ghuge, *ghuge.rahul2007@gmail.com*, Neetesh Agrawal, Bhiku Pithwa, Atul Khadse, Prashant R. Murumkar, Mange Ram Yadav. Faculty of Pharmacy, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India

As per WHO reports, cardiovascular diseases are the major cause of deaths globally. Hypertension, the major trigger for the CVDs, turns out to be the most common chronic diseased state affecting one in three adults in U. S. and about >1 billion population worldwide. Almost half of this population exhibits resistant hypertension and fails to achieve their BP targets. Hypertension remains the most prevalent problem although many treatments including combination of three or more antihypertensive agents are available for the management of hypertension. Therefore there is an urgent need of new antihypertensive treatments involving multi-target-directed ligands to target a broader patient population. Blood pressure and fluid balance in the body are regulated by both sympathetic nervous system (SNS) and renin-angiotensin system (RAS). SNS is activated through the adrenoceptors whereas RAS acts through the angiotensin II (All) receptors. α_1 - and AT_1 -receptors predominantly cover the major part of adrenoceptors and All receptors, respectively. Simultaneous antagonism on these two targets would be an effective approach to control the elevated BP. With this goal in mind, efforts were made to develop some multi-target-directed ligands having dual α_1 - and AT_1 -receptors antagonistic activity. In this direction, series of 6,7-dimethoxyquinazoline derivatives as multi-target-directed ligands have been designed, synthesized and evaluated for their α_1 - and AT_1 -receptors antagonistic activity. Interestingly, among all the synthesized derivatives, the most potent compound showed dual antagonism on both α_1 - and AT_1 -receptors (pA_2 for $\alpha_1 = 7.82$ and $AT_1 = 7.99$), comparable to the standard drugs terazosin and losartan.

MEDI 127

Synthesis and characterization of ibuprofen and diclofenac prodrugs

Jeffin J. James, *ja1305609@qu.edu.qa*, Hani D. Tabbal, Yousef M. Hijji. Department of Chemistry and Earth Sciences, Qatar University, Doha, Qatar

Prodrug synthesis is an approach that proved to be a good approach among strategies for improving drugs towards solving problems associated with their Solubility, Bioavailability, Stability, taste, or drug formulation. The method is developed to include synthesis of polymer- based prodrugs for sustained release of drugs.

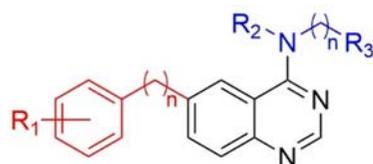
In this work, the parent drug (**Ibuprofen** or **Diclofenac**) carboxylic group is changed to the acid halide, followed by reaction with selected alcohol or amine. The produced respective esters or amides are fully identified using various spectroscopic techniques.

MEDI 128

4,6-Disubstituted quinazoline derivatives as inhibitors of the MEK5/ERK5 pathway

Saloni Patel¹, patels4@duq.edu, Austin J. Motta¹, Patrick T. Flaherty¹, Akshita Bhatt², Thomas Wright², Jane Cavanaugh². (1) Medicinal Chemistry, Duquesne University, Pittsburgh, Pennsylvania, United States (2) Pharmacology, Duquesne University, Pittsburgh, Pennsylvania, United States

The mitogen-activated protein kinase pathway (MAPK) is a three-tiered signal transduction pathway which involves sequential phosphorylation of interrelated serine/threonine and tyrosine protein kinases. In this pathway, the mitogen-activated protein kinase kinase (MAP2K or MEK) phosphorylates and activates an extracellular signal-regulated kinase (ERK) which in turn activates transcriptional factors to mediate important cellular functions like growth, division, and differentiation. Out of seven isoforms of MEK, MEK1 and 2 are extensively studied. However, increased expression of the less studied MEK5/ERK5 pathway is reported in various types of cancers, especially in triple negative breast cancer (TNBC). It was regarded as useful to develop selective MEK5 inhibitors as a pharmacological tool to understand the role of MEK5 in various biological processes relevant to TNBC. The quinazoline core has been suggested to bind to the hinge region of the ATP site of MEK5. *In-silico* docking studies, with a homology model of MEK5, permitted rational design of quinazoline derivatives as selective MEK5 inhibitors. Various aryl/alkyl substitutions at the C-6 of the quinazoline core have been synthesized using Suzuki/modified Suzuki reactions. A variety of amine derivatives have been substituted at C-4 of the quinazoline core. These derivatives were tested in breast cancer cell lines using western blot analysis. Inhibition of MEK5 and selectivity against MEK1/2 was evaluated by quantitation of pERK5 and pERK1/2. Our efforts resulted in the identification of promising leads for further optimization.



n= 0-2; **R**₁= alkyl or fused aryl; **R**₂= alkyl;
R₃= heterocyclic ring, phenyl, or substituted phenyl ring

MEDI 129

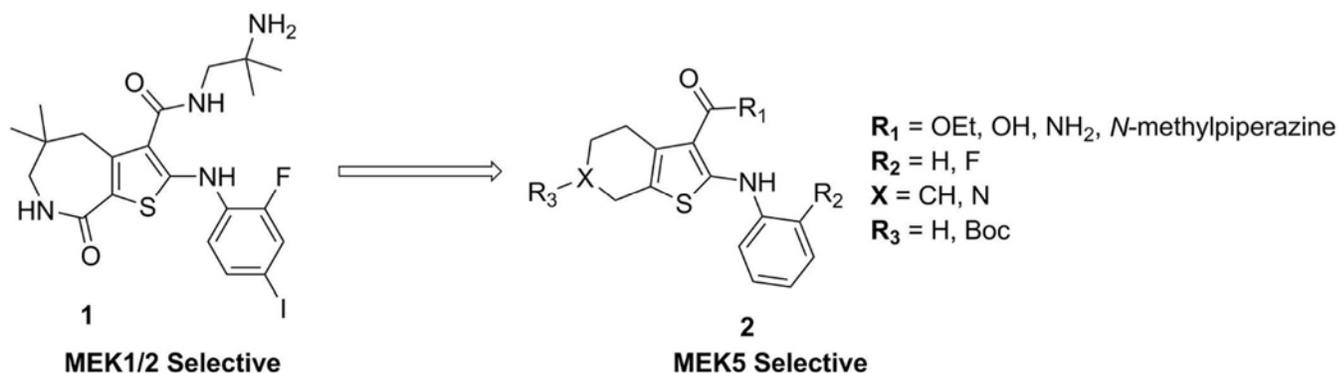
Selective allosteric inhibition of MEK5: novel target for cancer therapeutics

Mohit Gupta¹, guptam@duq.edu, Dhruv Shah¹, Patrick T. Flaherty¹, Thomas Wright², Akshita Bhatt², Jane Cavanaugh². (1) Medicinal Chemistry, Duquesne University, Pittsburgh, Pennsylvania, United States (2) Pharmacology, Duquesne University, Pittsburgh, Pennsylvania, United States

Mitogen-activated protein kinase kinase 5 (MEK5) is a component of mitogen-activated protein kinase (MAPK) signaling pathways. Mitogen-activated protein kinase kinase 2 (MEK2) activates MEK5, which in turn activates Extracellular signal-

Regulated Kinase (ERK5) forming a three-tiered phosphorylation cascade. Activated pERK5 activates transcription factors to increase cell proliferation, cell growth, cell differentiation, and angiogenesis. MEK5/ERK5 signaling is upregulated in various cancers, such as breast cancers, prostate cancers, and colon cancers; hyper-activation of MEK5 is correlated with poor prognosis for these cancers. Despite this strong correlation, selective MEK5 inhibitors have remained under-explored.

Using the x-ray crystal structure of MEK1 (PDB: 3SLS) bound to inhibitor **1**, a homology model of MEK5 was constructed. Based on the homology model and the previous SAR knowledge, series of thiophene analogs were designed for selective allosteric inhibition of MEK5. The design, synthesis, and biological activity will be presented.



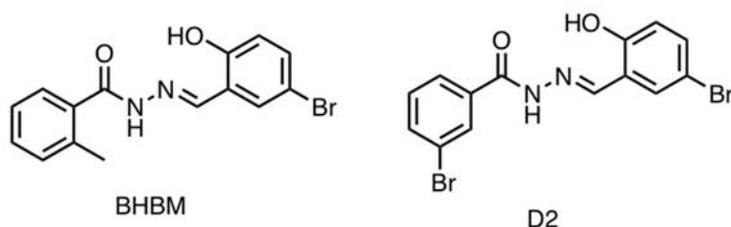
MEDI 130

SAR study of novel heterocyclic acylhydrazones as anti-fungal agents targeting the synthesis of fungal GlcCer

Yi Sun¹, yi.sun@stonybrook.edu, **Krupanandan H. Haranahalli**², **Cristina Lazzarini**³, **Maurizio D. Poeta**³, **Iwao Ojima**^{1,2}. (1) Chemistry Department, Stony Brook University, Stony Brook, New York, United States (2) Institute of Chemical Biology & Drug Discovery, Stony Brook, New York, United States (3) Molecular Genetics and Microbiology, Stony Brook University, Mount Sinai, New York, United States

During the last decade, fungal infections have been considered an increasing threat to human health. Despite the increasing need for efficient antifungal treatments, therapeutic options are still limited. The close relation between fungal and mammalian cells imposes a challenge for the development of new anti-fungal drugs. Recently, fungal sphingolipids have emerged as a potential target for new antifungals, because their biosynthesis in fungi is structurally different than that in mammals. Besides, some fungal sphingolipids play an important role in the regulation of virulence in a variety of fungi. Based on our previous SAR study, BHBM and D2 were found to be highly effective *in vitro* and *in vivo* against several pathogenic fungi. These two aromatic acylhydrazones were able to target the synthesis of sphingolipids, affect fungal cell morphology, and exhibit strong antifungal activity *in vitro* and *in vivo*. These results clearly indicate that BHBM and D2 would provide a good starting point for the discovery of next-generation antifungal agents. As our systematic approach to drug discovery and

development, a new library of heteroaromatic acylhydrazones was designed, synthesized, and evaluated for their activity against *C. neoformans*. Then, a number of these novel compounds were found to be more potent than BHBM/D2, and fungicidal with excellent *in vitro* killing activities. The chemistry, biological evaluations and SAR of these novel acylhydrazones will be presented.



MEDI 131

1H-pyrrolo[3,2-b]pyridine GluN2B-selective NMDA antagonists

Aki Soyode-Johnson, asoyode@its.jnj.com. Neuroscience Chemistry, Janssen, San Diego, California, United States

NMDA receptors are part of the glutamatergic network of neurotransmission and consist of four sub-units surrounding a cation-selective pore. Three major subtypes of these sub-units have been described: GluN1, GluN2A-D and GluN3A-B. Proof-of-concept clinical trials have shown GluN2B-selective NMDAR antagonists to be therapeutic in treatment-resistant depression. Consequently, medicinal chemistry efforts for the GluN2B program at Janssen were initiated with the goal of identifying a novel and selective GluN2B antagonist with putative therapeutic use in treatment resistant depression. This poster describes a new series of GluN2B-selective antagonists containing a 1H-pyrrolo[3,2-b]pyridine core. SAR of the 1- and 6-positions, as well as *in vitro* data such as metabolism, permeability, solubility and selectivity against related targets is presented. Good brain penetration and receptor occupancy was measured for select compounds and their *ex vivo* rat brain autoradiography data is described.

MEDI 132

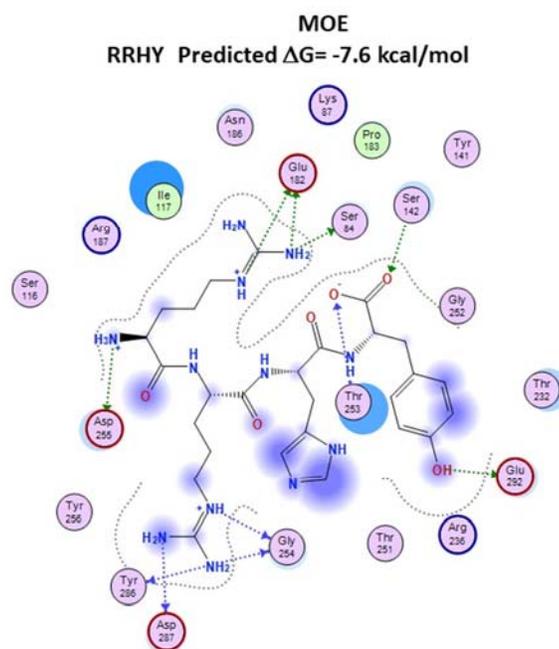
Discovery of linear and cyclic tetrapeptides inhibitors of Y-49 β -lactamase by structure-based drug design (SBDD) and molecular docking platforms empowered by MOE, AutoDock Vina and StarDrop-ADMET (Optibrium) module

Janet Gonzalez¹, **Cristina C. Clement**², clement.cristina624@gmail.com. (1) Natural Sciences, LaGuardia Community College, Long Island City, New York, United States (2) Pathology Chemistry, Albert Einstein Coll Med CUNY, Bronx, New York, United States

The hydrolysis of β -lactam drugs by β -lactamases is a highly-effective resistance mechanism to β -lactam antibiotics. One of the most powerful approach developed to overcome this resistance involves the discovery of new non β -lactam scaffolds inhibitors

of β -lactamases. Herein we report a structure-based drug design (SBDD) approach for the discovery of potential linear and cyclic peptides inhibitors of the Y-49 enzyme, a class A beta-lactamase, from *Mycobacterium tuberculosis*. A tetrapeptide pharmacophore scaffold was derived from the original sequence RRGHYY that was discovered to inhibit class A *Bacillus anthracis* Bla1, ($K_i = 42 \mu\text{M}$). *In silico* docking experiments were performed with *Autodock Vina* (Scripps Institute, USA) coupled with MOE (Chemical Computing Group, Canada) and StarDrop-ADMET module (Optibrium, UK). The beta-lactamase 3M6B.pdb was used as target protein while tetrapeptides with the sequence space [2HN-R-X-H-Y-COOH] were docked as potential active site directed, competitive inhibitors. X was varied with all 20 natural L- amino acids. New lead discovered linear tetrapeptides emerged from the *in vitro* screening of their ability to inhibit the recombinant Y-49 β -lactamase-mediated hydrolysis of nitrocefin substrate. Notably, dRRHY, dRGHY and dRVHY (where “d” defines the D-isomer) exhibited low micromolar K_i (5-0.7 μM). In most cases the replacement of L-isomer of Arg at the N-terminus with the D-isomer (dR) resulted in at least a two-fold enhanced inhibitory activity. In addition, the optimized SBDD approach enabled the expansion of the pharmacophore space and lead to the discovery of cyclo [RRHY] tetrapeptide that had at least six-fold higher affinity for the Y-49 β -lactamase than its linear sequence analogue (K_i of 1.9 μM for the cyclo [RRHY] analogue). AutoDock Vina and MOE provided statistically significant correlation ($p < 0.05$) between the experimental and *in silico* predicted free energy of interaction between the binders and the target protein (Pearson “r” coefficients ≥ 0.6). Consequently, our SBDD approach enabled the discovery of novel peptides with d- and unnatural amino acids with improved affinity for Y-49 β lactamase.

#	Fav	Peptide sequence	StarDrop-ADMET (Optibrium)										
			Estimated Affinity				LLE	LE	Tor.	MW	LogP	TPSA	2C9 pKi
			pM	nM	μM	mM							Optibrium
18	☆	RVH_18							575	-5.49	270.0		4.805
11	☆	RMH_11							607	-5.40	270.0		4.897
6	☆	RGH_6							533	-6.52	270.0		4.974
9	☆	RKH_9							605	-6.74	297.6		4.635
10	☆	RLH_10							589	-5.10	270.0		4.712
12	☆	RNH_12							590	-7.28	313.1		4.959
13	☆	RPH_13							573	-5.64	261.2		4.787
5	☆	RFH_5							623	-4.91	270.0		5.028
16	☆	RSH_16							563	-7.16	290.2		4.960
4	☆	REH_4							604	-7.62	310.1		4.729
19	☆	RWH_19							662	-4.43	285.8		5.169
3	☆	RDH_3							590	-8.01	310.1		4.959
1	☆	RAH_1							547	-6.13	270.0		4.987
20	☆	RVH_20							639	-5.20	290.2		5.097
17	☆	RTH_17							577	-6.77	290.2		4.973
7	☆	RHH_7							613	-6.18	298.7		5.053
15	☆	RRH_15							633	-9.02	336.0		4.784
2	☆	RCH_2							579	-5.84	270.0		5.003
14	☆	RQH_14							604	-6.89	313.1		4.729

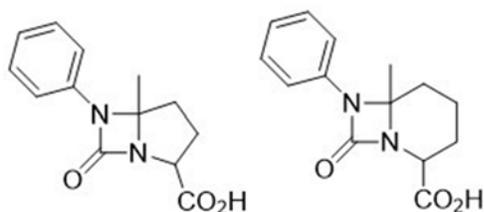


MEDI 133

Strategies for synthesis of various aza- β -lactam derivatives as potential β -lactamase inhibitors

Jonathan Fifer, jpf1012@wildcats.unh.edu, Marc A. Boudreau. Department of Chemistry, University of New Hampshire, Durham, New Hampshire, United States

With the growing global problem of antibiotic resistance, the search for new potential treatment options has been the focus of many research groups. One strategy to overcome this problem is to develop compounds that will inhibit the β -lactamase enzymes, which hydrolyze β -lactam antibiotics. By targeting these enzymes, the traditional β -lactam antibiotics will be able to function as normal. From many years of research, some compounds have shown promising inhibition towards β -lactamase and have even become commercially available. The β -lactamase inhibitor is paired with the traditional β -lactam antibiotic. This prevents hydrolysis of the β -lactam and allows it to attack the bacteria. Unfortunately, there are only a handful of clinically-used inhibitors of β -lactamases, and resistance to them has developed. Compounds containing an aza- β -lactam ring are hypothesized to be potential inhibitors of β -lactamases. In contrast to the β -lactam, an aza- β -lactam contains a second nitrogen atom in the lactam ring. Upon nucleophilic attack by the β -lactamase, the resulting acyl-enzyme intermediate (a carbamate) is expected to be more hydrolytically stable than the corresponding acyl-enzyme intermediate of a β -lactam (an ester) due to the increased resonance stabilization afforded by the nitrogen. Several strategies have been explored to synthesize a library of compounds that contain the aza- β -lactam ring, to then be tested for β -lactamase inhibitory activity. These approaches include both traditional batch chemistry and of flow chemistry.



MEDI 134

Development of thiol containing open lactam analogues targeting metallo-beta-lactamases

Marie-Josiane Ohoueu, mo1038@wildcats.unh.edu, Marc A. Boudreau. Department of Chemistry, University of New Hampshire, Durham, New Hampshire, United States

A majority of the population worldwide has been affected by bacterial infections at some point in their life. Although a portion of those infections are treatable, many have contracted bacterial infections for which an appropriate treatment is not yet available. In

the United States alone it has been reported that at least 2 million people are infected by drug resistant bacteria every year. Among those, an average of 23,000 end up dying as a direct consequence of their contracted infection. Bacteria acquire resistance by exhibiting various mechanisms including the production of enzymes such as β -lactamases, which are capable of breaking down and inactivating β -lactam antibiotics. The proposed research involves the synthesis of compounds which would enhance the potency of antibiotics to treat infections caused by resistant bacteria. These compounds would act as inhibitors of metallo- β -lactamase enzymes (MBLs), a sub-class of β -lactamases found in several clinically difficult to treat bacteria that are responsible for widespread β -lactam antibiotic resistance. It has been a challenge to inhibit MBLs due to their mechanism of action, and few approaches have been successful up to this day. The inhibitors to be synthesized contain specific functionalities such as a thioacid acid group (-COSH) and a strained 3-membered ring (thiirane or epoxide) to be introduced using organic synthesis methods. These are proposed to lead to irreversible binding of the inhibitors to the MBLs and prevent the antibiotics administered to be inactivated. Our target molecules, for which the initial synthetic steps have been achieved, will provide a better understanding of the enzyme mechanism and highlight future approaches to be taken to overcome antibiotic resistance.

MEDI 135

Synthesis and structure-activity relationships of quinolinone and quinoline-based P2X7 receptor antagonists and their anti-sphere formation activities in glioblastoma cells

Seung-Hwa Kwak², Bongki Ko¹, evitasky@gist.ac.kr, WooChan Kim¹, Jeheon Lee¹, Jae H. Jung¹, Yong-Chul Kim¹. (1) School of Life Sciences, GIST, Gwangju, Korea (the Republic of) (2) Chemistry, Duke University, Durham, North Carolina, United States

Screening a compound library of quinolinone derivatives identified compound **11a** as a new P2X7 receptor antagonist. To optimize its activity, we assessed structure-activity relationships (SAR) at three different positions, R₁, R₂ and R₃, of the quinolinone scaffold. SAR analysis suggested that a carboxylic acid ethyl ester group at the R₁ position, an adamantyl carboxamide group at R₂ and a 4-methoxy substitution at the R₃ position are the best substituents for the antagonism of P2X7R activity. However, since most of the quinolinone derivatives showed low inhibitory effects in an IL-1 β ELISA assay, the core structure was further modified to a quinoline skeleton with chloride or substituted phenyl groups. The optimized antagonists with the quinoline scaffold included 2-chloro-5-adamantyl-quinoline derivative (**16c**) and 2-(4-hydroxymethylphenyl)-5-adamantyl-quinoline derivative (**17k**), with IC₅₀ values of 4 and 3 nM, respectively. In contrast to the quinolinone derivatives, the antagonistic effects of the quinoline compounds (**16c** and **17k**) were paralleled by their ability to inhibit the release of the pro-inflammatory cytokine, IL-1 β , from LPS/IFN- γ /BzATP-stimulated THP-1 cells (IC₅₀ of 7 and 12 nM, respectively). In addition, potent P2X7R antagonists significantly inhibited the sphere size of TS15-88 glioblastoma cells.

MEDI 136

Synthesis of CD437 analogs: compounds with MRSA persister cell activity and antibiotic synergy

Wooseong Kim², **Colleen Keohane**¹, *colleen.keohane@gmail.com*, Andrew Steele¹, William M. Wuest¹, Frederick M. Ausubel^{3,4}, Eleftherios Mylonakis². (1) Chemistry, Emory University, Atlanta, Georgia, United States (2) Division of Infectious Diseases, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, Rhode Island, United States (3) Department of Molecular Biology, Massachusetts General Hospital, Boston, Massachusetts, United States (4) Genetics, Harvard Medical School, Boston, Massachusetts, United States

CD437 was identified in a high-throughput *C. elegans* screen in the Mylonakis lab at Brown University. It was selected based on its ability to kill MRSA persister cells. Persister cells remain a significant challenge as they are increasingly resistant to treatment with antibiotics, in often already resistant strains (i.e. MRSA). The identified mechanism of action of the compounds is membrane intercalation, which permits bactericidal activity as well as synergistic effects with gentamicin. Unfortunately, the compounds exhibited high levels of toxicity. Our synthetic background was utilized in generating a library of analogs that would meet two qualifications: less toxic and more potent. This work explores a novel class of membrane-damaging antibiotics that do not induce cell lysis.

MEDI 137

Synthesis, pharmacological activity and molecular modeling studies of a series of 2-amino-1,4,5,6-tetrahydropyrimidine-5-carboxylic acid analogues as betaine/GABA transporter 1 (BGT1) substrate-inhibitors

Stefanie Kicking¹, *stefanie.kicking@univie.ac.at*, Anas Al-Khawaja², Anne Stæhr Haugaard², Rebekka Löffler², Maria Damgaard², Gerhard F. Ecker¹, Bente Frølund², Petrine Wellendorph². (1) Pharmaceutical Chemistry, University of Vienna, Vienna, Austria (2) Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark

As a member of the GABAergic system, the GABA transporters (GATs) play a critical role in the regulation and termination of the GABA-mediated signaling as they function as key proteins in neurotransmitter uptake. We have previously identified 2-amino-1,4,5,6-tetrahydropyrimidine-5-carboxylic acid (ATPCA) as the most potent substrate-inhibitor of the betaine/GABA transporter 1 (BGT1) reported to date. In order to characterize the molecular basis of GABA-transporter subtype selectivity, a series of ATPCA analogues was synthesized and pharmacologically characterized in radioligand-based uptake assays at the four human GABA transporters (hGATs) recombinantly expressed in mammalian cells. Overall, the analogues retained subtype-selectivity for hBGT1, though with lower inhibitory activities compared to ATPCA. Further

characterization of five BGT1-active analogues in a fluorescence-based FMP assay revealed that the compounds are substrates for hBGT1, suggesting that they interact with the orthosteric site of the transporter. *In silico*-guided mutagenesis experiments showed that the non-conserved residues Q299 and E52 in hBGT1 potentially contribute to the subtype-selectivity of ATPCA and its analogues. Computational docking studies and molecular dynamics simulations suggested that these residues form stable hydrogen bonds with the guanidine or amidine moieties of ATPCA and its derivatives. Overall, this study provides new insights into the molecular interactions governing the subtype-selectivity of BGT1 substrate-inhibitors.

MEDI 138

Development of chemical tools for epigenetic reader proteins

Jarod Waybright², jarodw@unc.edu, Kimberly D. Barnash², Justin Rectenwald¹, Stephen V. Frye², Lindsey I. James². (1) Center for Integrative Chemical Biology and Drug Discovery, UNC Chapel Hill, Chapel Hill, North Carolina, United States (2) Center for Integrative Chemical Biology and Drug Discovery, Division of Chemical Biology and Medicinal Chemistry, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States

Chromatin regulation through the deposition, interpretation, and removal of a variety of posttranslational modifications (PTMs) has been repeatedly demonstrated as an important driver of biological processes. Lysine methylation (Kme) is a unique PTM as it can be implicated in the formation of both active (euchromatin) or inactive (heterochromatin) gene sites dictated by both the location and degree of lysine methylation. Proteins that interpret these marks, often referred to as 'readers,' are important in chromatin regulation as they are often members of or are essential in the establishment of protein complexes that alter chromatin structure making them an important node for cell signaling. We seek to understand how the interpretation of these marks by reader proteins drives biological processes through the development of molecules that perturb the interaction of the proteins with their native histone substrate. We have previously demonstrated the utility of tools targeting chromodomain-containing proteins of the Chromobox (CBX) family as well as CDYL2. Here, we describe our efforts to target another chromodomain-containing protein, M-phase Phosphoprotein 8 (MPP8); a reader of Histone 3 Lysine 9 trimethylation (H3K9me3) mark that is important for heterochromatin formation. MPP8 is a member of the Human Silencing Hub (HUSH) complex, a driver of genomic silencing that has been implicated in a variety of human diseases and is vital to silencing of retroviral DNA including that of human immunodeficiency virus (HIV). Through a one-bead-one-compound (OBOC) screening strategy, structure-guided design and a variety of cellular target engagement experiments we have developed a chemical tool for interrogating the role of MPP8 in cellular processes.

MEDI 139

Novel and highly selective dopamine D₃ receptor antagonists/partial agonists as potential treatments for opioid use disorders

Anerbasha Shaik², *aner.shaik@nih.gov*, Alessandro Bonifazi², Sophie Cemaj², JoLynn Giancola², Alexandra Gadiano^{2,1}, Rana Rais¹, Barbara Slusher¹, Amy H. Newman². (1) Johns Hopkins Drug Discovery and Department of Neurology, Johns Hopkins University, , Baltimore, Maryland, United States (2) NIDA IRP, Baltimore, Maryland, United States

The dopamine D₃ receptor (D₃R) is an attractive target for development of medications to treat neuropsychiatric conditions including substance use disorders. D₃R-selective ligands with high affinity have been discovered, affording critical tools for understanding mechanisms underlying addiction. D₃R antagonists have been extensively investigated and have shown promising results in rodent models of self-administration and relapse-like behaviors. Nevertheless, to date, advancement to human studies has been limited. A high resolution crystal structure of D₃R complexed with a D₂R/D₃R antagonist, eticlopride, provided a defined platform for the generation of novel and highly selective D₃R ligands (Chien et al., 2010). Recently, we reported **VK4-116** and **VK4-40** bearing an eticlopride-inspired substituted-phenylpiperazine as the primary pharmacophore (PP) and an indole amide as the secondary pharmacophore (SP), as high affinity and D₃R selective lead molecules for the treatment of opioid use disorders (Kumar et al., 2016). Both compounds showed excellent metabolic stability in rat liver microsomes and *in vivo* efficacy for oxycodone-related behaviors in rats. In continuation of our efforts to discover highly D₃R selective agents, we previously reported that 3-F analogs of another lead molecule, **(R)-PG648**, resulted in analogues with favorable pharmacological profiles (Kumar et al., 2014). Thus, we synthesized a series of novel analogs of the VK compounds by replacing the 3-OH with a F in the linker between the PP and SP. Among these, **ABS01-113**, and **ABS01-114** demonstrated high D₃R binding affinity with K_i=0.48 nM and 2.09 nM, respectively. **ABS01-113** was 191-fold selective for D₃R over D₂R. In addition, modification of the PP or SP with a 3,4-(methylenedioxy)-phenyl group was also examined. All the F containing VK compounds exhibited significant metabolic stability in rat liver microsomes and compared with the standard, buprenorphine (<1% at 60 minutes). In addition, the enantiomers of both **VK4-116** and **VK4-40** were resolved in order to identify the most promising enantiopure lead molecule. Off target binding affinities, functional efficacies and metabolic profiles of these new D₃R selective antagonists/partial agonists will be highlighted with the aim of discovering potential leads for clinical development.

MEDI 140

Annulation rescues the rodent potency of a series of inhibitors of receptor-interacting protein kinase 1 (RIPK1)

Gregory Hamilton, *gghamil@gmail.com*. Discovery Chemistry, Genentech, South San Francisco, California, United States

Receptor-interacting protein kinase 1 (RIPK1), a key component of the cellular necroptosis pathway, has gained recognition as an exciting therapeutic target. Pharmacologic inhibition or genetic modulation of RIPK1 has shown promise in models of disease ranging from acute ischemic conditions, chronic inflammation, and neurodegeneration. Due to a low sequence homology across species in the kinase domain of RIPK1, it has been difficult to find highly potent tool compounds for testing in preclinical models. We discovered that addition of a new ring with a particular orientation could dramatically improve the rodent potency of a series of RIPK1 inhibitors without affecting the degree of inhibition of the human enzyme. This change led to a new chemical subseries including compounds with highly desirable potency and pharmacokinetic attributes.

MEDI 141

Design, synthesis and biological evaluation of nitrate ester analogs of SCP-1

Madhurima Das¹, *madhurima.das.91@gmail.com*, **Nicolas G. Bazan**², **Mark Trudell**¹. (1) Department of Chemistry, University of New Orleans, New Orleans, Louisiana, United States (2) Neuroscience Center of Excellence, Louisiana State University Health Sciences Center, New Orleans, Louisiana, United States

Organic nitrate esters have been of interest lately as potential Nitric Oxide (NO) donors. A series of nitrate ester analogues of SCP-1 were prepared by acylating SCP-1 with chloroalkanoyl chlorides followed by nitration using AgNO₃ to give the corresponding nitrate ester. The chloroesters and nitrate esters were obtained in good yields. ¹H NMR and ¹³C NMR were used to characterize the compounds. X-Ray crystallographic analysis unequivocally confirmed the structures of the chloroester and the nitrate ester. The preliminary biological evaluation of the hepatotoxicity has shown these compounds to be well tolerated by human hepatocytes. The synthesis of nitrate ester derivatives of the analgesic SCP-1 and preliminary biological activity will be presented.

MEDI 142

Small organic molecules to modulate apoE, abca1, & LDLR protein levels for Alzheimer's therapy

Bhvandip S. Bajwa¹, *bsbajwa@mail.fresnostate.edu*, **Prarthana Kumar**², *pkumar97@mail.fresnostate.edu*, **Byungwook Kim**⁵, **Hande Karahan**⁵, **Inderpreet Bal**³, **Jungsu Kim**⁵, **Santanu Maitra**⁴. (1) Chemistry, California State University, Fresno, Folwer, California, United States (2) Chemistry, California State University, Fresno, Fresno, California, United States (3) Chemistry, California State University, Fresno, Fresno, California, United States (4) Chemistry Dept MS SB 70, California State

University Fresno, Fresno, California, United States (5) Neuroscience, Mayo Clinic, Jacksonville, Florida, United States

Targeting reduction of apolipoprotein E (apoE) level in conjunction with upregulation of ATP-binding Cassette Transporter A1 (abca1) protein and/or Low Density Lipoprotein Receptor (LDLR) with small molecules presents an excellent approach to the understanding and therapy of Alzheimer's disease (AD). The strongest genetic risk factor for Alzheimer's disease is the apoE4 genotype. More than half of Alzheimer's patients (65-80%) are carriers of the APOE4 allele, despite APOE4 allele frequency is estimated to be only 15-20% in the general population. We and others previously demonstrated that decreasing apoE protein levels leads to a dramatic decrease in amyloid plaque level and microgliosis. Therefore, targeting apoE with small molecules presents an excellent approach to the understanding and therapy of Alzheimer's disease. The triarylmethyl amines (TAMA) synthesized and studied by our research group were the first reported small organic molecules that decreased apoE level via Liver-X-Receptor (LXR) antagonism. The subsequent tertiary sulfonamides and arylmethyl amine leads identified through Structure-Activity Relationship (SAR) studies are the first known examples of small molecules that reduce apoE levels while increasing abca1/ldlr proteins. Lead optimization is underway through cell-based assays, mouse models, pharmacokinetic, and toxicology studies.

MEDI 143

Discovery, synthesis and characterization of a series of (1-alkyl-3-methyl-1H-pyrazolo-5-yl)-2-(5-aryl-2H-tetrazol-2-yl)acetamides as novel GIRK1/2 potassium channel activators

Swagat Sharma¹, swagat.sharma@unmc.edu, Krystian A. Kozek², Kristopher K. Abney³, David Weaver², Corey Hopkins¹. (1) Department of Pharmaceutical Sciences, College of Pharmacy, University of Nebraska Medical Center, Omaha, Nebraska, United States (2) Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee, United States (3) Department of Neuroscience and Pharmacology, Meharry Medical College, Nashville, Tennessee, United States

The G-protein gated inwardly rectifying potassium (GIRK, Kir-3) channels are members of a large family of inwardly rectifying potassium channels (Kir1-Kir7) and play a significant role in controlling the neuronal excitation by hyperpolarization of neurons upon activation by G protein-coupled receptors. GIRK channels are comprised of homo- or heterotetramers of four structurally and functionally different subunits (GIRK 1-4). Pharmacological investigations and genetic ablation studies over the years have identified and established the contribution of the GIRK 1/2 channel subunit, predominantly found in brain, in the pathophysiology of various neurological disorders including, but not limited to, epilepsy, anxiety, Parkinson's, pain, reward and addiction. Previously, our laboratory has identified urea and amide-based derivative as first-in-class GIRK 1/2 small molecule activators which led to an increased understanding of GIRK channel functionality and their therapeutic potential. However, these compounds

have limitations for *in vivo* utility due to pharmacokinetic liabilities and suboptimal selectivity for GIRK 1/2 subunit over other units. This poster details our work in the design, synthesis, and characterization of novel tetrazole based GIRK 1/2 channel activators resulting in multiple compounds with high potency and efforts to improve their pharmacokinetic properties.

MEDI 144

Structure-based drug discovery of a selective, covalent KRas G12C inhibitor with oral activity in animal models of cancer

John P. Fischer¹, jfischer@arraybiopharma.com, **Brian R. Baer**¹, **Joshua Ballard**¹, **James F. Blake**¹, **Karyn Bouhana**¹, **Barbara J. Brandhuber**¹, **David M. Briere**², **Laurence E. Burgess**¹, **Michael R. Burkard**¹, **Harrah Chiang**², **Mark J. Chicarelli**¹, **James G. Christensen**², **Kevin Davidson**¹, **John J. Gaudino**¹, **Jill Hallin**², **Lauren Hanson**¹, **Kenneth Hee**¹, **Erik J. Hicken**¹, **Ronald J. Hinklin**¹, **Matthew A. Marx**², **Macedonio J. Mejia**¹, **Peter Olson**², **Pavel Savechenkov**¹, **Niranjan Sudhakar**², **Tony P. Tang**¹, **Guy P. Vigers**¹, **Henry Zecca**¹, **Jay B. Fell**¹. (1) Array Biopharma Inc, Boulder, Colorado, United States (2) Mirati Therapeutics, San Diego, California, United States

KRAS is the most frequently mutated driver oncogene in human cancer and KRas mutations are commonly associated with poor prognosis and resistance to standard therapy. The ability to effectively target and block the function of mutated KRas has remained elusive despite decades of research. Recent findings have demonstrated that directly targeting KRas G12C with electrophile-containing small molecules that covalently modify the mutated codon 12 cysteine may be feasible. This approach effectively locks mutant KRas in an inactive state sparing inhibition of wild-type KRas in normal cells to dramatically lower the potential for off target effects. By solving a highly informative set of ligand complexed co-crystal structures coupled with iterative structure based drug design, a novel series of mutant selective KRas G12C inhibitors has been identified. This presentation will focus on the discovery and preclinical characterization of covalent inhibitors of KRas G12C. Compounds from this series demonstrate potent pathway inhibition in KRas G12C driven H358 cells and efficacy in tumor xenograft models. Additional efforts to identify an orally active compound for the treatment of mutant KRas G12C human tumors will also be discussed.

MEDI 145

Disruption of D1-D2 heterooligomers via synthetic peptides: A new therapeutic tool?

Margaret Champion, mmacknic@emich.edu, **Pouya Khazaei**, **Hedeel Evans**, **Deborah Heyl-Clegg**. Chemistry, Eastern Michigan University, Ypsilanti, Michigan, United States

Dopamine receptors D1 and D2 are thought to heterooligomerize, a process that recruits Gq/11 α subunit to initiate a phospholipase C mediated signaling cascade. This

signaling cascade is involved in neurological processes such as synaptic plasticity, long-term synaptic depression, and fine-tuning of calcium release. D1-D2 heteromers are implicated in neuropsychiatric diseases as diverse as depression, Parkinson's, and schizophrenia. Our research explores the interaction and kinetics of D1-D2 heterooligomerization. Using as template a purported interaction site between the carboxyl tail of the D1 receptor and the third intracellular loop of the D2 receptor, we synthesized several short peptides (4-8 amino acids long) designed to interfere with D1-D2 interactions. These peptides were tested using whole cell lysates of human brain tissue and dopamine receptor constructs. We report that a synthetic peptide, – EAARRAQE, is efficient in blocking D1-D2 heteromer formation, while shorter peptides (EERRAQ, ARRA and AARRAQ) had no effect. A D-isoform of EAARRAQE showed a greater ability to block heterooligomerization than its L-counterpart. Our research provides insight into D1-D2 heteromer formation, and may aid future drug development efforts that target this receptor complex.

MEDI 146

Synthesis and structure–activity relationship (SAR) studies of novel *Pyrazolopyridine* derivatives as inhibitors of *Enterovirus* replication

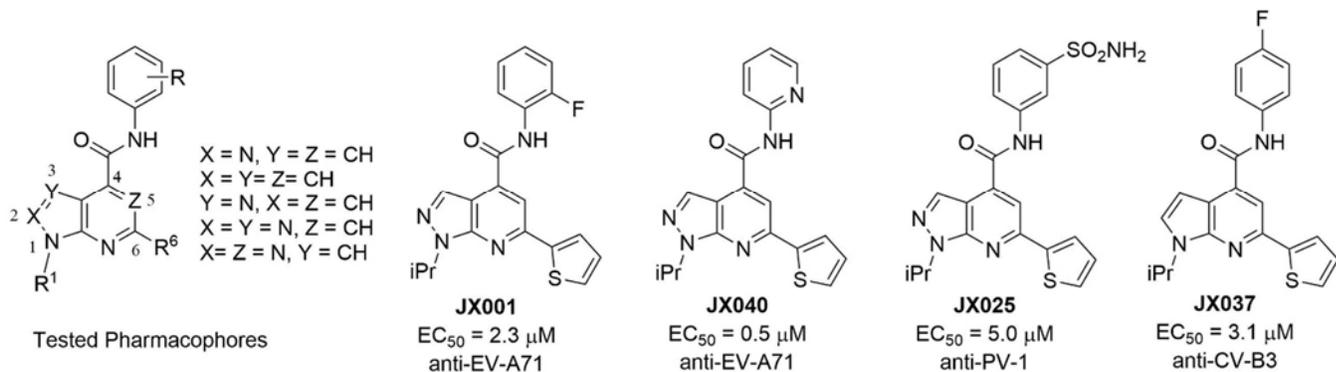
Yanpeng Xing¹, yanpengxing@gmail.com, Jun Zuo², Paul Krogstad^{3,4}, Michael E. Jung^{5,6}. (1) Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California, United States (2) Department of Pediatrics, University of California, Los Angeles, Los Angeles, California, United States (4) Department of Molecular and Medical Pharmacology, University of California, Los Angeles, Los Angeles, California, United States

Enteroviruses are small, non-enveloped RNA viruses responsible for poliomyelitis, encephalitis, acute heart failure or severe hepatitis in newborns. In the United States recent outbreaks of coxsackievirus B1 (CVB1) infections and coxsackievirus A6 served as reminders of the ongoing threat raised by these pathogens.

No antiviral agents are currently approved to treat enterovirus infections. Extensive studies in pursuit of candidate antiviral agents have targeted the viral capsid, the virus-encoded RNA polymerase and proteases, and other viral proteins involved in replication.

By applying a rapid, live virus assay to identify enterovirus inhibitors from nearly 86,000 compounds, a novel group of antienteroviral compounds: 1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxamides were identified. The target of these compounds was identified as the viral 2C protein, which plays a role in RNA replication. In order to establish a good structure–activity relationship (SAR) and identify the most 'druglike' members of this pharmacophore, a series of novel pyrazolopyridine compounds have been designed and prepared by a general synthetic route. Their activities against the replication of poliovirus-1, EV-A71, and CV-B3 enteroviruses were evaluated. The comprehensive understanding of the SAR was obtained by utilizing the variation of four positions, namely, N1, C6, C4, and linker unit. From the screened analogues, the inhibitors with the highest selectivity indices at 50% inhibition of viral replication (SI₅₀) were those with

isopropyl at the N1 position and thiophenyl-2-yl unit at C6 position. Furthermore, the C4 position offered the greatest potential for improvement because many different N-aryl groups had better antiviral activities and compatibilities than the lead compound **JX001**. For example, **JX040** with a 2-pyridyl group was the analogue with the most potent activity against non-polio enteroviruses, and **JX025**, possessing a 3-sulfamoylphenyl moiety, had the best activity against polioviruses. In addition, analogue **JX037**, possessing a novel pyrazolopyridine heterocycle, was also shown to have good antienteroviral activity, which further enlarges the compound space for antienteroviral drug design.



Tested Pharmacophores and Structures of **JX001**, **JX040**, **JX025** and **JX037**.

MEDI 147

Template alignment modeling of the structure-activity relationships of opioid ligands

Zhijun Wu¹, zj1234508536@yahoo.com, **Victor J. Hruby**². (1) ABC Resource, Plainsboro, New Jersey, United States (2) Univ of Arizona, Tucson, Arizona, United States

As is well known, opioid ligands are a large group of structurally diversified GPCR ligands, and their structure-activity relationships (SARs) are highly complicated.

Why can so diverse structures bind to the same binding pockets of opioid receptors? Are there structural correlations among them? How would they behave at the binding sites, with respect to their binding conformations, affinities and selectivity, etc.? Can we build a unified pharmacophore model for all the ligands? All these are the central issues involved in the long history of opioid ligand studies, while to solve them will be highly valuable for the improvement of current opioid drugs or the discovery of new agents.

Template alignment modeling is an innovative approach developed recently in our modeling-based studies in order to tackle the above issues. By aligning and comparing the various structural features of ligands with a model template, this approach can help to reveal the structural patterns as well as the correlations among the various ligands.

Even though still in testing and validating, this approach has appeared to be rather straight yet effective in interpretation of the SARs of various opioid ligands.

With this presentation, we will report our latest progress in the template alignment modeling on the three types of opioid ligands. We will apply a recently constructed artificial template along with typical examples to illustrate how to understand the potential structural correlations as well as the associated SARs of many opioid ligands,

MEDI 148

Overcoming fluoroquinolone resistance in bacterial with new binding interactions

Benjamin H. Williamson¹, *bhwillia@utica.edu*, **Robert J. Kerns**². (1) *Chemistry, Utica College, Yorkville, New York, United States* (2) *Pharmacy, University of Iowa, Iowa City, Iowa, United States*

Fluoroquinolones are successful small-molecule antibiotics that, through widespread use, suffer diminishing clinical utility due to emerging antibiotic resistance. The emergence of fluoroquinolone-resistant bacteria has been demonstrated clinically and is believed to be caused by evolution-driven changes in the targets of fluoroquinolone action. The targets of fluoroquinolones are the bacterial type-II topoisomerase enzymes DNA gyrase and topoisomerase IV. The function of DNA gyrase is the untangling of knots in bacterial DNA, whereas the function of topoisomerase-IV is the separation of sister chromatids in newly replicated bacterial DNA. Topoisomerases are therefore crucial to the replication of bacterial DNA, and consequently, cellular reproduction in bacteria. The binding site of fluoroquinolones is within a structure composed of bacterial DNA and topoisomerase enzyme. The complete structure, composed of bacterial DNA, topoisomerase enzyme, and fluoroquinolone is referred to as the ternary complex. The binding of the fluoroquinolone to form the ternary complex prevents DNA untangling by blocking topoisomerase religating DNA, which in turn halts cellular growth and leads to cell death. Compounds such as the fluoroquinolones that form stable ternary complexes and block DNA relegation are termed topoisomerase poisons.

The goal of the research described herein is the development of new fluoroquinolones that are able to poison both non-mutated “wild-type” type-II topoisomerases and mutated type-II topoisomerases that have demonstrated resistance to older fluoroquinolones. This was accomplished by the synthesis of fluoroquinolones that possess novel side chain structures that bind to sites in the ternary complex that are separate from the resistance-causing substitutions within the topoisomerase. The ability of these new fluoroquinolones to 1) poison bacterial topoisomerases and 2) not act on human topoisomerase was tested with purified bacterial and human type-II topoisomerase enzymes. The ability of these compounds to halt bacteria cell growth was tested in wild-type and mutant cell cultures.

MEDI 149

Towards the design of proteolysis targeting chimeras (PROTACs) for the degradation of polycomb group proteins

Frances M. Potjewyd¹, francesp@email.unc.edu, Kelsey N. Lamb¹, Oliver Bell², Lindsey I. James¹, Stephen V. Frye¹. (1) Center for Integrative Chemical Biology and Drug Discovery, Division of Chemical Biology and Medicinal Chemistry, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States (2) Institute of Molecular Biology of the Austrian Academy of Science, Vienna, Austria

The dynamic relationship between the multiprotein Polycomb group (PcG) complexes, Polycomb repressive complex 1 (PRC1) and PRC2, plays a critical role in regulating the propagation of repressive histone marks on chromatin. PcG protein misregulation and overexpression has been implicated in diseases such as cancer, and consequently much effort has been put forth in recent years to manipulate PRC function with small molecule inhibitors. As a complementary approach, we are exploring the selective degradation of PcG complex components to decipher the biological mechanism within these diseases.

Protein degradation using proteolysis targeting chimeras (PROTACs) is a valuable approach for difficult targets within drug discovery. For example, PROTACs can selectively degrade proteins when derived from promiscuous small molecule inhibitors and because degradation is believed to be catalytic a lower intracellular compound concentration may be necessary compared to small molecule inhibitors. Utilizing known PRC inhibitors, which can be functionalised with appropriate PEG linkers and E3 ligase recruiters, we aim to establish a chemical toolbox of polycomb-directed PROTAC reagents.



MEDI 150

Characterization of new CRBN binders: Impact on protein degradation efficiency and differentiated pharmacology compared to IMiDs

Nan Ji, Yi Zhang, yi@kymeratx.com, Matthew Weiss, Kamadurai Hari, Karen Yuan, Jesse Chen, Joseph F. Kelleher, Christine Loh, Nello Mainolfi. Kymera Therapeutics, Cambridge, Massachusetts, United States

Targeted protein degradation is a novel technology that utilizes small molecules that contain an E3 ligase-binding motif and a target protein-binding motif to catalyze the degradation of target proteins by the ubiquitin-proteasome system (UPS). Binders extensively used for the E3 ligase cereblon (CRBN) are immunomodulatory drugs (IMiDs, thalidomide and its analogs). Degraders based on IMiDs have been shown to degrade a diverse class of protein targets such as nuclear receptors, BET family proteins, and kinases among others. Although widely used as the E3 binders in the context of targeted protein degradation, IMiDs have only modest binding affinity to CRBN and IMiDs-based degraders can maintain pharmacology associated with IMiDs. Here, we describe the characterization of new CRBN binders with improved CRBN binding affinity, their impact on protein degradation efficiency and differentiated pharmacology compared to IMiDs.

MEDI 151

Identification of novel cyclic peptide-peptoid hybrid CXCR7 modulators

Chris Limberakis¹, chris.limberakis@pfizer.com, Markus Boehm², Kevin Beaumont², Rhys Jones², Amit S. Kalgutkar², Liying Zhang², Karen Atkinson¹, Guoyun Bai¹, Janice Brown¹, Heather Eng¹, Gilles H. Goetz¹, Bhagyashree Khunte¹, Sarah Lazzaro¹, Sangwoo Ryu¹, Laurie Tylaska¹, Rushia Turner³, Siegfried Leung^{4,5}, Mahesh Ramaseshan⁴, David Price², Spiros Liras², Matthew P. Jacobson⁵, David J. Earp⁴, Scott Lokey³, Alan Mathiowetz², Elnaz Menhaji-Klotz². (1) Pfizer Worldwide Research & Development-Groton, Groton, Connecticut, United States (2) Pfizer Worldwide Research & Development-Cambridge, Cambridge, Massachusetts, United States (3) Chemistry and Biochemistry, University of California, Santa Cruz, Santa Cruz, California, United States (4) Circle Pharma, South San Francisco, California, United States (5) Department of Pharmaceutical Chemistry, University of California, San Francisco, San Francisco, California, United States

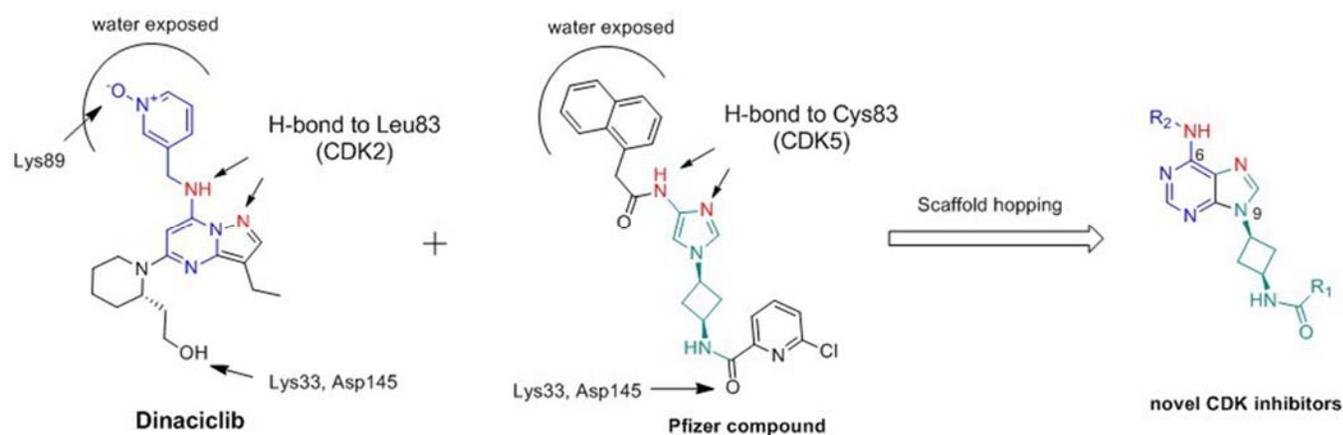
CXCR7 is a chemokine receptor belonging to the G-protein coupled receptor (GPCR) family with high affinity for the chemokine ligands CXCL11 and CXCL12. CXCR7's elevated expression has been linked to a variety of diseases/conditions including certain cancers, viral infections, encephalitis, rheumatoid arthritis, and acute renal failure. As part of our CXCR7 program, we designed and synthesized a novel set of potent cyclic peptide-peptoid hybrid CXCR7 modulators. To identify the cell-permeable modulators, we used EPSA, clogP, and passive permeability data which ultimately lead to an orally bioavailable compound.

MEDI 152

Synthesis and biological evaluation of N9-cis-cyclobutylpurine derivatives for use as cyclin-dependent kinase(CDK) inhibitors

Jaedu Ha, jdha@kriict.re.kr, Sun Jun Park, Eunjin Kim, Miyoun Yoo, Joo-young Lee, Chi Hoon Park, Jong Yeon Hwang. Therapeutics & Biotechnology Division, KRICT, Daejeon, Korea (the Republic of)

A novel 6-aminopurine scaffold bearing an N9-cis-cyclobutyl moiety was designed using structure-based molecular design based on two known CDK inhibitors, dinaciclib and Cmpd-27. A series of novel 6-aminopurine compounds was prepared for structure–activity relationship (SAR) studies of CDK2 and CDK5 inhibitors. Among the compounds synthesized, compound 81 displayed potent CDK2 and CDK5 inhibitory activities with low nanomolar ranges (IC₅₀ = 2.1 and 4.8 nM, respectively) and showed moderate cytotoxicity in HCT116 colon cancer and MCF7 breast cancer cell lines. Here, we report the synthesis and evaluation of novel 6-aminopurine derivatives and present molecular docking models of compound 81 with CDK2 and CDK5.



MEDI 153

CXCR2 receptor antagonists for the treatment of colorectal cancer

Caroline Black¹, blackcar@usc.edu, Kalyan C. Nagulapalli Venkata³, Melissa Labonte Wilson⁴, Heinz-Josef Lenz⁴, Stan G. Louie², Nicos A. Petasis^{1,2}. (1) Dept of Chemistry and Loker Hydrocarbon Institute, University of Southern California, Los Angeles, California, United States (2) School of Pharmacy, University of Southern California, Los Angeles, California, United States (3) College of Pharmacy, Larkin Health Sciences Institute, Miami, Florida, United States (4) Keck School of Medicine, University of Southern California, Los Angeles, California, United States

The chemokine interleukin 8 (IL-8) and its GPCR receptor CXCR2 are implicated in colorectal cancer growth, progression, invasion, metastases, angiogenesis, and

chemoresistance. Both IL-8 and CXCR2 are significantly upregulated in the tumor and its microenvironment, indicating that effective antagonists of the IL-8/CXCR2 pathway would be of interest for the treatment of colorectal cancer. Towards this goal we have designed, synthesized and studied a new type of potential CXCR2 receptor antagonists, and have been investigating their potential effects in colorectal cancer.

MEDI 154

Pheophorbide a suppresses toll-like receptor signaling via IKK β /NF κ B/TBK1/IRF3 to improve survival in septic mice

Kim Taekyun, ktk160@naver.com. Gwangju Institute of Science and Technology, Gwangju, Korea (the Republic of)

Toll-like receptors (TLRs) play an important role in the host defense against invading microbial pathogens by initiating immune and inflammatory responses. Dysregulation of TLRs has been linked to various inflammatory diseases; as such, phytochemicals targeting TLR activity is a potentially beneficial strategy for treating immune disorders. In this study, we investigated the effect of pheophorbide a (Pa) on TLR signaling via myeloid differentiation primary response (MyD)88- and Toll/interleukin-1 receptor domain-containing adapter-inducing interferon- β (TRIF)-dependent pathways. Pa suppressed the mRNA and protein expression of tumor necrosis factor (TNF)- α , interleukin (IL)-6 and -12, cyclooxygenase-2, interferon- β , regulated on activation normal T cell expressed and secreted, and inducible nitric oxide synthase (iNOS) in macrophages stimulated with lipopolysaccharide (LPS) or poly(I:C). Pa also blocked nuclear factor kappa light chain enhancer of activated B cells (NF κ B) activation induced by TRIF, MyD88, receptor-interacting serine/threonine protein kinase 1, and p65, and inhibited in vitro I κ B kinase β and TNF receptor-associated factor family member-associated NF-kappa-B activator-binding kinase (TBK)1 activities. Activation or phosphorylation of NF κ B and I κ B- α induced by LPS or CpG (TLR9 ligand) was suppressed by Pa, as was interferon regulatory factor (IRF)3 activation induced by TRIF, TBK1, and IRF3. The activation, phosphorylation, and nuclear translocation of IRF3 induced by LPS or poly(I:C) was inhibited by Pa, leading to the suppression of IRF3-dependent gene expression. Importantly, Pa inhibited TNF- α and IL-6 gene expression and liver inflammation, resulting in increased survival of mice with LPS-induced endotoxemia. These results indicate that Pa has therapeutic potential for mitigating sepsis-related inflammation via modulation of TLR signaling.

MEDI 155

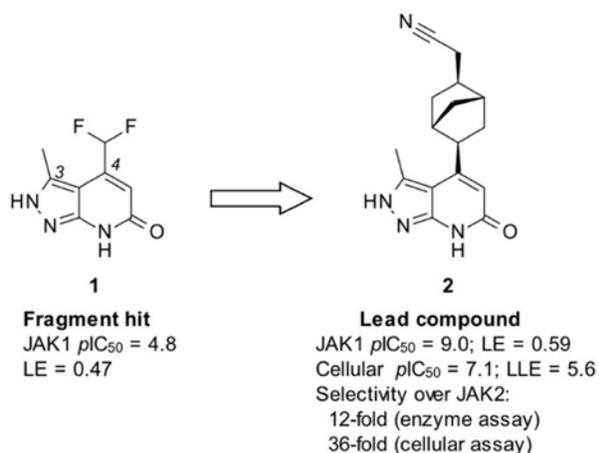
Fragment-based discovery of pyrazolopyridones as JAK1 inhibitors with excellent subtype selectivity

Andreas Ritzen¹, andreas.ritzen@leo-pharma.com, Thomas Vifian¹, Rikke Sindet¹, Bettina B. Hansen¹, Mogens Larsen¹, Tue H. Jepsen¹, Jens Larsen¹, Jimmi G. Seitzberg¹, Sanjay Rai², Venkatarathnam R. Nasipireddy², Martin A. Carnerup¹, Anders

Jerre¹, Christina Mølck¹. (1) LEO Pharma A/S, Ballerup, Denmark (2) GVK BIO, Hyderabad, India

The Janus kinase (JAK) family of tyrosine kinases plays a central role in the cytokine-dependent regulation of proliferation and function of cells involved in immune response. It consists of four closely related proteins (JAK1, JAK2, JAK3 and TYK2) that transduce signaling from cytokine receptors by phosphorylation and subsequent activation of signal transducers and activators of transcription (STAT). Recently, subtype-selective JAK1 inhibitors have attracted attention as possible therapeutic agents for atopic dermatitis, and the most advanced compounds are now in phase III clinical trials for this indication. High selectivity over JAK2 may reduce the side-effect burden of the first-generation JAK inhibitors, e.g. tofacitinib (Xeljanz®).

Herein, we report the discovery of a series of JAK1-selective kinase inhibitors with high potency, excellent JAK family subtype selectivity and promising *in vitro* and *in vivo* pharmacokinetic properties. A fragment screening hit (**1**) was selected as the starting point. X-ray crystallography was unsuccessful for this compound, but initial SAR indicated that the kinase hinge region interacts with at least one of the NH donors of the scaffold. Thus, analogs with aromatic and aliphatic rings appended to the 4-position of the scaffold were targeted. This led to a large increase in potency, and importantly allowed us to obtain an X-ray crystal structure. With the binding mode known, we proceeded to optimize the substituent in the 4-position. A selection of mono- and bicyclic aliphatic ring systems were investigated, and a trend towards higher potency with increasing steric bulk was observed. In particular, the norbornane scaffold was selected for further exploration due to its balance of good potency without excessive lipophilicity. Norbornane acetonitrile **2** showed excellent potency and selectivity, and we profiled this compound further in *in vitro* and *in vivo* metabolism studies. The results of these studies indicate that **2** may be a viable lead compound for the development of highly subtype-selective JAK1 inhibitors.



MEDI 156

Synthesis and biological evaluation of some novel heterocyclic compounds as potential anti-thrombotic agents

Atul N. Khadse, *atulkhadse@yahoo.co.in*, Shabnam Khan, Navnit Prajapati, Rahul B. Ghuge, Prashant R. Murumkar, Sadhana Rajput, Mange Ram Yadav. Faculty of Pharmacy, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India

Thromboembolic diseases like arterial and venous thromboses are the major cause of morbidity and mortality worldwide today. Current antithrombotic drugs like warfarin and heparin have limited therapeutic applications against these diseases due to their narrow therapeutic windows, bleeding risks, food- and drug-drug interactions requiring constant monitoring. Hence there is an urgent need to develop orally active agents with a high efficacy and safety suitable for both acute and chronic treatment. Direct inhibition of different coagulation factors carries significant promise for development of effective and safe antithrombotic agents. Thrombin, final mediator in coagulation cascade, plays a central role in the initiation and propagation of thrombosis by converting insoluble fibrinogen into stable fibrin clots and activation of platelets. Hence thrombin inhibitors have been well recognized as potential therapeutic agents in antithrombotic therapy. So far, dabigatran etexilate is the only available oral direct thrombin inhibitor used in thrombotic complications. From the fragment-based drug design approach, a novel series of furanopyrimidinone derivatives as direct thrombin inhibitors have been designed and synthesized. The synthesized compounds were evaluated for *ex vivo* prothrombin time (PT) and activated partial thromboplastin time (aPTT) prolongation in rats. Among the series of compounds, two compounds exhibited significant biological activity with PT 11.5 and 12.5 sec. and aPTT >300 and 116.1 sec. respectively. Thus, furanopyrimidinone can act as an excellent lead for further development of potential antithrombotic agents.

MEDI 157

Inducing the activity of NK cells with NKp30 small organic ligands

Pedro Pinheiro^{2,1}, *pedro.pinheiro@ist.utl.pt*, Gonçalo C. Justino², Joana P. Miranda², M Matilde Marques². (1) Instituto de Investigação do Medicamento, Faculdade de Farmácia - ULisboa, Lisbon, Portugal (2) Centro de Química Estrutural, Instituto Superior Técnico, ULisboa, Lisboa, Portugal

Natural killer (NK) cells provide rapid responses to viral-infected cells, and play a critical role in tumor immunosurveillance by directly inducing the death of tumor cells. Instead of acting via antigen-specific receptors, lysis of tumor cells by NK cells is mediated by alternative receptors, including NKG2D, NKp44, NKp46 and NKp30.

B7H6, a surface protein present on a broad panel of tumor cells, including lymphoma, melanoma and neuroblastoma, was identified as a ligand for the NKp30 receptor, namely through the structural elucidation of the NKp30-B7H6 complex. The comparison between the 3D structures of unbound and B7H6-bound NKp30 demonstrated marked conformational changes that may be a key-factor for the NK-response activation role of B7H6. Due to the difficulties in promoting the over-expression of the B7H6 marker in tumor cells, and the limited access to recombinant proteins and synthetic peptides, we set to design a family of small organic molecules (SOMs) capable of mimicking the

effect of B7H6 on the NKp30 receptor.

Using computational tools (namely AutoDoc Vina) we designed a family of SOMs based on the structure of the NKp30 receptor. Synthetic, stability and overall binding score considerations were used to select a subfamily of ca. 15 compounds for synthesis. From these, 10 completely characterized entities were tested in an MS-based binding assay using the recombinant extracellular portion of the receptor, which led to the identification of one lead compound. Further refining of the lead structure, based on computational and synthetic approaches, was performed to improve the overall properties in terms of solubility, serum protein binding and stability. Cytotoxicity of the lead compound was evaluated in the HepG2 cell line, showing no relevant effects up to 200 μM over 24h in the MTT assay.

The capacity of the lead compound to induce NK cell-mediated killing of tumor cells is currently being tested on both an NK cell line and freshly isolated PBMCs. The stimulation of NK cells by the lead compound is being assessed through TNF- α - and IFN- γ -specific assays (ELISA), whereas the specificity of the lead compound towards the NKp30 receptor is being evaluated by antibody-ligand competitive binding in immunofluorescence assays. Further work aims to derivatize the ligands capable of inducing an NK cell response with tumor-targeting molecules, toward an increase in the specificity of the induced response.

MEDI 158

Exploration of (hetero)aryl derived thienylchalcones for antiviral and anticancer activities

Vikrant Patil², Siddappa A. Patil², Renukadevi Patil¹, Alejandro Bugarin³, Kenneth Beaman⁴, Shivaputra Patil¹, shivaputrap@yahoo.com. (1) Pharmaceutical Sciences, Rosalind Franklin University, North Chicago, Illinois, United States (2) Centre for Nano and Material Sciences, Jain University, Bangalore, Karnataka, India (3) Department of Chemistry & Biochemistry, University of Texas at Arlington, Arlington, Texas, United States (4) Department of Microbiology and Immunology, Rosalind Franklin University of Medicine and Science, North Chicato, Illinois, United States

With the aim of identifying the broad acting antiviral and anticancer agents, we discovered substituted aryl/heteroaryl derived thienyl chalcones as antiviral and anticancer agents. All thienyl chalcone derivatives **II-VI** displayed moderate to excellent antiviral activity towards several viruses tested. Compounds **V** and **VI** were turned out to be active compounds towards human cytomegalovirus for both normal strain (AD169) as well as resistant isolate (GDGr K17). Particularly, compound **V** showed very high potency (EC_{50} : $<0.05 \mu\text{M}$) towards AD169 strain of HCMV compared to standard drug Ganciclovir (EC_{50} : $0.12 \mu\text{M}$). Additionally, it showed moderate activity in secondary assay (AD169; EC_{50} : $2.30 \mu\text{M}$). The thienyl chalcone **IV** displayed high potency towards Rift Valley fever virus (RVFV) and Tacaribe virus (TCRV). Compound **IV** is nearly 28 times more potent in our initial *in vitro* visual assay (EC_{50} : $0.39 \mu\text{g/ml}$) and nearly 17 times more potent in neutral red assay (EC_{50} : $0.71 \mu\text{g/ml}$) compared to the standard drug Ribavirin (EC_{50} : $11 \mu\text{g/ml}$; visual assay and EC_{50} : $12 \mu\text{g/ml}$; neutral red assay). It is

nearly 12 times more potent in our initial *in vitro* visual assay (EC₅₀: >1 µg/ml) and nearly 8 times more potent in neutral red assay (EC₅₀: >1.3 µg/ml) compared to the standard drug Ribavirin (EC₅₀: 12 µg/ml; visual assay and EC₅₀: 9.9 µg/ml; neutral red assay) towards Tacaribe virus (TCRV). Additionally, compound **IV** has shown strong growth inhibitory activity towards three major cancer (colon, breast and leukemia) cell lines and moderate growth inhibition shown towards other cancer cell lines screened. Compounds **V** and **VI** were demonstrated viral inhibition towards Human cytomegalovirus whereas compound **IV** towards Rift Valley fever virus and Tacaribe virus. Additionally, compound **IV** has displayed very good cytotoxicity towards colon, breast and leukemia cell lines *in vitro*.

MEDI 159

Rapid and accessible *in silico* macrocycle design – application to BRD4

Sylvie Sciammetta, *sylvie.sciammetta@gmail.com*, **Matthias Bauer**, **Robert Scoffin**, **Giovanna Tedesco**, **Mark D. Mackey**. *Cresset, Cambridge, United Kingdom*

Macrocyclization of pharmaceutical compounds plays an increasing role in drug discovery. Macrocycles can provide several advantages such as favorable drug-like properties, increased selectivity and improved binding affinity.

Macrocyclization of an existing lead series is not always easy. There are often multiple potential locations where the molecule could be cyclized, each with its own constraints in terms of synthetic feasibility, ideal linker length, required linker conformation, and pharmacophoric requirements from the active site. Challenging syntheses make it impractical to fully explore the possibilities in the lab.

Here we present a case study of designing macrocyclization strategies for reported BRD4 inhibitors with Spark, Cresset's bioisostere replacement and scaffold hopping tool. The Spark algorithms enable a rapid assessment of the ideal linker length and suggested chemistry for each cyclization option.

MEDI 160

Structure-based design of inhibitors for STE20-like kinase (SLK)

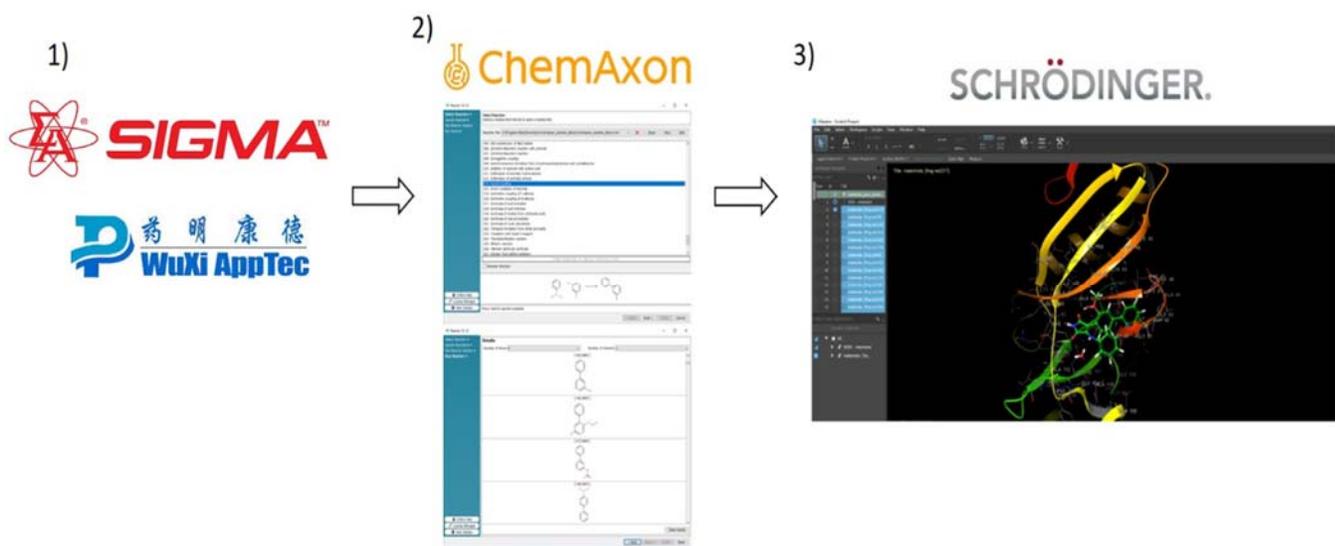
Ricardo A. Serafim¹, *ramserafim@gmail.com*, **Stanley Vasconcelos**², **William Zuercher**³, **Tim Willson**⁴, **James Bennett**⁵, **Fiona Sorrell**⁵, **Katlin B. Massirer**¹, **Jonathan M. Elkins**⁵. (1) *Structural Genomics Consortium - SGC/UNICAMP, Campinas, Brazil* (3) *Structural Genomics Consortium - SGC/UNC, Chapel Hill, North Carolina, United States* (5) *Structural Genomics Consortium - SGC/Oxford, Oxford, United Kingdom*

In the human kinome there are more than 500 protein kinases, but only about 10% have been extensively studied, showing the need for a better kinase inhibitor pipeline. The understudied kinase SLK has been linked to cell multiplication processes and studies suggest that SLK inhibition might be able to decrease the invasive and metastatic process. According to our previous *in vitro* screening, a maleimide scaffold provides an

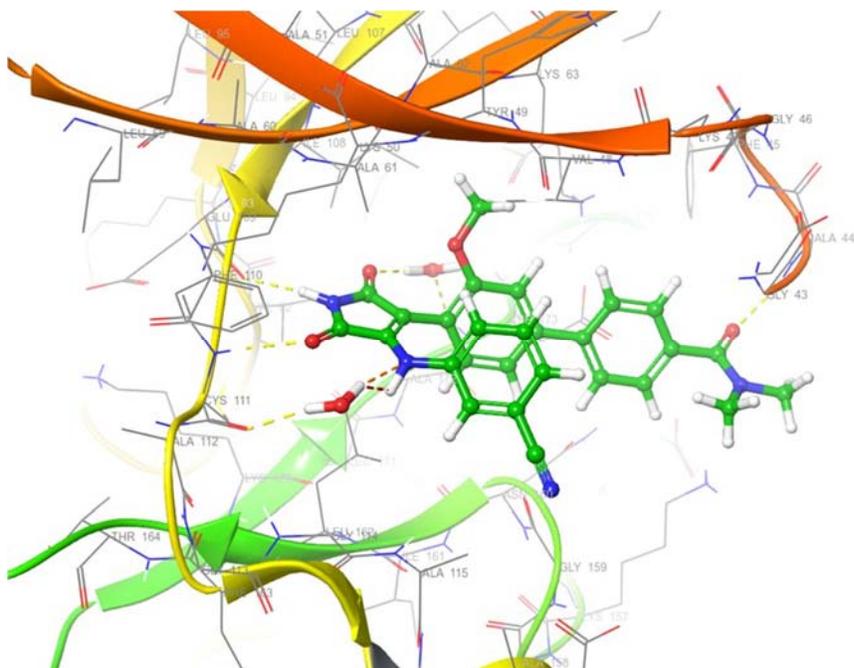
interesting starting point towards an SLK inhibitor. A co-crystal structure of the first SLK/maleimide complex was obtained at 1.6 Å resolution and this information was used to design new compounds by an automated computational approach, selecting the best ranked molecules to be synthesized. The automated virtual screening pipeline used a virtual library (>10,000) of new maleimides derived from commercially available building blocks (Wuxi and Sigma-Aldrich), the co-crystal structure, docking and scoring (Schrödinger molecular modeling package) to get new insights into molecules that could have improved potency and selectivity (*Figure 1*).

Based on the docking score results and visual inspection of the ligand-target interactions involved in the binding site (*Figure 2*), a diverse selection of new maleimide compounds were chosen and were synthesized using a four-step synthetic route to be tested in SLK binding assays.

The prototype maleimide has nM affinity with the kinase target. The compounds designed had good docking scores and were successfully synthesized (reasonable to good yields). The inhibition assays are ongoing.



The automated virtual screening pipeline.



Ligand-target interactions according to docking results.

MEDI 161

Discovery and structure–activity relationship study of dihydropyrano [2,3-c] pyrazoles as inhibitors of USP7

Antonella Pepe¹, antopepe24@gmail.com, **Nicole Hjortland**², Andrew D. Mesecar^{3,2}. (1) Purdue Center for Cancer Research, Purdue University, West Lafayette, Indiana, United States (2) Department of Biological Sciences, Purdue University, West Lafayette, Indiana, United States (3) Purdue University, West Lafayette, Indiana, United States

Ubiquitin is a highly conserved 76-amino acid protein that is covalently attached to a protein substrate as post-translational modification that labels the protein for proteasomal degradation. This reversible process controls the stability of proteins and its deregulation is among the causes of several human diseases, including cancer. Ubiquitination is catalyzed by the concerted action of E1-E3 ligases, while deubiquitination is facilitated by proteases called deubiquitinases (DUBs). The most studied of the DUBs is ubiquitin specific protease 7 (USP7), which has been shown to play an important role in cancer through the regulation of the activity and cellular levels of tumor suppressor proteins such as p53, PTEN, and FOXO4. USP7 represents a potential target for the development of anticancer therapies. We have discovered a novel class of USP7 inhibitors with the dihydropyrano [2,3-c] pyrazole as core scaffold. Our structure-activity relationship study has led to the identification of several active compounds that act as partial non-competitive inhibitors of USP7.

MEDI 162

Discovery of novel hVMAT2 ligands

Brian A. Provencher^{1,2}, provencherb@gmail.com, Amy J. Eshleman³, Robert A. Johnson³, Olga Kryatova², Jared Nelson², Jianhua Tian², Peter C. Meltzer², Aaron Janowsky³. (1) Merrimack College, North Andover, Massachusetts, United States (2) Organix Inc., Woburn, Massachusetts, United States (3) Oregon Health and Science University, Portland, Oregon, United States

Methamphetamine is a widely abused stimulant drug. A ligand for the human vesicular monoamine transporter (hVMAT2), methamphetamine is known to release dopamine from the vesicles into the cytosol of presynaptic neurons, thus increasing extracellular dopamine. There are few available radioligands to assess hVMAT2 binding and all reported radioligands have considerable liabilities. We report the synthesis and development of novel arylpiperidinyquinazolines (APQ) ligands which are potent inhibitors of [³H]reserpine binding at hVMAT2. Furthermore, experimentation shows that the APQ ligands also bind to a unique site on hVMAT2, and may be a useful tool for characterizing drug-induced effects on hVMAT2 expression and function.

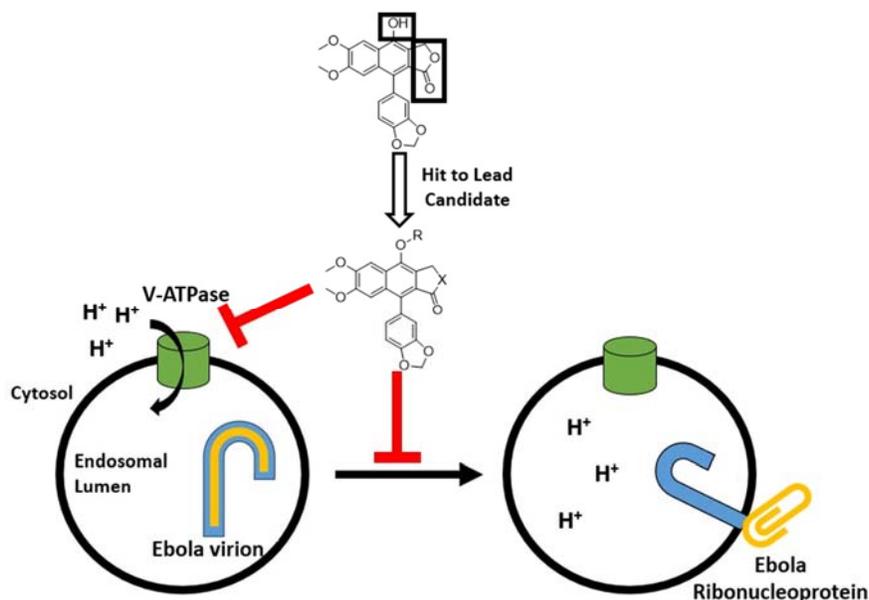
MEDI 163

Discovery of selective filoviral inhibitors through phenotypic screening of an aryl naphthalene lignan library

Aaron Lindstrom¹, alindst@purdue.edu, Dino P. Petrov², Vincent J. Davisson³. (1) Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette, Indiana, United States (2) Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette, Indiana, United States (3) Purdue University, W Lafayette, Indiana, United States

Filoviruses are highly contagious, lethal viruses that cause severe hemorrhagic fever in humans and primates. Like many viruses, Filoviruses utilize the endosomal pathway to gain entry to the cytosol of host cells and enable cellular infection. Acidification of virus-containing endosomes by the host protein Vacuolar-ATPase (V-ATPase) allows the virus to fuse with the endosomal membrane. Fusion permits the virus to release its ribonucleoprotein into the cytosol and initiate infection. Inhibition of V-ATPase has been shown to stop infection of many viruses, including Ebolavirus, a subtype of filoviruses. The natural product diphyllin was recently shown to be a potent inhibitor of V-ATPase with a significantly different chemotype from previous inhibitors. Our lab synthesized several different series of diphyllin derivatives of the lactone and phenol groups and assayed them for activity against Filoviral infection. To identify which hit compounds from the initial screen selectively inhibit endosomal acidification, derivatives were further screened for activity against acidification and cytotoxicity in several human cell models. Interesting differences between the different classes became apparent during the second screening, with basic phenol derivatives appearing as selective inhibitors of

endosomal acidification and filoviral infection. Selective inhibitors also directly inhibited V-ATPase activity and retained selectivity and potency against Ebolavirus infection of primary human macrophages. Thus, our phenotypic screens could be used to isolate novel, selective inhibitors of filoviral infection and provide direction in the development of diphyllin-based therapies.



MEDI 164

How far can we use human serum transferrin to transport drugs?

Gonçalo C. Justino, jose.justino@ist.utl.pt, M Matilde Marques. Centro de Química Estrutural, Instituto Superior Técnico, ULisboa, Lisboa, Portugal

Highly proliferative cells have an increased need for iron which results in the upregulation of human transferrin receptor expression. This insight makes the transferrin receptor on these cells an excellent candidate for targeted therapeutics. It has been shown that human serum transferrin, hTf, is able to accommodate various metal oxyanions, and it has been demonstrated that hTf is also able to bind vanadium complexes. The knowledge on the binding of metal ions, oxyanions, and complexes to serum proteins and how metals might be transported in blood and up-taken by cells has received much attention during the last decade.

Building on the existing molecular dynamics GROMOS force fields, we have expanded the force field parameters to include parameters for V(III), V(IV)O²⁺ and V(V) oxyanions, as well as for iron and metal ions in diverse oxidation states. The force field was validated by analysing 10 ns molecular dynamics runs on model systems consisting of the three known conformations of transferrin (closed, open and relaxed) and metal ion – inorganic synergistic anions.

The coordination geometries obtained replicate the data available experimentally in terms of amino acid residue interactions. The metal ions and synergistic anions interact with the same residues responsible for iron binding and with second-shell residues and are also strongly bound to the amino acid residues and the protein skeleton via extensive networks of hydrogen bonds

We also studied model transferrin ligands that form complexes with vanadium, in particular oxydiacetate, lactate and acetylacetonate. The results of molecular dynamics runs indicate strong interactions between the ligands and both the metal and the protein, and a set of amino acid residues has been identified as being conserved among the various simulations.

These conserved residues are crucial to effectively bind and transport protein ligands, with potential therapeutic activity, and will be used to guide the adaptation of existing drugs to obtain effective drugs that can be transported by human serum transferrin and delivered via hTf internalization. However, results also indicate that the region of the ligand that binds hTf must be relatively small, even if part of the ligand still protrudes from the metal binding pocket.

MEDI 165

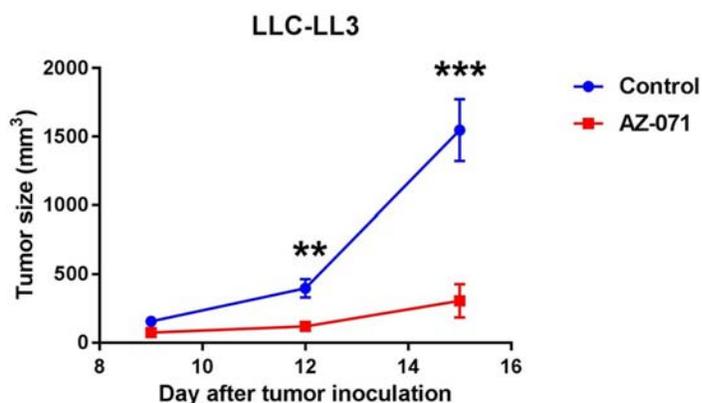
Optimization of penfluridol for use in anticancer therapy

Md Ashraf Uz Zaman, md.ashraf@ttuhsc.edu, Md Sanaullah Sajib, Constantinos Mikelis, Nadezhda A. German. Department of Pharmaceutical Sciences, Texas Tech University HSC, Amarillo, Texas, United States

Penfluridol, an antipsychotic drug is used to treat chronic schizophrenia and similar psychotic disorders since 1968. In the late 80's, Mortensen PB revealed the potential of antipsychotic drugs as antineoplastic agents. Later, several groups have investigated penfluridol as a potential chemotherapeutic using a variety of cancer in vivo models. However, no studies were reported to address an issue associated with the receptor-mediated central nervous system (CNS) toxicity of penfluridol. In our in vivo study (mice), we found that daily dosing of penfluridol for ten days leads to accumulation of the drug in the brain at the level of 0.5 μ M- 1 μ M. Such concentration is enough to block all major sub-classes of serotonin (K_i 316-2131 nm), dopamine (K_i 38-135 nm), opioid (K_i 70 -1526 nm) and sigma receptors (K_i 48-189 nm). Thus, potential repurposing of penfluridol as an anticancer agent can be complicated by a range of extrapyramidal symptoms and CNS-related disorders, such as depression, caused by the strong interaction of this drug with the CNS receptors.

In our study, we proposed to optimize penfluridol structure to eliminate CNS toxicity. One of the strategies we used was to remove the ability of new analogs to cross the blood-brain barrier, hence, to interact with the CNS receptors. Based on the reported structure-activity studies for both antipsychotic and anticancer property of penfluridol, we designed and synthesized a series of compounds and evaluated them using cell-

cytotoxicity assay (for the anticancer property) and MPO score combined with *in vitro* BBB model (for the BBB permeability). Further, we have determined that in mice our lead compound accumulates preferentially in lungs and fat. Therefore, we have assessed its *in vivo* activity using lung cancer model, where our compound has shown 80% tumor weight reduction (Lewis Lung Carcinoma xenograft model). In conclusion, we have identified a novel analog of penfluridol with the reduced CNS toxicity and ability to reduce tumor by 80% *in vivo*.



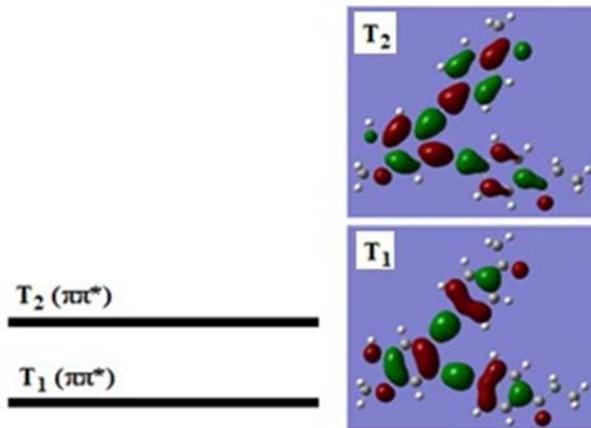
Tumor growth reduction in LLC Xenograft model in mice

MEDI 166

Photochemical release of glycine from excited state dendrimer: An example of novel drug delivery

Jong I. Lee¹, jilee@york.cuny.edu, **Jeonghee Kang**². (1) Department of Chemistry, York College of City University of New York, Jamaica, New York, United States (2) Chemistry, St. Joseph's College, Douglaston, New York, United States

A conjugated Dendron with a photo cleavable linkage to glycine, Glycine caged bis-1,2 - (4-acetylphenylethynyl)-4,5- dimethoxybenzene, is synthesized as a model for photochemical drug delivery. The Dendron is successfully synthesized in convergent manner and has tested for photoreactivity under various conditions. Photo reaction is observed in aqueous acetonitrile by NMR and UV- visible spectrometer. The products are isolated and being characterized. The detailed mechanism including molecular modeling study will be also presented.



MEDI 167

Metal binding antimicrobial peptoids

Jasmin Portelinha¹, jasmin.portelinha@uconn.edu, **Alfredo M. Angeles Boza**², **Steven Cobb**³. (1) Chemistry, University of Connecticut, Storrs, Connecticut, United States (2) University of Connecticut, Storrs, Connecticut, United States (3) Durham University, Durham, United Kingdom

Antimicrobial peptides (AMPs) are used by a multitude of organisms as a defensive mechanism against pathogens. The Amino Terminal Copper and Nickel Binding Unit (ATCUN) is found in many natural AMPs and consists of an XXH motif at the N terminus. When this motif is present, it causes inhibition of pathogens by binding divalent Cu and Ni to form reactive oxygen species (ROS) that damage the membrane or DNA. AMPs have long been considered possible therapeutics however, they can be hemolytic, are rapidly degraded by proteases in the body, and have solubility issues. Currently, only topical AMP therapeutics are available. Peptoids, are peptidomimetics with the side chain being attached to the amide nitrogen and not the α carbon (Figure 1). Peptoids have many advantages when compared to peptides such as thermal stability, high bioavailability, low cytotoxicity, and resistance to protease degradation. Previously we have shown that the addition of an ATCUN motif to an AMP increases the antimicrobial activity, therefore, we have added an ATCUN motif to known antimicrobial peptoids. In this work, a library of ATCUN peptoids were synthesized using arginine-, lysine-, and phenylalanine-like residues. Variations on the ATCUN motif were synthesized using L and D amino acids, as well as an ATCUN motif constructed from peptoid monomers. The structure was determined to be a polyproline type I helix due to the cis bonded monomers. These peptoids are helical, broad spectrum antimicrobial agents that target the membrane of bacteria. This nonspecific mechanism of action is difficult for bacteria to become resistant to, making ATCUN peptoids potential therapeutics. The ATCUN peptoids act synergistically with Cu^{2+} to kill bacteria.

MEDI 168

Roles of mitochondrial fusion promoter in ischemia/reperfusion injury

Shanshan Hou, *houyishan1990@gmail.com*. Michigan Technological University, Houghton, Michigan, United States

Mitochondria are highly dynamic organelles in continuous fusion and fission processes in response to various cellular stress. Mitochondrial dynamics, including mitochondrial fission/fusion and turnover, are important for the mitochondrial quality control. An imbalance between mitochondrial fission and fusion has been shown to contribute to many pathologies including ischemia/reperfusion (I/R) injury. Previous studies have shown that during the reperfusion period mitochondria undergo fission and that there is absence or reduction in mitochondrial fusion. Mitochondria fission renders cells highly susceptible to mitochondrial permeability transition pore (mPTP) opening, leading to an activation of the apoptotic pathway during reperfusion period. Pharmacological modulation of mitochondrial dynamics may have protective effects against I/R injury. Recently, we found that treatment of human umbilical vein endothelial cells with a small molecule, LPTC could significantly increase the percentage of cells containing tubular mitochondria and reduced cell death after simulated I/R. Furthermore, we demonstrated that LPTC could restore tubular network in response to genetically induced mitochondrial fragmentation in the Mfn1 knockout (Mfn1^{-/-}) and Mfn2 knockout (Mfn2^{-/-}) MEF cells. Our data showed that pharmacological modulation of mitochondrial fission/fusion by LPTC had an anti-apoptotic effect in the I/R experimental models.

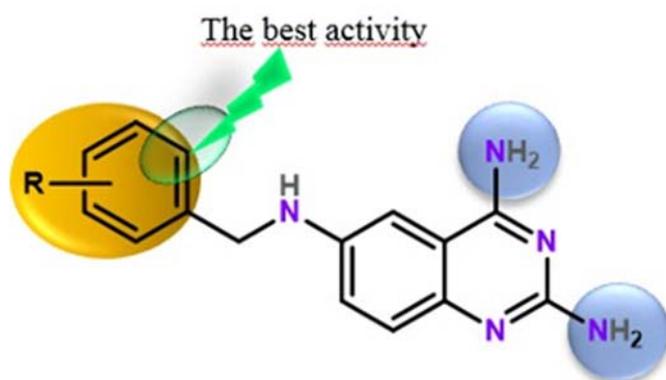
MEDI 169

Synthesis, characterization, cytotoxic and genotoxic evaluation of N⁶-benzylquinazoline-2,4,6-triamine derivatives

Audifas-Salvador Matus-Meza¹, *audi_matus@hotmail.com*, **Mayra Herrera-Martínez**², **Bibiana Chávez-Munguía**³, **Patricia Talamás-Rohana**³, **Marco A. Velasco-Velazquez**⁴, **Cynthia Ordaz-Pichardo**⁵, **Francisco Hernández-Luis**¹. (1) *Farmacia, Universidad Nacional Autónoma de México, Ciudad de México, México, Mexico* (2) *Instituto de Farmacología, Universidad de la Cañada, Oaxaca de Juárez, Oaxaca, Mexico* (3) *Departamento de Infectómica y Patogénesis Molecular, Centro de Investigación y de Estudios Avanzados, IPN, Ciudad de México, México, Mexico* (4) *Facultad de Medicina, Departamento de Farmacología y Unidad Periférica de Biomedicina Translacional, Universidad Nacional Autónoma de México, Ciudad de México, México, Mexico* (5) *Laboratorio de Biología Celular y Productos Naturales, Escuela Nacional de Medicina y Homeopatía, Instituto Politécnico Nacional, Ciudad de México, México, Mexico*

Cancer is a disease that is defined as the alteration of the mechanisms that govern the process of cell division, which causes cells to multiply without control and autonomously, invading locally or remotely other tissues. Currently, this condition represents high mortality rates worldwide both men and women. The treatments that

exist mostly have high economic costs, in addition to generating large adverse effects and toxic such as mutations in ADN. In this tenor, there is a need to look for new alternatives and one of them is the use of privileged molecules, such as quinazolines. In this work, we report the synthesis of 21 quinazoline-2,4,6-triamine derivatives, which are analogous to anticancer drugs such as gefitinib, which is characterized by having a quinazoline scaffold. All compounds were characterized by spectroscopic and spectrometric methods and evaluated in 3 cancer cell lines: HCT-15, MDA-MB-231 and SKOV-3 (colorectal, breast and ovarian cancer respectively). Interestingly, we found that the quinazoline derivatives with electron withdrawing substituents and preferably with the substitution in the *ortho* position of the benzenoid ring that is substituted in the 6 position of the quinazoline nucleus were those that showed the best cytotoxic activity in the three cell lines. On the other hand, the study of confocal microscopy and transmission electronic microscopy showed us that one of the quinazoline derivatives generates cell death by apoptosis. Additionally, the determination of genotoxicity by ames test turned out to be negative to mutagenesis.



MEDI 170

Homology model template selection benchmarking: Global versus local similarity measures

Paige Castleman¹, pncastleman@gmail.com, Abby L. Parrill-Baker², Daniel L. Baker³. (1) Chemistry, The University of Memphis, Memphis, Tennessee, United States (2) The University of Memphis, Memphis, Tennessee, United States (3) Univ of Memphis, Memphis, Tennessee, United States

GPCR are integral membrane proteins involved in cell signaling in a variety of cell types which makes them highly sought after targets for drug development. While GPCR are attractive drug targets, a significant number remain orphans; GPCR having unknown endogenous ligands. Ligand identification efforts have various starting points with computational methods becoming increasingly popular. Homology modeling is a widely used computational tool that generates models of proteins with unknown structures via sequence commonality to proteins of similar structure and function. Traditionally, homology modeling template selection (protein of known structure) is based on global sequence identity, however better models may result from templates with highly

localized sequence identity. For example, high sequence identity localized within the ligand binding pocket may produce better models to examine protein-ligand interactions. This in silico benchmark study examined the performance of global versus local template selection methods for 6 crystallized class A GPCR (CXCR4, FFAR1, NOP, P2Y12, OPRK, and muscarinic-M1) with the long term goal of optimizing ligand identification efforts in orphan GPCR. Global, 61-residue weighted, and 8-residue weighted all-atom and alpha carbon RMSD of models versus crystal structures were calculated. The 61 residues used are common to GPCR ligand binding pockets and the 8 residues selected have strong interactions in 70% of class A GPCR ligand binding. Overall, 4 of the 6 (3 of the 6) local template models gave better 61-residue weighted RMSD (8-residue weighted RMSD) than the global template models. Of the local template models with worse correlations, the RMSD were similar to that of the global template models. These data suggest that locally weighted templates may provide better models of GPCR ligand binding pocket. RMSD of ligand poses suggest that locally selected template models better mimic the crystallographic ligand position. Additional evaluations of ligand docking performance are ongoing to verify these results.

MEDI 171

Phototoxicity of 7-oxycoumarins with keratinocytes

Jaya Saxena¹, jas709@lehigh.edu, Jeffrey Laskin², Diane Heck³, Christophe D. Guillon¹, Ned D. Heindel¹. (1) Chemistry, Lehigh University, Bethlehem, Pennsylvania, United States (2) EOHSI, Rutgers University, Piscataway, New Jersey, United States (3) Environmental Health Science, New York Medical College, Valhalla, New York, United States

Natural product 7-hydroxycoumarins, their ethers and glycosides as well as linear fused-ring furocoumarins (psoralens), have broad pharmaceutical utility as anti-microbials, immune-modulators, anti-inflammatories, therapeutics for hyperproliferative skin diseases, anti-virals, and cancer chemotherapeutics. Several members of the related extended ring system, the psoralens, are FDA-approved phototherapeutics but such utility has not been demonstrated in the 7-hydroxycoumarins. Several research teams have concluded that simple coumarins such as umbelliferone, show no phototoxic effects. We have synthesized and screened >70 diverse 7-oxy coumarins substituted on the 3, 4, 6, 7, and 8 positions with halogen, hydroxyl, trifluoromethyl, amino, nitro, alkyl, alkenyl, alkynyl, and alkoxy moieties against the PAM 212 line of murine keratinocytes. IC₅₀ values were determined with and without exposure to UVA radiation. With irradiation, IC₅₀ values as low as 1.0 μ M were observed while without radiation, no toxicity was observed. Structure-activity correlations were apparent in those oxy-coumarins which possessed highest activity. Optimum analogs displayed bromo or iodo on ring position three or on pendant alkyl side chains. Free phenolic functions were generally less active than their corresponding ethers. Electron withdrawing groups (trifluoromethyl, fluoro, cyano, and nitro) suppressed activity. Plasmid DNA unwinding experiments also demonstrated that the most photo cytotoxic compounds had the greatest effects.

MEDI 172

Antibacterial activities of auranofin analogs

*Bin Wu*¹, *bin_wu1@student.uml.edu*, *Xiaojian Yang*¹, *Mingdi Yan*². (1) *Umass Lowell, Lowell, Massachusetts, United States* (2) *Dept of Chemistry, University of Massachusetts Lowell, Lowell, Massachusetts, United States*

Infections caused by antibiotic-resistant bacteria are a rising public health threat and make the identification of new antimicrobial strategy a priority. One such strategy is antibiotic repurposing. Auranofin is approved by the FDA as an orally administered drug for treating rheumatoid arthritis. Recently, auranofin has been reported to have potent antibacterial activity toward *Clostridium difficile*, *Enterococcus faecium*, *Enterococcus faecalis*, *Treponema denticola*, MRSA, replicating and non-replicating *M. tuberculosis*. We have synthesized a series of auranofin analogs. In this presentation, the synthesis of these compounds will be presented. The antibacterial activity of these compounds were tested against a panel of bacteria and results will also be presented.

MEDI 173

Selective targeting of breast cancer brain metastases by cisplatin prodrug nanoformulation

Bapura Surnar, *bapusurnar@gmail.com*, *Shanta Dhar*. *Biochemistry and Molecular Biology, University of Miami, Miami, Florida, United States*

Breast cancer brain metastases (BCBMs) are common in patients with advanced breast cancer diseases. This is one of the breast cancer subtypes and its performance status are the major determinants of the course of the disease and survival time following a diagnosis of brain metastasis. The unique challenges specific to the management of BCBMs includes, overcoming the blood-brain barrier (BBB) and resistance to conventional systemic therapies, as BCBMs typically occur in the pretreated patient population. The development of new systemic and selective targeting nanoformulation based therapies for BCBMs has become increasingly important. In this work, we developed a cisplatin prodrug loaded brain accumulating nanoparticle to deliver the active drug cisplatin to the mitochondria of the cancer cells. Though, the brain cell matrix is very complex and heterogeneous, we were able to show the selective targeting ability of these nanoparticles towards the BCM cells over non-cancerous brain cells by crossing the BBB.

MEDI 174

NAADP-BODIPY dye conjugates for characterizing NAADP binding proteins

Zhong Guan, *zguan@rockets.utoledo.edu*, *James Slama*. *Medicinal and Biological Chemistry, University of Toledo, Toledo, Ohio, United States*

Ca²⁺ is one of the most versatile and important intracellular messenger since it controls numerous cellular process. Nicotinic acid adenine dinucleotide phosphate (NAADP) functions as an intracellular 2nd messenger causing Ca²⁺ release from acidic and vacuolar Ca²⁺ stores. Signaling through NAADP is widespread and important, but the process is not yet been completely understood. To determine cellular localization and potential changes in cell distribution of NAADP binding proteins we propose to use NAADP-dye conjugates. NAADP-dye conjugates can be produced from 5-(3-aminopropyl)-NAADP, linking it through an amide linkage to a dye which in turn contains a carboxylic acid. An oligo-ethylene glycol could also be introduced between the NAADP analog and the dye as a hydrophilic spacer. To start the synthesis, BODIPY dyes are particularly attractive, since they are intense, do not photobleach, are uncharged, and can be produced with long wavelength fluorescent emission if desired. Once the first generation of NAADP dye conjugates has been produced its biological activity will be characterized using sea urchin NAADP binding proteins. We can further apply NAADP-dye conjugates for the development of fluorescence depolarization assays of NAADP binding in future work. A successful depolarization assay would enable us to develop automated assays of NAADP binding to sea urchin egg homogenates and subsequently to screen libraries of drug like molecules to find stable and bioavailable NAADP agonists and antagonists.

MEDI 175

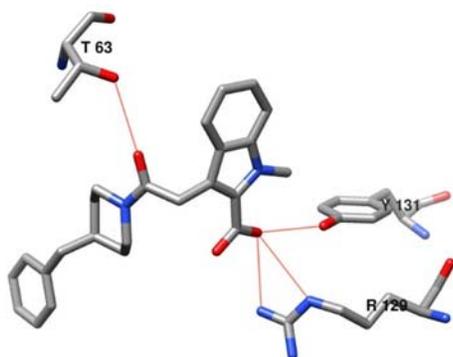
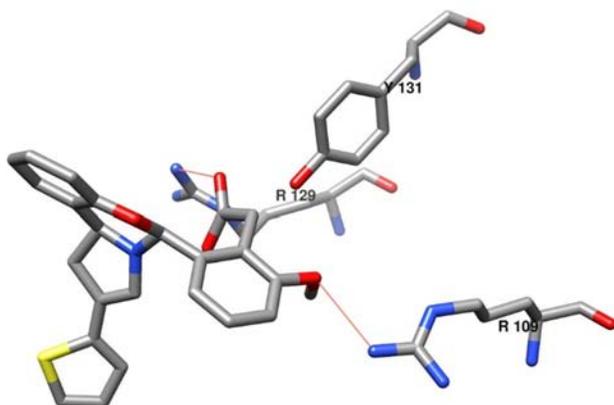
Design, synthesis, and SAR of inhibitors of lipid chaperones (FABPs) toward next-generation therapeutic agents for chronic pain and cancer

Monaf Awwa¹, awwamonaf@hotmail.com, Su Yan¹, Matthew Elmes³, Jessica Li⁴, Kiana Ziadkhanpour⁵, Martin Kaczocho^{6,2}, Robert C. Rizzo^{7,2}, Dale Deutsch^{3,2}, Iwao Ojima². (1) Chemistry, Stony Brook University, Stony Brook, New York, United States (2) Chem Dept/ICBDD, Stony Brook University, Stony Brook, New York, United States (3) Biochemistry and Cell Biology, Stony Brook University, Stony Brook, New York, United States (4) Pingry School, Basking Ridge, New Jersey, United States (5) John F Kennedy High School, Plainview, New York, United States (6) Anesthesiology, Stony Brook University, Stony Brook, New York, United States (7) Applied Math and Statistics, Stony Brook University, Stony Brook, New York, United States

Several lipid chaperones, such as fatty acid binding protein (FABPs), exist in the mammalian genome which enable the diffusion of highly hydrophobic molecules across membranes. Inhibition of specific subtypes of FABPs has been demonstrated to provide potential therapeutic benefit for chronic pain and may also for certain cancers. In particular, the inhibition of FABP5 has been shown to elicit analgesia through inhibiting reuptake of anandamide, hence increasing its extracellular concentration to show physiological effects. By acting through the cannabinoid receptor, anandamide has also been shown to decrease inflammation. The prospect of a less addictive mechanism of action is especially desired due to the epidemic of prescription opioid associated overdose deaths.

Based on the *in-silico* screening of over a million compounds from the ZINC database,

followed by *in vitro* FABP-binding affinity assay, we have discovered a unique α -truxillic acid derivative, SB-FI-26, as a hit/lead compound. SB-FI-26 exhibited potent anti-nociceptive activities when tested *in vivo* in mice models of pain. The optimization of SB-FI-26 is actively underway in our laboratories. The same *in-silico* screening and *in vitro* affinity assay identified two more active hit compounds, SB-FI-19 and SB-FI-31. Therefore, in this study we performed structure-based computer-aided optimization of these two hit compounds for FABP5, which produced a series of analogs with promising docking energy scores and predicted pharmacological properties. The design, synthesis and biological evaluation of selected hit compounds will be presented.



MEDI 176

Exploiting solvent effects in drug design and optimization

Alain Ajamian, **Christopher Williams**, cw@chemcomp.com. Chemical Computing Group, Montreal, Quebec, Canada

There is significant interest in understanding the behavior of water molecules as it relates to ligand-receptor interactions. In specific cases, ambiguous and counterintuitive SAR seems to be linked to solvent effects. Ligand affinity and specificity appear to be

influenced by the action of water molecules on the solvated ligand-receptor complex. As such, a deeper analysis of solvent effects would expose potential ligand design opportunities that were previously not conceivable. Here we report the application of the 3D Reference Interaction Site Model as a potential method to account for such solvent effects.

MEDI 177

Hepatitis C virus NS3/4A protease inhibitors incorporating flexible P2 quinoxalines target drug resistant viral variants

Jacqueto Zephyr², jacqueto.zephyr@umassmed.edu, Ashley N. Matthew¹, Nese Kurt-Yilmaz², Celia A. Schiffer³, Akbar Ali⁴. (1) of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, Massachusetts, United States (2) Biochemistry and Molecular Pharmacology, , University of Massachusetts Medical School, Worcester, Massachusetts, United States (3) Univ of Massachusetts Med Schl, Worcester, Massachusetts, United States (4) Biochemistry and Molecular Pharmacology, UMass Medical School, Worcester, Massachusetts, United States

A substrate envelope-guided design strategy is reported for improving the resistance profile of HCV NS3/4A protease inhibitors. Analogues of 5172-mcP1P3 were designed by incorporating diverse quinoxalines at the P2 position that predominantly interact with the invariant catalytic triad of the protease. Exploration of structure– activity relationships showed that inhibitors with small hydrophobic substituents at the 3-position of P2 quinoxaline maintain better potency against drug resistant variants, likely due to reduced interactions with residues in the S2 subsite. In contrast, inhibitors with larger groups at this position were highly susceptible to mutations at Arg155, Ala156, and Asp168. Excitingly, several inhibitors exhibited exceptional potency profiles with EC50 values less than 5 nM against major drug resistant HCV variants. These findings support that inhibitors designed to interact with evolutionarily constrained regions of the protease, while avoiding interactions with residues not essential for substrate recognition, are less likely to be susceptible to drug resistance.

MEDI 178

Investigating the efficacy of functionalized hybrid gold nanoparticles as theranostic platforms in dialysis related amyloidosis and Alzheimer's disease

Ricardo Burke¹, rburke@claflin.edu, Derrick J. Swinton², Marlena P. Washington¹, Hongxia Zhang³, Arezue Boroujerdi¹. (1) Chemistry, Claflin University, Orangeburg, South Carolina, United States (2) Lincoln University, Lincoln Univ, Pennsylvania, United States

Silica functional gold nanoparticles (Au@SiO₂) have unique physiochemical properties enabling them to be used in the diagnosis and treatment of diseases (Theranostic). In addition to their tunable localized surface plasmon resonance (LSPR), Au@SiO₂

nanoparticles are localized heat sources and can be used in hypothermal cancer treatment (ref). The goal of this project is to design hybrid nanoparticles capable of diagnosing and disrupting protein aggregation. The Au@SiO₂ will be functionalized with molecules enhancing their transport mechanisms enabling them to overcome barriers encountered in their usage in clinical applications, particularly penetration across cell and tissue barriers. The specific aims are as follow: (1) investigate the interaction of Au@SiO₂ nanoparticles with two amyloidogenic proteins, Amyloid Peptide (A β) and β -2-Microglobulin (β 2M); (2) introduce specificity to the A β and β 2m by functionalizing Au@SiO₂ with peptides and other molecules complimentary to regions of each amyloid protein responsible for protein aggregation; (3) examine the potential neurotoxicity, neuromodulatory, and cytotoxicity effects of Au@SiO₂ nanoparticles utilizing human neuroblastoma, human iPSC cortical, and SH-SY5Y cell lines. The proposed research will shed insight into the interactions of nanoparticles with biomolecules and biological systems, thus providing researchers with design principles to engineer nanoparticles effective in diagnostic and therapeutic technologies.

MEDI 179

Discovery and optimization of macrocyclic peptide dimerization inhibitors of BRAFwt

Chad Beneker¹, cbeneker@email.sc.edu, Magdalini Rovoli², Michael Roring³, George Kontopidis², Tilman Brummer³, Campbell McInnes¹. (1) Drug Discovery and Biomedical Sciences, University of South Carolina, Columbia, South Carolina, United States (2) Biochemistry, University of Thessaly, Karditsa, Greece (3) Molecular Medicine, University of Freiburg, Freiburg, Germany

The mitogen-activated protein kinase (MAPK) pathway modulates cell proliferation through regulation of the communication between extracellular signaling and intranuclear transcription. BRAF, a Ser/Thr kinase in the MAPK pathway, is frequently mutated in cases of metastatic melanoma, most frequent of which is the phosphorylation mimicking V600E mutation. The FDA approved ATP-competitive inhibitor, vemurafenib, effectively inhibits signal transduction in the context of BRAF(V600E), but upon binding to BRAF(wt), paradoxical activation of the second RAF monomer within the dimer is induced, and drug resistance develops in the form of mutant RAS-driven tumorigenesis. The Brummer group rationalized that paradoxical activation identified the key residues for dimer formation and therefore peptides were designed to encompass this interface. The BRAF (wt) dimerization inhibiting linear has been tested and shown to inhibit downstream phosphorylation events in a dose-dependent manner in the presence of vemurafenib. The initial peptide exhibited a K_d = 3.84 μ M in a direct binding assay and truncation of this sequence led to a 30-fold increase in potency, potentially due to electrostatic stabilization of a pseudo-cyclic conformation. An alanine scan was then completed to identify key binding residues and included those critical for dimerization in the full length protein context. Peptides were cyclized to decrease the entropic cost of binding by covalently stabilizing their bioactive β -turn conformation. Cyclic peptides exhibit sub-micromolar binding affinities and the

ring size is currently being optimized to promote potent binding interactions. Lead molecules have been shown to inhibit paradoxical signaling in metastatic melanoma cell lines. The ultimate goal is to systematically replace segments of the optimized cyclic peptide and to generate a macrocyclic BRAF(wt) dimerization inhibitor which is cell permeable and proteolytically stable. This approach of inhibiting BRAF(wt) dimerization is a novel method of avoiding paradoxical activation of BRAF during treatment with vemurafenib in metastatic melanoma patients, while inhibiting mutant RAS-driven tumorigenesis.

MEDI 180

Anticancer properties of ruthenium(II) complexes and their application for photodynamic therapy and photoactivated chemotherapy

Raphael Ryan, raphael.ryan@uky.edu, David K. Heidary, Kimberly C. Stevens, John P. Selegue, Edith C. Glazer. Department of Chemistry, University of Kentucky, Lexington, Kentucky, United States

Control over where and how chemotherapeutic agents react in a patient is a key component to developing new drugs that limit side effects and maintain high efficacy. This control can be achieved by using light to activate an inert drug to generate cytotoxic species. This method of activation can be achieved through either photodynamic therapy (PDT) or photoactivated chemotherapy (PACT). PDT uses inactive photosensitizers to generate singlet oxygen and other reactive oxygen species upon light irradiation. PACT, in contrast converts an inert prodrug to a toxic new chemical entity through the cleavage of select bonds when irradiated with light. Photosensitizers that are currently used in the clinic, suffer from poor performance due to low aqueous solubility as well as side effects resulting from slow drug clearance from the body. Ruthenium(II) complexes have been demonstrated to be promising new photosensitizers and anticancer agents due to their increased solubility and tunable photophysics. A series of Ru(II) complexes containing bidentate and tridentate N-heterocyclic carbenes will be described, along with complexes containing strained ligands. These complexes show promising anticancer properties, with low toxicity, ($IC_{50} > 100 \mu\text{M}$) in the absence of light, and good activity (IC_{50} values $< 7 \mu\text{M}$) in the presence of light. This study will report the synthesis, photophysics, cellular localization, and anticancer properties for a series of photoactive Ru(II) complexes.

MEDI 181

Alternative synthetic pathway for a cytotoxic compound for lymphocytic leukemia

Danny Belmona, dbelmona@mail.niagara.edu, Luis Sanchez. Department of Biochemistry, Chemistry, and Physics, Niagara University, Niagara University, New York, United States

(-)-Communesin F is a naturally occurring compound isolated from marine and terrestrial Penicillium fungi. This compound sparked interest in the scientific community due to its significant cytotoxicity against lymphocytic leukemia cells in humans. (-)-Communesin F also has minimal effects on other cells making it highly selective against leukemia, however, extracting even trace amounts from natural sources is extremely costly, difficult, and time-consuming. Research on this compound has revealed that it can be biosynthesized from another natural product, (-)-aurantioclavine. Our goal is to efficiently synthesize (-)-aurantioclavine at a minimal cost, to be able to produce the final material in appropriate quantities. We are currently comparing two potential starting materials, tryptamine and 3-indolepropionic acid, which give us an inexpensive platform to start the synthesis. Our key synthetic steps include a Schmidt reaction and a Meyers chiral formamidinium-based alkylation, to install two important structural features found in auranoclavine: a seven-membered ring and a benzylic chirality center. Our progress in these efforts will be presented.

MEDI 182

Development of structure-activity relationships of cjoc42 for targeting Gankyrin

Joseph Almasri², joseph.almasri15@my.stjohns.edu, Pamela Farrales¹, Ehab Abo-Ali¹, Younos Otmankhel¹, Abdul Shaik¹, Vikas Dukhande¹, Vivek Gupta¹, Aaron Muth¹, mutha@stjohns.edu. (1) Pharmaceutical Sciences, St. John's University, Bellerose, New York, United States (2) Chemistry, St. John's University, Queens, New York, United States

Gankyrin is a small, but crucial oncoprotein involved in regulating numerous pathways important to cell growth, signaling, proliferation and death. The overexpression of gankyrin and subsequent increased interactions with other proteins play an integral role in the onset and development of a variety of cancers. One particular protein-protein interaction is gankyrin-S6 ATPase of the 26S proteasome. This interaction is necessary for the proteasome to properly degrade a variety of polyubiquitinated proteins, including tumor suppressor proteins such as p53 and p21. Therefore, increased interaction between gankyrin and the S6 ATPase results in decreased p53 levels and an increase in cell proliferation.

Consequently, small-molecules which prevent the gankyrin-S6 ATPase interaction as well as other gankyrin-mediated protein-protein interactions are promising therapeutic strategies for the treatment of certain cancers. Recently, the first small-molecule binder of gankyrin was developed (cjoc42) which also exhibited an ability to prevent gankyrin-S6 ATPase binding. As a result, cjoc42 set the stage for a new category of anti-cancer therapeutics. Using a rational approach guided by molecular modeling, we have set out to develop an extensive SAR for this scaffold in an effort to improve its ability to prevent the gankyrin-S6 ATPase interaction and inhibit cancer cell proliferation.

MEDI 183

Development of small molecule- and peptide-based probes for targeting Gankyrin

Dipti Kanabar, *dipti.kanabar17@my.stjohns.edu*, Aaron Muth. *Pharmaceutical Sciences, St. John's University, Queens, New York, United States*

Overexpression of the ankyrin repeat protein gankyrin is directly linked to the onset, proliferation, and/or metastasis of many cancers. This is primarily accomplished by gankyrin-related protein-protein interactions which subsequently regulate numerous oncogenic pathways. Specifically, gankyrin-retinoblastoma protein (Rb) binding results in Rb phosphorylation (pRb) and its subsequent inactivation. Gankyrin also directly binds with MDM2 causing enhanced ubiquitination of p53 and subsequent degradation. Furthermore, gankyrin regulates proteasomal degradation of numerous proteins through its binding to the S6 ATPase of the 26S proteasome. This includes degradation of tumor suppressor proteins such as p53, p21 and pRb. Early studies have shown that disrupting the gankyrin-S6 ATPase interaction is a promising therapeutic strategy for the treatment of certain cancers which overexpress Gankyrin. This resulted in the first small-molecule binder of gankyrin, cjoc42, which also demonstrated an ability to prevent gankyrin from binding to the S6 ATPase of the 26S proteasome. This inhibitor proved to be useful in the generation of a novel class of anti-cancer therapeutics.

This discovery has also set the stage for the development of gankyrin-binding fluorescent probes. Utilizing both the cjoc42 scaffold as well as a known gankyrin-binding peptide sequence as starting points, a series of fluorescently-conjugated probes were developed. These probes will be utilized to develop high-throughput screening assays (i.e., fluorescence polarization and FRET) for future inhibitors as well as provide novel diagnostic and imaging tools for gankyrin-related cancers.

MEDI 184

Lobaric acid and pseudodepsidones from the lichen *Stereocaulon paschale* inhibit NF- κ B signaling pathway

Claudia Carpentier^{1,2}, *claudia.carpentier.1@ulaval.ca*, Xavier Barbeau³, Daniel Grenier⁴, Patrick Lagüe³, Normand Voyer¹. (1) *Chemistry Department, Université Laval, Quebec, Quebec, Canada* (2) *SiliCycle, Quebec, Quebec, Canada* (3) *Pavillon Charles-Eugene-Marchand, Laval University, Quebec, Quebec, Canada* (4) *Médecine Dentaire, Université Laval, Quebec, Quebec, Canada*

In response to environmental stress, lichens produce a rich diversity of highly bioactive defence compounds to protect the symbiotic partners. Therefore, lichens of Northern Quebec represent a source of potential bioactive natural products due to the extreme growing conditions in the Nunavik region. Chemical investigation of the lichen *Stereocaulon paschale* has led to the isolation and identification of two new dibenzofurans and 11 metabolites known in other lichen species. Six pseudodepsidone-type metabolites were identified, deriving from the cleavage of the depsidone linkage of lobaric acid, the major compound of the crude methanolic extract. Lobaric acid and pseudodepsidones metabolites demonstrated significant *in vitro* inhibitory activity against major pro-inflammatory targets (NF- κ B, TNF- α and IL-1 β). Docking simulations were performed to investigate the mechanism of action involved. To further investigate

their anti-inflammatory potency, we have developed a synthetic methodology that gives access the metabolites studied, but also to a variety of other lichen metabolites. Isolation, identification, synthesis and inhibitory activity against pro-inflammatory targets will be presented.

MEDI 185

Synthesis and biological evaluation of novel 6-substituted thieno[3,2-d]pyrimidines as targeted antifolates

Tasdiq M. Quadery¹, tasdiq.bd7@gmail.com, Farhana Islam¹, Larry H. Matherly², Aleem Gangjee¹. (1) Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, Pennsylvania, United States (2) Department of Oncology, Wayne State University School of Medicine, Detroit, Michigan, United States

Reduced folates are indispensable cofactors for *de novo* biosynthesis of purines and pyrimidines. Antifolates that inhibit the folate-related enzymes are important agents for anticancer chemotherapy. However, dose-limiting toxicities of clinically used antifolates hinder their clinical utility. These toxicities are most likely due to their cellular uptake into normal tissues, as well as into tumors. Three specialized systems for folate transport exist in humans which include the reduced folate carrier (RFC), folate receptors (FRs) α and β , and the proton-coupled folate transporter (PCFT). Selectively transported novel targeted antifolates via FRs and PCFTs over the ubiquitously expressed RFC would circumvent major toxicities of currently used antifolates. We previously reported a series of targeted 6- substituted thieno[2, 3- d] pyrimidine classical antifolates that are specifically taken up by the folate receptor (FR) and inhibit FR expressing tumor cells (KB and IGROV1) at nanomolar IC₅₀ values. In this study, we synthesized and evaluated the regioisomeric bicyclic scaffold *i.e.* the thieno[3,2- d] pyrimidine ring as novel targeted antifolates. Regioselective bromination was used to selectively functionalize the 6-position of the scaffold. This report will discuss the design, synthesis, molecular modeling and biological activity of these compounds.

MEDI 186

Regulation of AIMP2-DX2, oncogenic splicing variant using small molecule

Srigouri Huddar¹, srigouri@krict.re.kr, Sukyung Lee², Chul Min Park³. (1) Centre for Convergence of Emerging Virus, Korea Research Institute of Chemical Technology, Daejeon, Korea (the Republic of) (2) Medicinal Chemistry, Korea Research Institute of Chemical Technology, Daejeon, Korea (the Republic of) (3) KRICT, Jupiter, Florida, United States

Aminoacyl-tRNA synthetase-interacting multifunctional protein 2 (AIMP2) is a potent tumor suppressor inducing apoptosis upon various signals. AIMP2-DX2, an exon2-deleted splicing variant of AIMP2, is upregulated in several cancer cells and

competitively suppresses the pro-apoptotic activity of AIMP2 resulting in tumorigenesis. Additionally, it has been identified that AIMP2-DX2 interacts with K-Ras, oncogene, following the stabilization of K-Ras, and promotes the evolution of cancer. Then, we tried to find a series of compounds which inhibit the interaction between AIMP2-DX2 and K-Ras using Nanobit screening system. We identified that a series of hydrazone derivatives inhibited the expression of AIMP2-DX2. Herein, we report that 1) How new scaffolds were designed and validated; 2) Optimization process through syntheses and evaluation of derivatives; 3) Structure-activity relationship (SAR) analysis of a series of compounds; 4) Profiles of validated hits. Additionally we disclose the results of in vivo assay.

MEDI 187

Re-defining the oxindole chemotype to identify narrow spectrum inhibitors of the dark kinases TLK2 and PKMYT1

Christopher R. Asquith^{1,2}, chris.asquith@unc.edu, Michael P. East¹, Tuomo Laitinen³, Graham J. Tizzard⁴, David H. Drewry², Gary L. Johnson¹, Tim Willson². (1) Department of Pharmacology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States (2) Structural Genomics Consortium, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States (3) Department of Pharmacy, University of Eastern Finland, Kuopio, Finland (4) UK National Crystallography Service, School of Chemistry, Highfield Campus, University of Southampton, Southampton, Hampshire, United Kingdom

Kinase drug discovery has focused around gaining potency on target, with selectivity being an important, but secondary consideration. This problem is particularly acute when exploring the biology of the 'dark-kinome' where only promiscuous small molecule inhibitors are known. Interrogation of observed phenotypes is confounded by the off-target activity of these inhibitors. Protein kinase, membrane associated tyrosine/threonine 1 (PKMYT1) and Tausel-like kinase 2 (TLK2) are both dark kinases that are amplified in the breast cancer genome atlas data sets and are highly expressed in triple negative breast cancer cell lines. PKMYT1 is a key regulator of the G2 checkpoint, which acts to inhibit Cdc2 (Cell division control protein 2), while TLK2 is involved in chromatin assembly, DNA repair and transcription. Knock-down/Knock-out growth phenotypes in triple negative SUM159PT breast cancer cells have shown particularly encouraging results. We have identified two oxindole chemotypes that have activities on PKMYT1 and TLK2, respectively. The oxindole chemotype is notorious for kinome promiscuity, but we have observed through steric and electronic manipulations that this activity can be honed towards our targets of interest. We will describe on-going efforts to optimise these oxindole analogs into high quality chemical probes for use in the elucidation of PKMYT1 and TLK2 biology in cells and *in vivo*.

MEDI 188

Design, synthesis and biological evaluation of novel aromatic/heterocyclic sulfonamides as carbonic anhydrase inhibitors with selectivity for tumor-overexpressed isozyme IX

Utpal K. Mondal¹, tuf08263@temple.edu, Elizabeth Mcduffie¹, Sabina Zamanova¹, Claudiu T. Supuran², Marc A. Ilies¹. (1) Pharmaceutical Sciences, Temple University, Philadelphia, Pennsylvania, United States (2) Univ Florence Lab Chim Bioorg, Sesto Fiorentino, Italy

Carbonic anhydrase (CA) is a zinc metalloprotein that catalyzes the reversible hydration of CO₂ to bicarbonate and protons. Fourteen isozymes were identified in humans, with different subcellular localization and tissue distribution. Particularly important is the isozyme CA IX, found to be overexpressed in tumors as a result of tumor hypoxia. CA IX inhibition was shown to be an efficient way to kill tumor cells, with CA IX inhibitors such as SLC0111 being currently in clinical trials for treatment of hypoxic solid tumors. Our team has a long-standing interest in designing selective CA IX inhibitors. We will present our latest achievements into this direction, supported by X-ray crystallography that allowed us to draw valuable structure-activity relationships. Structure-property relationships will be also presented, correlating the potency and lipophilicity of the CA inhibitors with their ability to kill tumor cells and to act as novel anticancer agents.

MEDI 189

Design and synthesis of anxiolytic, anticonvulsant and antinociceptive benzodiazepine/GABA(A)ergic receptor subtype selective ligands as potential non-sedating treatment for anxiety disorders, epilepsy and pain disorders

Guanguan Li², guanguan.li@yahoo.com, Jeffrey Witkin³, Jeffrey Schkeryantz³, Rok Cerne³, Jun-Xu Li⁴, Lakeisha Lewter⁴, Kevin Freeman⁵, Douglas Stafford², Leggy Arnold¹, James M. Cook². (1) University of Wisconsin Milwaukee, Milwaukee, Wisconsin, United States (2) Univ of Wisconsin, Milwaukee, Wisconsin, United States (3) Eli Lilly and Company, Indianapolis, Indiana, United States (4) Pharmacology and Toxicology, University at Buffalo, Buffalo, New York, United States (5) Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, Mississippi, United States

Benzodiazepines (BZD) are a common class of psychoactive medications for the treatment of CNS disorders such as anxiety, epilepsy, neuropathic pain, schizophrenia, depression and other diseases. However, not all patients have a positive response to BZDs, as well as the presence of serious side effects including amnesia, sedation, addiction, ataxia, withdraw and drug resistance. An alpha 2/alpha 3 GABA(A)R subtype-selective ligand Hz-166 (**1**) was the initial lead imidazobenzodiazepine (IBZ, Zeilhofer et al.) and was found to be anxiolytic in primates (Fischer et al.), an anticonvulsant in rats and mice (Rivas et al.), antihyperalgesia in a pain model (Paul et al.) with no tolerance

and less sedative or ataxia effects were observed. However, the ester moiety in **1** was metabolized very rapidly in rodents to its corresponding carboxylic acid, which did not readily pass the blood-brain barrier, which would interfere with ADME TOX in rodents. Therefore, a series of novel ester bioisosteres at C-3 in place of the labile ester group were then designed and synthesized to improve the metabolic stability and achieve enhanced pharmacological effects. Among the series of novel bioisosteres, one of the most promising ligands, a 1,3-oxazole KRM-II-81 (**2**), was identified as an alpha 2/alpha 3 GABA(A)R subtype-selective ligand very little or no alpha 1 nor alpha 5 efficacy. KRM-II-81 had an excellent metabolic profile in vitro in human, mice, and rat liver microsomes, as compared to the parent ligand **1**. The ligand **2** exhibited an anxiolytic effect in a rat Vogel conflict test and a mouse marble-burying assay without rotorod failures. Most recently, the ligand **2** (30 micro M) significantly attenuated the firing rates in human epileptic cortical tissue on a 60 microelectrode array and has a wider margin of effect compared to motor-impairment than diazepam. Moreover, **2** reduces tactile-induced allodynia after CFA-induced pain in rats, and the behavior effects can be attenuated by the BZD receptor antagonist flumazenil. In addition, **2** did not develop tolerance to the antinociceptive effects in rats, nor decreased the respiration rate. The results here indicated that the oxazole **2** could be a potential anxiolytic, anticonvulsant and analgesic for the treatment of anxiety disorders, epilepsy and pain disorders. Recent results will be presented.

MEDI 190

Cholesteryl ester vesicle mediated delivery of nucleic acids into neural cells *in vitro*

Sarah Andres¹, sandres@mail.niagara.edu, Mary Q. Irving³, Alexander Kovacs¹, John Fraser-McArthur², Julie Hughes¹, Jerome Schentag³, **Lawrence Mielnicki**¹, Imm@niagara.edu, Mary McCourt¹. (1) Chemistry Dept, Niagara Univ, Niagara Univ, New York, United States (2) Pharmacy and Pharmaceutical Sciences, State University of New York at Buffalo, Buffalo, New York, United States (3) CPL Associates, Buffalo, New York, United States

This laboratory has developed a neutral lipid based vesicle that uses naturally occurring cholesteryl esters to encapsulate and deliver a wide variety of substances, including fluorescein isothiocyanate (FITC) and other small molecules, vancomycin and other antibiotics, insulin and other peptides, IgG antibodies and other proteins as well as plasmid DNA and other nucleic acids. Previous work has shown cholesteryl ester vesicle-mediated delivery of FITC-labeled peptides into various mouse tissues (including brain) after oral administration. Cholesteryl ester vesicles could therefore be used to orally deliver compounds for which intravenous administration is the only effective dosing route. Particularly exciting is the potential to orally deliver nucleic acid therapeutics. The present study reports preliminary work on the encapsulation and delivery of plasmid DNA encoding Green Fluorescent Protein (GFP), a molecule widely used as a co-transfection marker and to study protein interaction and localization. Successful transfection of this plasmid results in a cell that displays green fluorescence

when excited with light of the appropriate wavelength. In the present study GFP was encapsulated and the resulting preparations were characterized for vesicle size as well as lipid and DNA content. Cholesteryl ester vesicle delivery of GFP plasmid into several neural cell lines including SHSY5Y, LUHMES and U373 was demonstrated. These studies suggest the potential for cholesteryl ester vesicle-mediated delivery of treatments for neurodegenerative diseases.

MEDI 191

Isolation and synthesis of luffariellolide derivatives and evaluation of antibacterial activities against Gram-negative bacteria

Jihoon Lee, jihoonlee@kiost.ac.kr, A-Young Shin, Hyi-Seung Lee. Korea Institute of Ocean Science Technology, Busan, Korea (the Republic of)

Luffariellolide, an anti-inflammatory sesterterpene, was originally isolated as a major metabolite from the hexane extract of the Palauan sponge *Luffariella variabilis*. Initially, luffariellolide has been reported to exhibit reversible inhibitory activity against phospholipase A₂ (PLA₂), which is a mediator for inflammation. During the course of our research to identify marine invertebrates producing pharmacologically useful metabolites, luffariellolide was isolated from the marine sponge *Suberea sp.*, which was collected offshore of the Philippines. Chemical diversification on the g-hydroxylbutenolide core of luffariellolide revealed that pyridazinone-type derivatives can enhance the antimicrobial activity toward *K. pneumonia* up to 32 times (MIC = 2 mg/mL), compared to that of the natural product (MIC > 64 mg/mL). Also, N-pyridinyl pyridazinone analogue exhibited selective anti-cancer activity against A375SM with an EC₅₀ value of 6.3 mM/mL (luffariellolide, EC₅₀ = 24 mg/mL), while luffariellolide showed non-selective cytotoxicity against most of cancer cell lines.

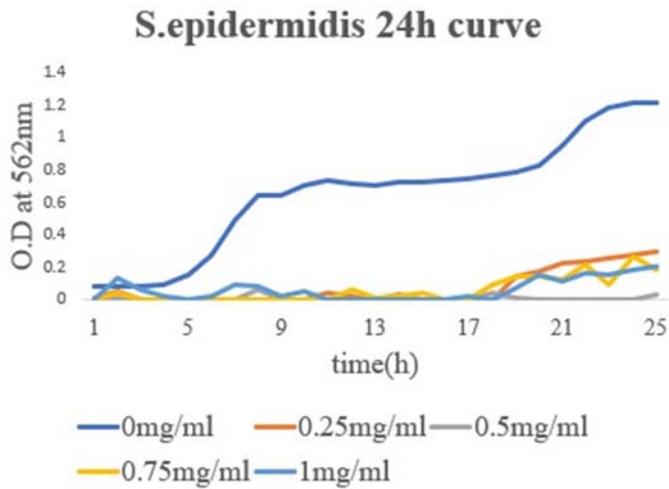
MEDI 192

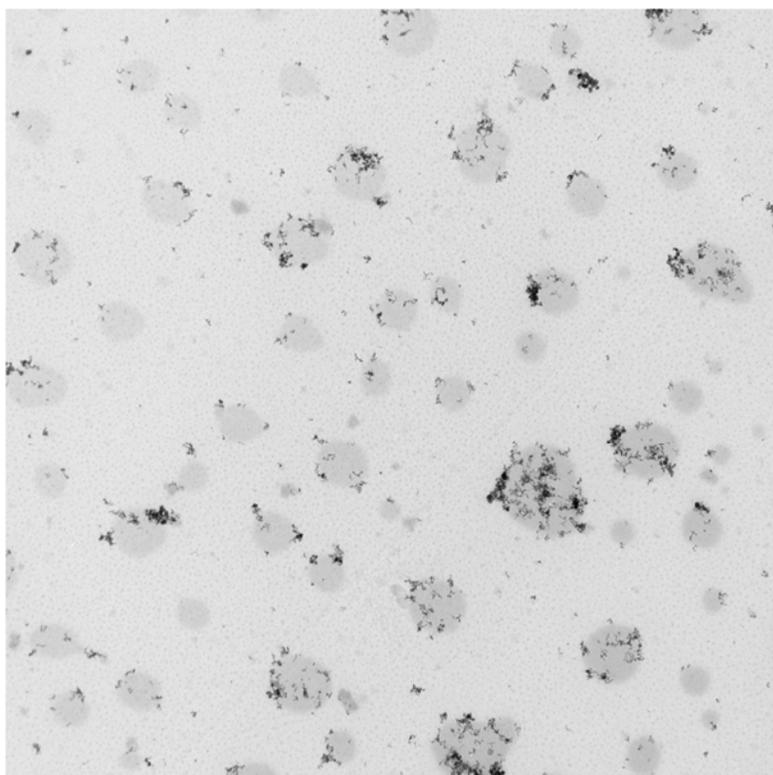
Electro-responsive ceria nanoparticle-embedded ferrocene-polyethyleneimine nanocarriers for the treatment of bacterial infections

Siqi Zhao¹, zhao.siq@husky.neu.edu, Nicole Bassous². (1) northeastern university, Malden, Massachusetts, United States (2) Chemical Engineering, Northeastern University, Boston, Massachusetts, United States

Contemporarily, with the overuse of antibiotics, bacterial strains are continually developing a resistance to conventional drugs. These multi-drug-resistant bacteria (MDR bacteria) are more difficult to kill and can result in severe infections that are difficult to treat. Cerium oxide nanoparticles have aroused interest from the scientific community due to their good antimicrobial performance, antioxidant properties, and biocompatibility. Since large concentrations of ceria are toxic to mammalian cells and tissues, it is necessary to control the release rate, transport, and kinetics of ceria within

the body. Therefore, here we have developed an electro-responsive drug delivery system by encapsulating ceria inside ferrocene-modified polyethyleneimine nanocarriers. From the TEM picture, we could see that ceria has been successfully encapsulated into polymer micelles. The antibacterial test also shows ceria has a obvious effect on killing the gram-positive bacteria. The electro-responsive property of this system will be tested soon.





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500 nm
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MEDI 193

New insights into salvinorin A from an activated kappa opioid receptor structure

Philip D. Mosier¹, pdmosier@vcu.edu, ***Tao Che***², ***Bryan L. Roth***². (1) *Medicinal Chemistry, Virginia Commonwealth University, Richmond, Virginia, United States* (2) *Pharmacology, University of North Carolina, Chapel Hill, North Carolina, United States*

We recently determined the structure of an activated kappa opioid receptor (KOR)–agonist–nanobody complex using X-ray crystallography, demonstrating for the first time the molecular basis of KOP activation, and shedding light on kappa opioid receptor ligand selectivity and biased agonism. The mechanism by which the highly affine and non-basic natural product salvinorin A and its analogs interact with and modulate the function of the KOR has not been determined to date and is not only intriguing from a receptor–ligand interaction standpoint but is also a key to the development of potential treatments for widespread debilitating conditions such as chronic pain, itch and addiction disorders. Using the newly-determined activated KOR structure, we present a structure-guided hypothesis for the binding of salvinorin A and a series of its selected analogs, and also provide a rationale for the opioid receptor subtype selectivity and biased agonism properties of the analogs.

MEDI 194

Structure-activity relationship study of otilonium bromide as an antimicrobial agent

Jayce Rhodes¹, *rhodes.jayce@gmail.com*, **Hua-Yu Wang**¹, **Ashley Cunningham**², **Bryan Daives**², **Stanton F. McHardy**¹. (1) University of Texas at San Antonio, San Antonio, Texas, United States (2) University of Texas at Austin, Austin, Texas, United States

Quaternary amine compounds is a class of small molecules consisting of a positively charged quaternary amine head with a lipophilic tail. These types of compounds have a wide variety of uses including surfactants in common household cleaning products as well as antimicrobial agents. Otilonium bromide is a potential antimicrobial agent within this class, but like other quaternary amine compounds it exhibits the adverse side effect of hemolysis. To mitigate the killing of red blood cells while maintain its antimicrobial properties, a structure-activity relationship study is done to study the effects of each part of the molecule on potency and hemolysis. As a result of over 80 analogs of Otilonium bromide being synthesized and tested, multiple lead compounds have been established that maintain potency while significantly decreasing or eliminating hemolysis. The project's future goals include further improving the properties and therapeutic index as well as diving deeper into the mechanism of action in stopping bacterial growth.

MEDI 195

Interactions of pyridine based aromatic hydrazides and amides with model membrane interfaces

Benjamin J. Peters¹, **Cameron an Cleave**¹, **Keisha Giffen-Kent**¹, **Dean Crick**¹, **Audra Sostarecz**², **Debbie C. Crans**¹, *Debbie.Crans@ColoState.edu*. (1) Colorado State University, Fort Collins, Colorado, United States (2) Chemistry, Monmouth College, Monmouth, Illinois, United States

Pyridine based small molecule drugs, vitamins, and cofactors are vital for many cellular processes, but little is known about their interactions with membrane interfaces. These specific membrane interactions can help the molecules diffuse across membranes or even reach their membrane bound target. This study explored how minor differences in pyridine based small molecules (isoniazid, benzhydrazide, isonicotinamide, benzamide, nicotinamide, and picolinamide) interact with model membranes to demine if small differences in structure can affect their membrane interactions. Compression isotherms of the first model membrane of this study, Langmuir monolayers of dipalmitoylphosphatidylcholine (DPPC) or dipalmitoylphosphatidylethanolamine (DPPE), in the presence of the pyridine derivatives of interest was able to show that isoniazid and isonicotinamide affect the DPPE monolayer at lower concentrations than the DPPC monolayer and the nitrogen content and stereochemistry can affect the phospholipid monolayers differently. To obtain a molecular perspective of the interactions of the

molecules mentioned above, ^1H 1D NMR and ^1H - ^1H 2D NMR techniques were utilized to obtain information about position and orientation of the pyridine based molecules of interest within the second model membrane, Aerosol-OT (AOT) reverse micelles. These studies were able to show that all six of the molecules resided near the AOT sulfonate headgroups and ester linkages in similar positions, but does show nicotinamide and picolinamide tilt at the water-AOT interface to varying degrees. Combined, these studies demonstrate that small structural changes of small molecules can affect their specific interactions with membrane-like interfaces and their interactions with specific phospholipids which may play a role in their diffusion across bilayers, and specificity toward specific cells.

MEDI 196

Multi-target molecular profiling using MOE: A CYP450 isoform selectivity case study

Michael R. Goldsmith, r.goldsmith@chemcomp.com, Christopher Williams. Chemical Computing Group, Montreal, Quebec, Canada

Abductive reasoning applied to modeling chemical biology can only be made possible if both quality datasets (i.e. in vitro, HTS or expert curation) and versatile cheminformatics and molecular modeling methods are available. Identifying compounds that are susceptible to metabolic degradation via cytochrome P450 (CYP450) pathways, and identifying which major isoform is responsible is an ongoing problem. Here we demonstrate using a combination of 2D and 3D cheminformatics and modeling tools built into MOE (Molecular Operating Environment) how a rational workflow can be developed to predict CYP450 isoform specificity. Using a combination of carefully curated in vitro CYP450 data and a variety of modeling techniques implemented in MOE (binary classification trees, 2D-molecular fingerprints, pharmacophores) we developed efficient computational approaches to identify putative CYP interacting ligands. These models are easily further integrated into a KNIME workflow, using the MOE extensions for KNIME. The tiered molecular triage workflow we developed using MOE can be used to interrogate large datasets of compounds for potential CYP450 binders with sub-type profiling capabilities. These modeling approaches can be directly generalized to other protein families (i.e. nuclear receptors or the kinome), in which isoform specificity and poly-pharmacological interactions are of interest. These studies place emphasis on the need for accurate curated data in addition to versatile and inter-operable modeling platforms, such as MOE, that enable multi-dimensional modeling approaches for interrogating chemical biology for large scale molecular profiling.

MEDI 197

Computational approach for performing medicinal chemistry transformations within a 3D active site

Nels Thorsteinson¹, Alain Deschenes², alain.deschenes@unb.ca. (1) Chemical Computing Group Inc, Montreal, Quebec, Canada (2) Chemical Computing Group, Montreal, Quebec, Canada

In this work, MedChem Transformations, a modeling application for performing medicinal chemistry transformations in the context of the 3D receptor and ranking the resulting molecules is presented. The methodology is outlined and a test study using a PDE5A-Sildenafil complex is performed. The results demonstrate that including pocket atoms and preserving key interactions help generate promising candidates that are relevant to the PDE5A receptor as well as a known PDE5A ligand (Vardenafil) from the original Sildenafil molecule.

MEDI 198

MOEsaic: Application of matched molecular pairs to interactive SAR exploration

Alain Ajamian, aajamian@chemcomp.com. Chemical Computing Group, Montreal, Quebec, Canada

The ability to effectively manage the structure activity relationships (SAR) generated in a medicinal chemistry programme is of paramount importance to drug discovery. This is not a trivial task as the number of synthesised molecules can grow very rapidly. Additionally, a substantial number of molecules can be routinely tested in multiple biological and physico-chemical assays, leading to the generation of hundreds to thousands of data points for each chemical series. Therefore, distilling the information to a manageable discrete set for guiding ligand design is a serious challenge.

Here we describe a new application which is a single framework dedicated to the analysis of SAR data and the design of novel chemical targets. The application can be used to quickly address typical medicinal chemistry workflows aimed at interrogating the SAR data through the use of filters, plots and a versatile structure visualiser. Additionally, the application can be used to smoothly navigate complex SAR data (using matched molecular pairs) to quickly identify the key SAR trends and investigate if SAR can be transferred between the different templates present in the dataset.

MEDI 199

Organizing 3D project data for structure-based drug design

Alain Ajamian, aajamian@chemcomp.com. Chemical Computing Group, Montreal, Quebec, Canada

It is often desirable to organize disparate crystallographic project data into a common homogeneous format, ready to use for modelling. We present a web-based application that permits users to specify numerous options controlling superposition and alignment of structures in a family or project, ligand specification, and whether electron densities

or other grids are to be included. The final result is a project database containing superposed structures all in the same frame of reference. From here, structures can be dynamically regrouped, for example by scaffold class, for easy management, and can be easily browsed and used as a starting point for further research. The system is able to handle multi-subunit complexes, including structures which may be missing subunits, by using a novel algorithm to determine which subunits of each complex correspond to each other.

MEDI 200

Direct electrochemical differentiations of cancer and normal cells on the titanate

Hanan Alismail^{1,2}, halismai@email.uark.edu, Yuchun Du^{3,1}, Jianhong Zhou³, Z.Ryan Tian^{4,1}. (1) Cell and Molecular Biology, University of Arkansas, Fayetteville, Arkansas, United States (2) Institute for Nanoscience/Engineering, University of Arkansas, Fayetteville, Arkansas, United States (3) Biological Sciences, University of Arkansas, Fayetteville, Arkansas, United States (4) Chemistry/ Biochemistry, University of Arkansas, Fayetteville, Arkansas, United States

In the development of new cancer diagnostic tools, inventing a new technology that can differentiate cancer cells from normal cells are critical to the cancer cell sensors with minimized false negative and false positive signals. In parallel, the cancer cell sensors reported in the literature to date are mostly based on some signal transductions on a materials surface far from that of a typical bioscaffold, which detects the cancerous cells in a foreign environment with some built-in physical and/or chemical stresses onto the cells. Here we report a new invention that turns a bioscaffold into an electrochemical sensor, which has been seldom reported in the literature to the best of our knowledge. This bioscaffold-based sensor has distinguished cancer cells from normal cells simply, directly, sensitively, and reproducibly for the first time. In this work, the electrochemically sensory nanofibers of titanate (low-cost bioceramics) were grown and entangled into the bioscaffolds first of all on top of a titanium metal, which were characterized by means of XRD, SEM, TEM, etc. The bioscaffolds were then incubated with two types of human breast cancer cells, benign and aggressive, and one type of normal breast cells, in both separate and mixed cases. The different cells have reproducibly shown significant differences in impedance change at high frequencies on the sensory bioscaffolds. On this basis, different ratios of the cancer cells in the normal cells shifted the mixture's impedance signals quantitatively and reproducibly. This new discovery has suggested that the cancer cells have altered the bioscaffolds surface charge-density much more than the normal cells while binding to the surface of nanofibers of the bioscaffold. This disruptive sensor is potentially useful in electrochemical sensing of both cancerous cells and bacteria at ultra low-cost and in real-time, which are potentially doable even *in vivo* thanks to the implantable nature of the bioscaffold.

MEDI 201

Application of extended Huckel theory to pharmacophore modeling

Alain Ajamian, aajamian@chemcomp.com. Chemical Computing Group, Montreal, Quebec, Canada

Pharmacophore models play an essential role in drug discovery. Generating pharmacophore models which encode accurate molecular recognition features are highly dependent on properly defined annotation points. Simplistic or ill-defined pharmacophore annotations that do not capture subtle electronic or geometric effects lead to many inaccuracies. Rule-based methods, which typically employ SMARTS patterns to specify annotation rules, are subject to such inaccuracies. Here we have developed a new approach for pharmacophore modeling which is based on a semi-empirical method using Extended Hückel Theory (EHT). In contrast to rule-based approaches, the EHT method is chemically aware and uses a model to assign annotation points and generate features. The pharmacophore features generated through the EHT annotation scheme take into account ligand resonance and electron withdrawing effects and are sensitive to non-standard interactions, such as C-H and halogen bond interactions, during pharmacophore screening. The EHT method provides a new approach for pharmacophore screens that is more in line with physicochemical principles.

MEDI 202

Discovery of highly potent PI4KIII β inhibitors against rhinovirus replication

Prashant Chakrasali^{1,2}, prashant@krikt.re.kr, Han Soo Bong^{1,2}, Young-Sik Jung^{1,2}. (1) Division of Bio and Drug Discovery, Korea Research Institute of Chemical Technology, Daejeon, Korea (the Republic of) (2) Department of Medicinal and Pharmaceutical Chemistry, University of Science and Technology, Daejeon, Korea (the Republic of)

Human Rhinoviruses (hRVs) are major pathogens for both upper and lower respiratory tract. These infections are serious threat to patients with asthma, chronic obstructive pulmonary disorder (COPD), or cystic fibrosis in whom respiratory tract infections with RVs can lead to exacerbations.

Phosphatidylinositol 4-kinase III β (PI4K β) is critical for mediating viral replication of number of RNA viruses through the generation of PI4P-enriched viral replication platform. These membranous enriched PI4P plays essential roles in spatially concentrating viral replication proteins and are key in intracellular viral replication. Therefore, the inhibition of this PI4K isoforms leads to the arrest of viral replication. Here in we report on the synthesis of PI4KIII β inhibitors, through combination of high throughput screening (HTS) and known PI4K inhibitors. Synthesized compounds shows sub Nano molar anti hRV activity with high selective indices

MEDI 203

Amphipathic fatty acyl-cyclic [W₄R₄K] peptides as antimicrobial agents against pathogenic bacteria

Ajayi D. Akinwale¹, akinw100@mail.chapman.edu, Jason Yamaki², Keykavous Parang¹, Rakesh Tiwari¹. (1) Center for Targeted Drug Delivery, Department of Biomedical & Pharmaceutical Sciences, Chapman University School of Pharmacy, Irvine, California, United States (2) Department of Pharmacy Practice, Chapman University School of Pharmacy, Irvine, California, United States

Antibacterial peptides are emerging class of agents that have activities against multidrug-resistant Gram-positive and Gram-negative organisms. The cyclic peptide [W₄R₄] containing positively-charged arginine (R) and hydrophobic tryptophan (W) residues had antibacterial activity with a minimum inhibitory concentration (MIC) value of 4 mg/mL against methicillin resistant *Staphylococcus aureus* (MRSA) and 42 mg/mL against *Pseudomonas aeruginosa* (PSA). The purpose of this study was to optimize antibacterial activity of cyclic peptide by conjugation to various fatty acid chains with different lengths. The antimicrobial effects were determined against MRSA, *Klebsiella pneumoniae* (KPC), *Pseudomonas aeruginosa* (PSA), and *Escherichia coli* using meropenem and vancomycin as controls and compared with [W₄R₄]. Cyclic peptide [W₄R₄K] was synthesized using Fmoc-based chemistry. The linear peptide was further cyclized by a condensation reaction between N-terminal and C-terminal of the linear peptide. The cyclic peptide was characterized by Matrix-Assisted Laser Desorption/Ionization Time of Flight mass spectroscopy (MALDI-TOF) and purified with high performance liquid chromatography (HPLC). Fatty acyl anhydrides (RCO-O-COR) where R= CH₃, CH₃(CH₂)_{2n-2}- were conjugated with purified peptides to obtain [W₄R₄K(C₂)], -[W₄R₄K(C₄)], -[W₄R₄K(C₆)], -[W₄R₄K(C₈)], [W₄R₄K(C₁₀)], [W₄R₄K(C₁₂)], and [W₄R₄K(C₁₄)]. MIC values against MRSA, PSA, KPC and *E. coli* were 32 mg/mL, 128 mg/mL, 64 mg/mL, and 64 mg/mL for [W₄R₄K(C₄)], respectively, and 64 mg/mL, 256 mg/mL, 256 mg/mL, and 256 mg/mL for [W₄R₄K(C₂)], respectively. Minimum bactericidal concentration (MBC) values were 64 mg/mL, 256 mg/mL, 64 mg/mL, 64 mg/mL for [W₄R₄K(C₄)], respectively. The results of controlled drugs and parent drug moiety [W₄R₄] were also obtained. The fatty acyl cyclic peptide [W₄R₄K(C₄)] demonstrated higher antibacterial activity than [W₄R₄K(C₂)] while it showed less activity than [W₄R₄]. While [W₄R₄K(C₂)] had virtually no effect on Gram-negative strains *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, [W₄R₄K(C₄)] had antibacterial activity against these strains.

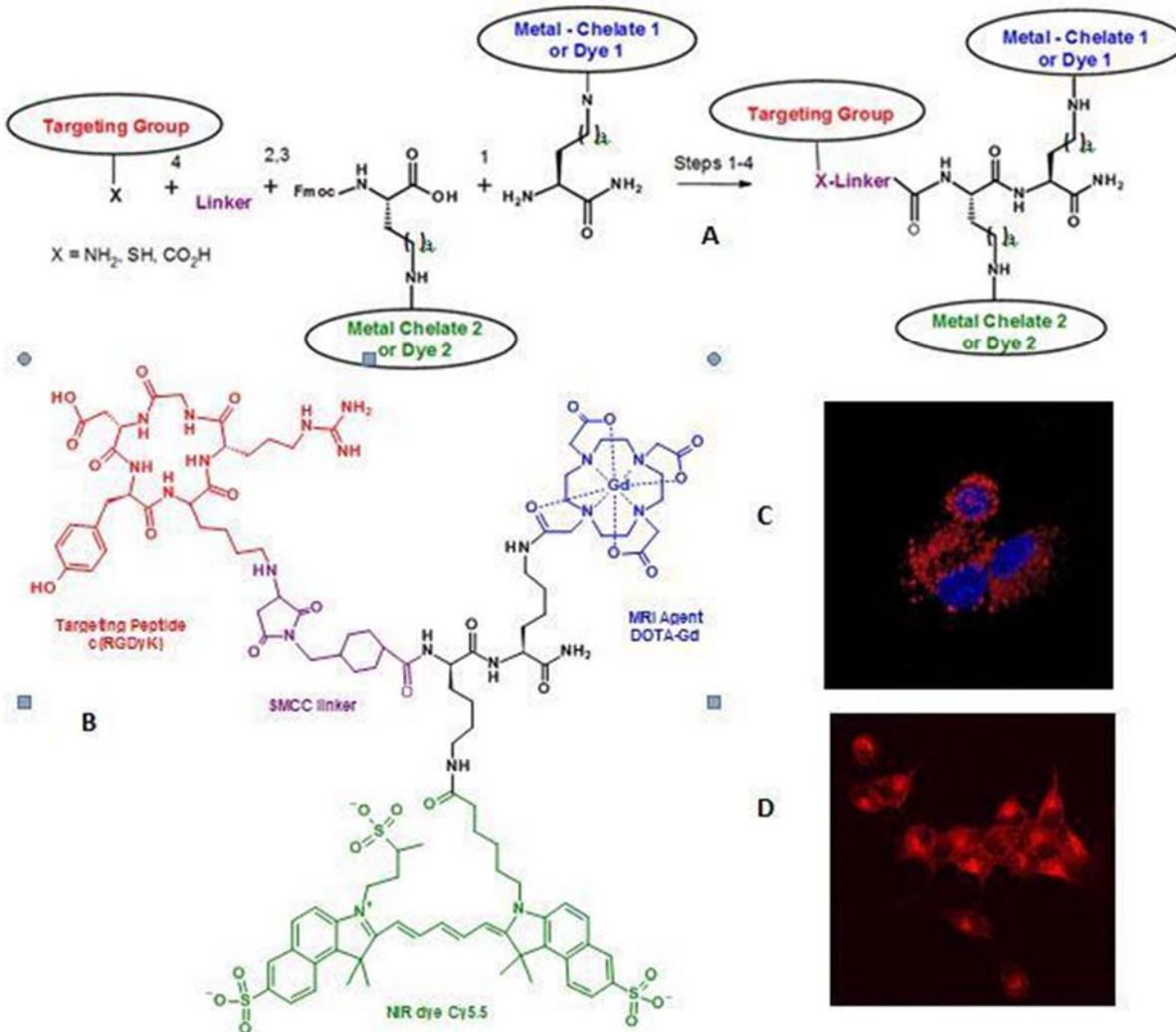
MEDI 204

Modular synthesis of peptide-based single and multimodal targeted molecular imaging agents

Hans F. Schmitthenner^{9,2}, hfssch@rit.edu, Taylor Barrett^{3,9}, Stephanie Beach^{9,5}, Lauren Heese^{1,4}, Anne Marie Sweeny-Jones^{9,6}, Chelsea Weidman^{9,5}, Kelsea Jones⁷,

damien Dobson⁹, Xinyu Xu⁹, Henry Ophardt⁸, Karim Embong⁹, Irene Evans⁸. (1) Chemistry College of Science , Rochester Institute of Technology, Rush, New York, United States (2) Center for Imaging Science, Rochester Institute of Technology, Rochester, New York, United States (3) University of Pennsylvania, Philadelphia, Pennsylvania, United States (4) M.D. Anderson Cancer Center, Houston, Texas, United States (5) Chemistry, Boston University, Boston, Massachusetts, United States (6) Chemistry, Georgia Institute of Technology, Atlanta, Georgia, United States (7) Chemistry, Rochester Institute of Technology, Rochester, New York, United States (8) School of Life Sciences, Rochester Institute of Technology, Rochester, New York, United States (9) School of Chemistry and Materials Science, Rochester Institute of Technology, Rochester, New York, United States

Compact, stabilized peptides have advantages in bioavailability and tissue penetration when utilized as scaffolds for imaging agents used in MRI, PET and optical imaging. The aim was to assemble these through a modular method in which imaging agents are pre-attached to the side chains of lysines, then coupled together, followed by conjugating to linkers and targeting groups. The result is a method for selectively combining two different dyes, or two metals, or mixing dyes with metals to create dual-dye, dual-metal, or dual-modal targeted imaging agents. Also via this route, a variety of targeting groups can be conjugated to a given imaging system in the final steps of synthesis. In an enabling discovery, it was found that a metal introduced early can serve as a protecting group for the chelator DOTA, allowing synthesis of high-relaxivity di-Gd MRI agents, or dual modal metal-dye agents for MRI-OMI. It was further discovered that lanthanides La or Ce may be used as place-holders in DOTA, and readily transmetalated in mild acid by Cu, In, Y, or Ga used in PET in the last step. Conversely, Gd was stable, thus yielding a route to targeted PET-MRI agents in which the final radioactive metal can be introduced easily in the clinic. A variety of single modal agents, and dual-modal agents for OMI-MRI and PET-MRI were synthesized utilizing RGDyK for targeting lung cancer, and the PSMA inhibitor DCL for targeting prostate cancer. Selective targeting of cancer cells was verified by in-vitro imaging with confocal fluorescence microscopy.



A. Modular synthesis of dual modal targeted imaging agents, B. c(RGDyK) targeted dual modal agent for OMI-MRI, C. CFM of A549 lung cancer cells using B, D. CFM image of C42B (PSMA+) prostate cancer cells with targeted, modular agent.

MEDI 205

Vinblastine and effects of its metabolites on nausea associated receptors

Caroline M. Chagas, cmc723@mun.ca, Laleh Alisaraie. School of Pharmacy, Memorial University of Newfoundland, St. John's, Newfoundland, Canada

Vinblastine (VLB) is a vinca alkaloid drug that inhibits the polymerization of microtubules (MTs) and promotes cell arrest. VLB causes a variety of adverse drug reactions (ADRs). Our research results show that it mainly affects the gastrointestinal tract, myeloid tissue and hair follicle pathways. Similar to many other anticancer drugs, VLB has been strongly associated with nausea. Despite advances in the medicinal chemistry field that aims to reduce drug toxicity, the cause and mechanism of VLB-induced ADRs remain

poorly understood. ADRs are complex and sometimes considered idiosyncratic events, however, there is a strong relationship among drug metabolites and ADRs. I have found that VLB can be metabolized into 35 metabolites, whose effects concerning nausea associated receptors have not yet been characterized. We have recently identified major receptors associated with nausea protein interaction network that includes histaminic, dopaminergic and muscarinic receptors. Utilizing molecular docking approach as well as an accurate *in silico* pharmacological property-predictor, my research unveiled potential interactions of the VLB metabolites with our identified off-targets sites. We have found that despite weak affinities of the majority of the metabolites for histaminic H₁ and H₃, and dopaminergic D₂ receptors, they have strong interactions with muscarinic M₁, M₄ and M₅ receptors. Interestingly, VLB has a better binding affinity than the natural substrate acetylcholine for M₅R. Molecular docking of VLB and metabolites into the drug's binding site, at the interface of α - and β -tubulin, demonstrates that metabolite 20-Hydroxy-VLB has stronger binding affinity (-13.4 kJ/mol) than VLB (-11.2 kJ/mol) for tubulin. They, as well, show similar pharmacological properties. These novel findings provide knowledge of which VLB metabolites are likely to be associated with nausea during chemotherapy, as well as their binding interactions with the receptors involved in this pathway. By precisely determining the mechanism of VLB and metabolites interaction with the off-targets sites, ADRs such as nausea can be avoided. Furthermore, our lab has demonstrated the possibility of VLB delivery by single-walled carbon nanotubes (SWNT) due to their strong drug-carrier interactions. This study proposes effective modifications on the chemical structure of VLB that along with applications of nanoparticles for its delivery could result in reducing ADRs.

MEDI 206

Pro-soft drug modulators of sphingosine-1-phosphate receptor 1 (S1PR1)

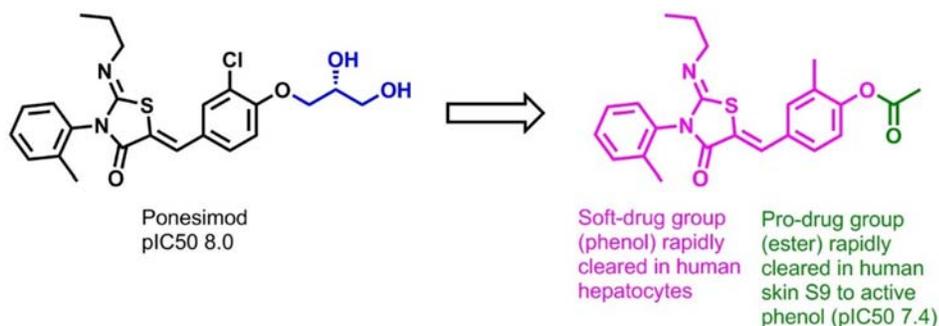
Colin Robinson¹, cxrobinson@dundee.ac.uk, Mark Bell¹, David Foley¹, Claire Naylor¹, Gavin Wood¹, Jennifer Riley¹, Ola Epemolu¹, Lucy Ellis¹, Paul Scullion¹, Yoko Shishikura¹, Daniel Fletcher¹, Elad Katz¹, W. H. Irwin McLean², Paul Wyatt¹, Kevin Read¹, Andrew Woodland¹. (1) Drug Discovery Unit, University of Dundee, Dundee, United Kingdom (2) Dermatology and Genetic Medicine, Division of Molecular Medicine, University of Dundee, Dundee, United Kingdom

Psoriasis is a common chronic inflammatory skin disease that affects 2% of the population, resulting in red, flaky plaques of skin over a significant area of a patient's body. In a recent survey, from the National Psoriasis Foundation, 52% of patients expressed their dissatisfaction with current treatments. For example, treatments for mild to moderate psoriasis suffer from a lack of efficacy and a potential for prohibitive side-effects resulting from chronic use.

Oral S1PR1 modulators are emerging as efficacious drugs for the treatment of psoriasis, but their use is also limited by systemic side effects such as lymphopenia, bradycardia and dyspnoea. To overcome these side effects we set out to design topical

soft drug S1PR1 modulators. These compounds would be active at the site of disease (i.e. the skin) but would be rapidly metabolised and cleared upon reaching systemic circulation potentially alleviating side effects.

Using a fast follower approach starting from the clinically validated drug ponesimod we developed an active phenolic S1PR1 series. Unfortunately, this series proved to be chemically unstable. This issue was overcome by protection of the phenol soft group as an ester providing a pro-soft drug that is converted by enzymatic hydrolysis in human skin S9 to the active phenolic species, which in turn was shown to be rapidly cleared by human hepatocytes. This tool compound has the potential to shed light on the use of topical soft-drugs to overcome the toxicity of S1PR1 inhibitors.



MEDI 207

Synthesis of novel, potent phosphatidyl-choline specific phospholipase C inhibitors

Lisa I. Pilkington¹, lisa.pilkington@auckland.ac.nz, **Michelle van Rensburg**¹, **Johannes Reynisson**¹, **Euphemia Leung**², **William A. Denny**², **David Barker**¹. (1) School of Chemical Sciences, University of Auckland, Auckland, New Zealand (2) Cancer Society Research Centre, University of Auckland, Auckland, New Zealand

Association of abnormal metabolism of choline-containing phospholipids with various cancers has resulted in the identification of enzymes involved in the phosphocholine cycle as potential therapeutic targets. Phosphatidyl-choline specific phospholipase C (PC-PLC) plays a pivotal role in this cycle and has been implicated in many signalling processes, demonstrating overexpression in various cancerous tumours, thus providing a viable target for inhibition of cancer cell growth.

By virtue of virtual high throughput screening, a number of lead compounds were identified as inhibitors of the PC-PLC enzyme, including 4-amino-*N*-benzylanilines and pyrido[3,4-*b*]indoles, all of which were identified to bind to key zinc atoms at the active site. To study the PC-PLC inhibitory activity of these compounds and to verify their SAR, an extensive range of novel analogues have been synthesised, varying a number of different structural features (fig. 1).

Analysis of the biological activity of the synthesised analogues showed significantly improved inhibitory activity over the only well-documented PC-PLC inhibitor, D609. These results, as well as the antiproliferative activities of the synthesised compounds

will be reported, providing a comprehensive SAR of these potent compounds and their potential therapeutic applications.

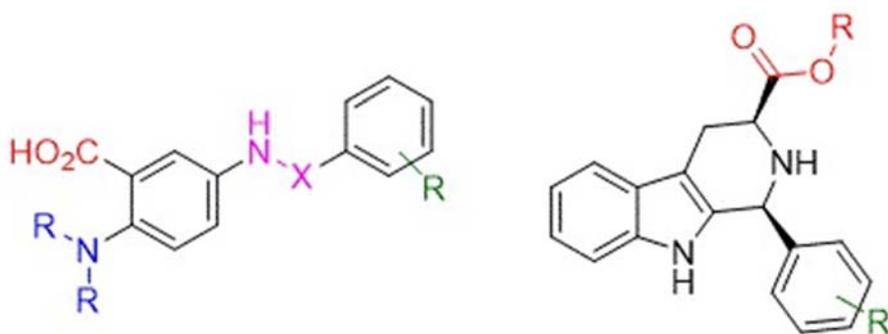
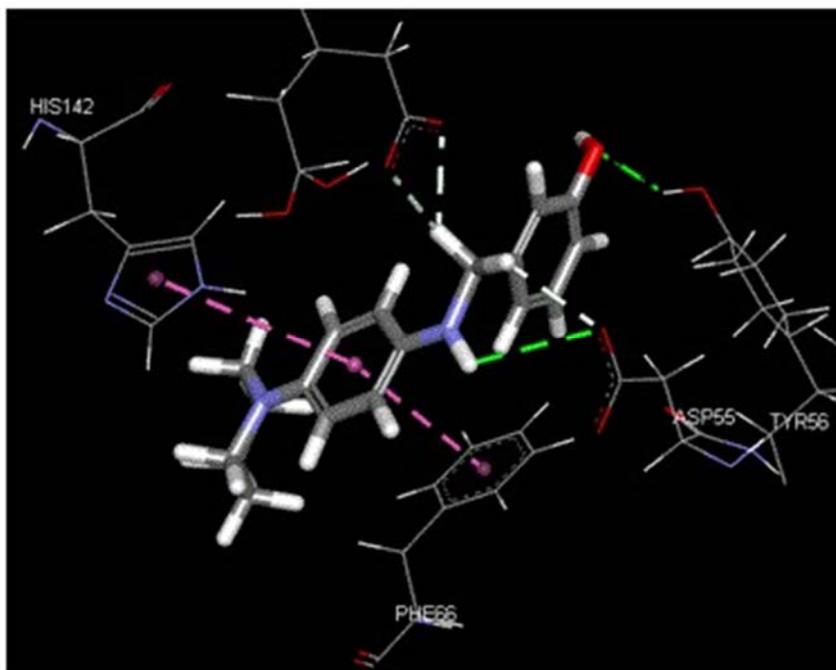


Figure 1: Binding of an inhibitor to the PC-PLC binding site and compounds investigated.

MEDI 208

Investigating the scope of 3-oxabicyclo[4.1.0]heptane as a bioisostere for morpholine in kinase hinge binding fragments

Declan M. Summers^{1,2}, declan.m.summers@gsk.com, **Simon Peace**², **Craig Jamieson**¹, **Heather Hobbs**², **Sandeep Pal**³. (1) Pure and Applied Chemistry, University of Strathclyde, Hatfield, Hertfordshire, United Kingdom (2) Fibrosis and Lung Injury DPU, GlaxoSmithKline, Stevenage, Hertfordshire, United Kingdom (3) Molecular Design UK Team, GlaxoSmithKline, Stevenage, Hertfordshire, United Kingdom

Kinases are attractive drug targets due to their key role in various cellular activities including proliferation, survival, apoptosis, metabolism and differentiation. Commonly small molecule inhibitors compete directly with ATP and form vital hydrogen bonding interactions with the kinase hinge region. In Phosphoinositide 3-kinase (PI3K) inhibitors this interaction is often made *via* an aryl morpholine hinge binding moiety (**1**). Coplanarity between these two rings is a requirement for activity and thus ring systems which adopt orthogonal conformations such as aryl tetrahydropyran (**2**) are ineffective as morpholine isosteres, whereas unsaturated systems (**3**) are often considered undesirable.

We have identified 3-oxabicyclo[4.1.0]heptane (**4**) as the first example of a saturated, carbon linked hinge binding moiety for the PI3K family of kinases. Cyclopropyl carbon-carbon bonds are known to form stabilising interactions with adjacent π -systems when in a favourable orientation and DFT conformational studies have suggested low energy co-planar conformations for aryl 3-oxabicyclo[4.1.0]heptane systems. We have subsequently synthesised a series of tool compounds to aid investigation into the application and limitation of this potential morpholine isostere.

We have utilised; predictive DFT calculations, X-ray crystallography (**figure 1**), NMR studies and biological evaluation of these tool compounds to comprehensively investigate the conformational preference of 3-oxabicyclo[4.1.0]heptane when attached to a range of 6-membered heterocyclic rings. We will report our findings which suggest a subtle stereoelectronic balance to conformation with a significant impact for applicability of 3-oxabicyclo[4.1.0]heptane as a general morpholine isostere.

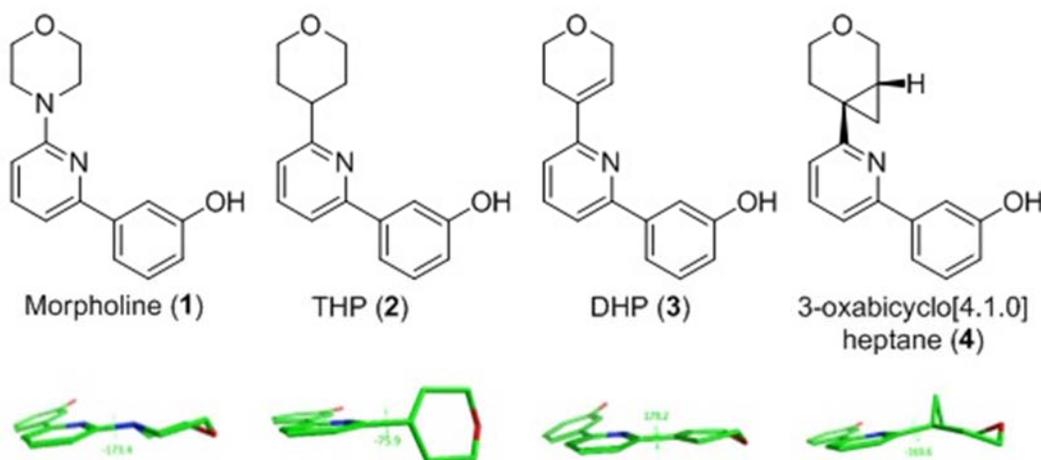


Figure 1: 2-pyridyl tool compound small molecule X-ray crystal structures to investigate the conformational preference of varying hinge binding fragments.

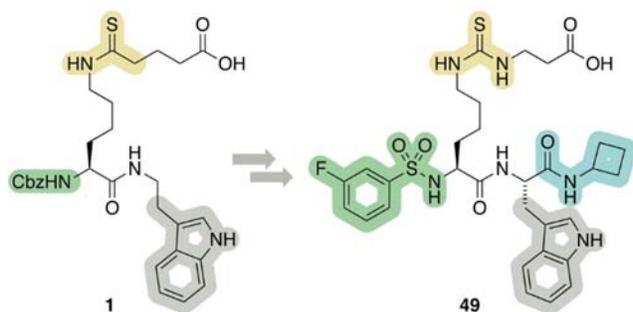
MEDI 209

Mechanism-based inhibitors of the human sirtuin 5 deacylase

Kathrin Troelsen, *kathrin.troelsen@sund.ku.dk*, Nima Rajabi, Andreas S. Madsen, Christian A. Olsen. Department of Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark

Sirtuins are a family of NAD⁺-dependent lysine deacylases, that catalyze the removal of e-N-acyllysine post translational modifications (PTMs). These enzymes have been connected to various cancers, neurodegenerative diseases, and metabolic disorders. The sirtuins may therefore be potential therapeutic targets through either activation or inhibition by small molecules. There are seven different mammalian sirtuin isoforms (SIRT1–7) and recently it has become evident that different enzyme isotypes exhibit preference for different PTMs.

By taking advantage of the acyl-substrate specificity of SIRT5 a series of novel mechanism-based SIRT5 inhibitors have been synthesized. This extensive iterative structure-activity relationship (SAR) study has furnished SIRT5 selective inhibitors with >100-fold improvement in potency from lead to final compound, affording the most potent SIRT5 inhibitor to date. The mode of binding has been elucidated by solving co-crystal structures of selected inhibitors in complex with both human and zebrafish SIRT5. Furthermore, the first co-crystal structures with thiourea-based sirtuin inhibitors have been obtained, confirming their suggested mode of inhibition. Finally, performing continuous assays revealed slow, tight-binding kinetics of the inhibitors, which is unprecedented for SIRT5. This study has provided insight for future optimization of inhibitors with more “drug-like” properties.



MEDI 210

Generation of cell-permeable protein mimetics through structural stabilization of protein fragments by membrane anchoring

N Tarasova, *nadya.tarasova@nih.gov*, Karen Stefanisko, Lyuba Khavrutskii, Sergey Tarasov. Center for Cancer Research, National Cancer Institute, Frederick, Maryland, United States

Targeting protein-protein interactions can provide plentiful opportunities for the discovery of novel drug candidates and powerful chemical biology tools. However, the majority of these interactions are ‘undruggable”, and we still know very little about the structural mechanisms and functions for the vast majority of them. We have developed a rational approach that allows for the straightforward development of cell-permeable

metabolically stable inhibitors of protein-protein interactions. The approach is based on structural stabilization of peptides by membrane anchoring. Proximity to the membrane facilitates interactions of hydrophobic side chains of amphiphilic peptides with the bilayer and stabilizes natural folds of not only helical but also stretched and hairpin-type peptides. Membrane tethering is achieved through facile derivatization of peptides with fatty acids of appropriate length that depends on peptide's hydrophobicity. Lipidation facilitates cell entry and allows intracellular delivery of peptides up to 14-16 residues long. Negative charges can interfere with the entry, while positive charges generally have little effect. Wide applicability of this method was confirmed by generation of selective and highly potent dominant negative inhibitors of RAS oncogenes, b-catenin, STAT1, STAT3 and STAT5 N-domains, IL10R1, IFNGR1 and other non-druggable targets. Rational design of inhibitors can be accomplished even in the absence of the target tertiary structure by using conservation of certain sequence parts during the evolution. High throughput generation of selective chemical biology tools allows for effective interrogation of protein-protein interactions leading to discovery of mechanistic details of molecular signaling that could not be obtained with the help of genetic approaches.

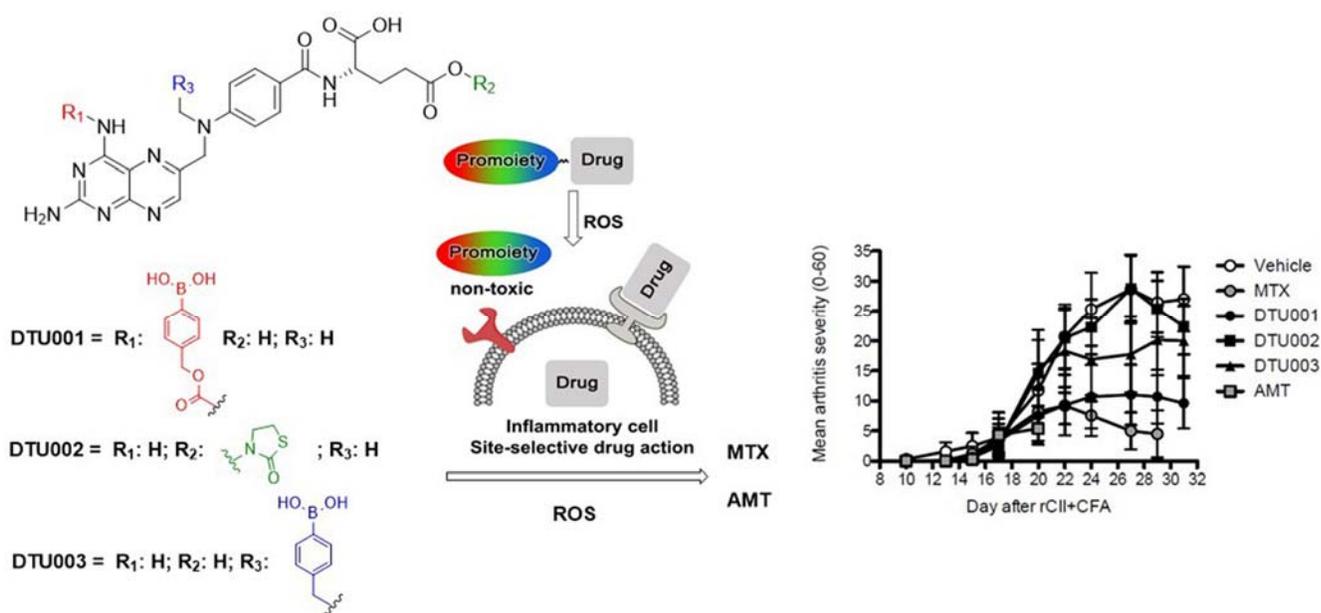
MEDI 211

Synthesis and evaluation of hydrogen peroxide sensitive prodrugs of methotrexate and aminopterin for the treatment of rheumatoid arthritis

Viola Previtali, viola.previtali@gmail.com, Jorge P. Cadahía, Nikolaj Andersen, Mads Clausen. Center for Nanomedicine and Theranostics, Department of Chemistry, Technical University of Denmark, Kemitorvet 207, 2800, Kgs Lyngby, Denmark

Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes joints damage and other extra-articular manifestations. Despite the efficacy of aminopterin (AMT) and low-dose methotrexate (LD-MTX) in RA treatment, their adverse effects are the predominant reasons for discontinuation of therapy. Reactive oxygen species (ROS) have been shown to have a critical role in the pathophysiology of RA and as a therapeutic strategy, the presence of increased concentrations of H₂O₂ in the inflammatory environment can serve as the stimulus for prodrug activation in site-selective drug delivery systems.

Herein, we describe the synthesis of new arylboronic acid- (**DTU001** and **DTU003**) and thiazolidinone-based (**DTU002**) hydrogen peroxide-sensitive prodrugs of MTX and AMT for site-selective delivery to inflammatory tissue associated with RA, with the aim of reducing side effects in RA therapy. The prodrug concept was validated by H₂O₂ activation assays and by *in vitro* studies against MTX and AMT sensitive cancer cell lines. Among the prodrugs synthesized, **DTU001** showed the best physicochemical and pharmacokinetic properties. *In vivo* efficacy was demonstrated in collagen-induced arthritis (CIA) rodent models of RA and **DTU001** also had significantly reduced toxicity compared to the parent drug. **DTU001** now represents our first choice as lead candidate for further preclinical evaluation.



MEDI 212

Development of a potent blood-brain barrier penetrating EGFR tyrosine kinase inhibitor against malignant brain tumors

Lorenz M. Urner¹, urner@chem.ucla.edu, **Jonathan Tsang**⁴, **Gyudong Kim**¹, **Peter M. Clark**^{4,2}, **Timothy F. Cloughesy**^{2,3}, **Michael E. Jung**¹, **David A. Nathanson**^{4,2}. (1) Department of Chemistry and Biochemistry, UCLA, Los Angeles, California, United States (2) Jonsson Comprehensive Cancer Center, David Geffen UCLA School of Medicine, Los Angeles, California, United States (3) Department of Neurology, David Geffen UCLA School of Medicine, Los Angeles, California, United States (4) Department of Molecular and Medical Pharmacology, David Geffen UCLA School of Medicine, Los Angeles, California, United States

Glioblastoma (GBM) is the most common malignant brain tumor in adults and the most lethal. The epidermal growth factor receptor (EGFR) is altered in nearly 60% of GBM tumors, and therefore offers a suitable target for small molecule inhibitors. Despite the fact that EGFR protein kinase inhibitors have been proven clinically successful in e.g. non-small cell lung cancer, these known inhibitors have failed so far to be efficacious for GBM patients. This can, at least in part, be attributed to the inability of conventional EGFR TKIs to effectively cross the blood-brain-barrier (BBB) and achieve adequate pharmacological levels for tumor response. Herein, we performed a structure-activity relationship (SAR) of a series of small molecule EGFR TKIs to improve brain penetration by modifications of physicochemical properties amenable to BBB penetration aided by multiparameter optimization models. We identified novel EGFR TKIs with high potency against EGFR mutant, GBM patient-derived cells in culture, high BBB penetration (2:1 brain-to-plasma ratio), and improved efficacy in orthotopic GBM xenografts relative to conventional EGFR TKIs.

MEDI 213

Fluorescence quenching studies of the human serum albumin (HSA) - quercetin complex by addition of divalent cations

Ruben M. Savizky, *rsavizky@cooper.edu*, Udochukwu Okorafor, Chonghag Kim. *Chemistry Dept, The Cooper Union, New York, New York, United States*

Fluorescence quenching studies were performed on a human serum albumin (HSA)-quercetin complex by adding six different divalent metal ions (Cu(II), Ni(II), Mn(II), Cd(II), Zn(II), and Co(II)) to form a tertiary complex. Upon binding to human serum albumin, quercetin fluoresces after excitation at 295 or 450 nm. Two different quercetin moieties in the HSA-quercetin complex were observed to fluoresce, namely QC1 and QC2. The band shape of the QC1 emission peak was relatively sensitive to the nature of the quencher and the temperature. In contrast, the emission band of QC2 was not shifted upon changing the temperature, but was shifted if tryptophan or tyrosine emission were quenched. The divalent metal ions acted as quenchers for both QC1 and QC2 emissions. Results were analyzed using the Stern-Volmer relationship by plotting the relative intensity vs. the quencher concentration. From the Stern-Volmer plots, QC1 and QC2 emission peaks were seen to be quenched by collisional quenching, with a minor contribution due to static quenching in the presence of Cu(II). When Mn(II) was added to the complex, QC1 was quenched by collision only while QC2 was quenched by the combination of both mechanisms, although collisional quenching was the dominant mechanism. Cd(II) and Co(II) acted as quenchers for both QC1 and QC2. Zn(II) enhanced QC1 and QC2. In the presence of Cd(II), a combination of static and collisional quenching was responsible for the quenching of QC1 and QC2. Collisional quenching was the dominant mechanism for QC1. For QC2, static quenching was the dominant mechanism for concentrations equal to and below 30 μM and collisional quenching was the dominant mechanism for concentrations above 30 μM . In the presence of Co(II), QC1 was quenched statically while QC2 was quenched both statically and collisionally, with static being the dominant quenching mechanism. In the case of QC2 quenching by Ni(II), the interpretation of the Stern-Volmer relationship was difficult since changing the temperature did not alter the ratio of the fluorescence intensity in the absence and presence of the quencher (F_0/F) at the original temperature. Even though the change was small in the Stern-Volmer plots, it can be stated that the QC2 emission band is possibly due to complex formation with Ni(II).

MEDI 214

Modular synthesis of allosteric inhibitors of p97 AAA ATPase

Evan Carder, *ejc26@pitt.edu*, Donna M. Huryn, Peter Wipf. *University of Pittsburgh, Pittsburgh, Pennsylvania, United States*

The p97 AAA ATPase is an active regulator of protein homeostasis, influencing protein degradation and translocation. Dysregulated p97 is adversely associated in aging,

cancer, and neurodegeneration; therefore, p97 is an emerging biological target for therapeutic development. Our pursuit toward a p97 small molecule modulator led to the elaboration and optimization of a series of allosteric inhibitors that perturb p97 ATPase activity. These compounds were robustly constructed from an advanced intermediate with a common heterocyclic core, employing a convergent synthetic strategy of thioalkylations, Williamson etherifications, Sonogashira couplings, and carbamoylations, which efficiently provided final products in high overall yields. The established medicinal chemistry discovery routes enabled rapid derivation of analogs that were strategically designed to enhance biological properties.

MEDI 215

Discovery of a novel class of orally active CGRP receptor antagonists for the treatment of migraine

Ian M. Bell, ian_bell@merck.com. Merck & Co., Inc, West Point, Pennsylvania, United States

Calcitonin gene-related peptide (CGRP) plays an important role in migraine headache and several small molecule CGRP receptor antagonists have demonstrated clinical efficacy for the acute treatment of migraine. More recently, CGRP blockade has been shown to be effective for migraine prevention with both small molecule and monoclonal antibody modalities. As part of a program to identify orally active CGRP receptor antagonists, we focused on a novel aminoquinoline lead identified in a high-throughput screen. This aminoquinoline had low molecular weight and a ligand efficiency that rivaled highly optimized clinical candidates. Docking studies based on a crystal structure of the CGRP receptor extracellular domain suggested that the receptor affinity of the aminoquinoline lead could be enhanced by incorporating groups that would engage in hydrogen bonding with the protein backbone. These studies inspired the discovery of novel subnanomolar CGRP receptor antagonists that maintained high ligand efficiency. Mutagenesis studies demonstrated that these novel CGRP receptor antagonists took advantage of a key interaction with an aspartate residue in the CGRP receptor binding site, in contrast to other small molecule CGRP receptor antagonists like telcagepant. Further optimization of this series was based on increasing the lipophilic ligand efficiency (LLE) of the compounds in order to improve their selectivity, solubility, and pharmacokinetic profiles. This led to the identification of novel aminopyridine-based CGRP receptor antagonists with good oral bioavailability and excellent overall profiles.

MEDI 216

Pharmacodynamics-driven skeleton synthesis with unravel of unique chemical reactivity feature: Exploring promising pharmaceutical agent

Meenu Saini, meenu.saini65@gmail.com, Divyani Sumkaria, Vikas Chaudhary, sankar Guchhait. Medicinal chemistry, NIPER Mohali, Mohali, India

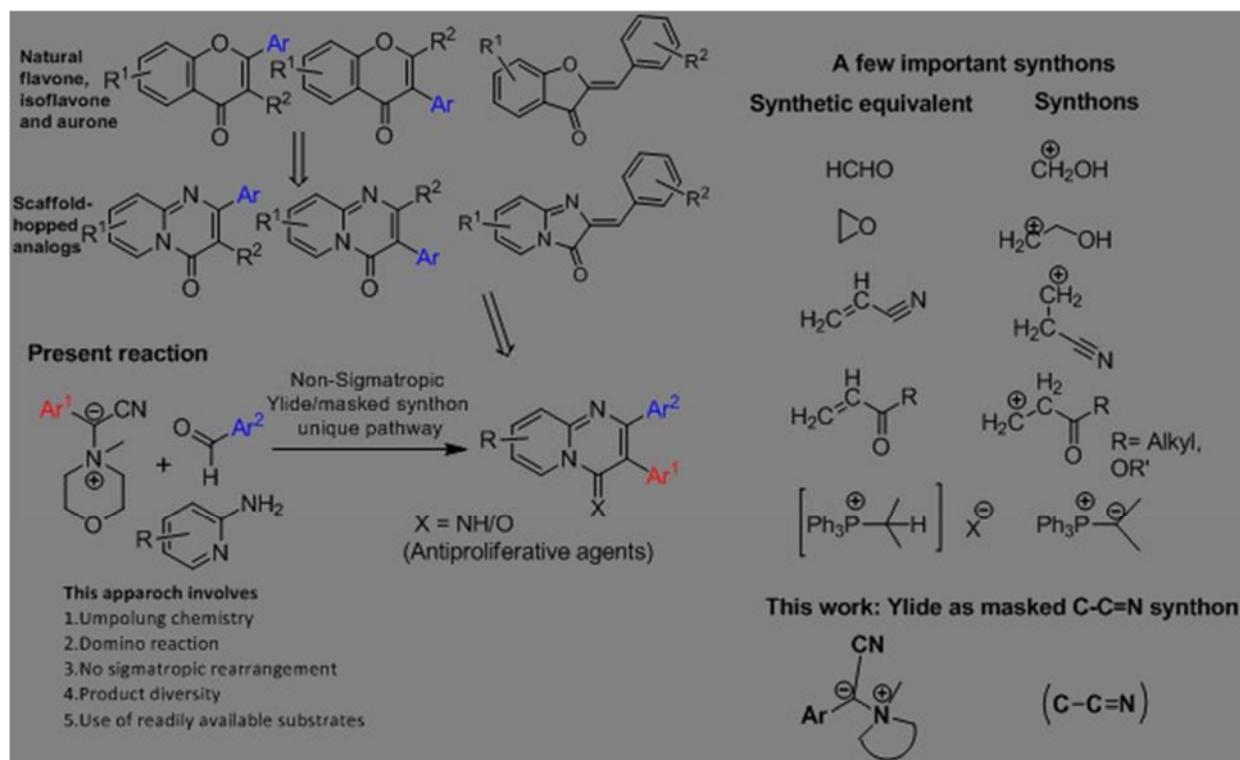
Natural products (NPs) play a valuable role in the drug discovery and development. Around 79% of anticancer drugs approved by USFDA during the period of 1981-2010 are either natural products or their based/mimicked-compounds, according to a report by Newman and Cragg.

Flavones and isoflavones display anticancer activities by various mechanisms. Flavopiridol, a semisynthetic flavone analog, acts as CDK9 inhibitor and is USFDA-approved orphan drug for treating acute myeloid leukemia.

Scaffold-hopped analogs of flavone, isoflavone and aurone in the form of pyridopyrimidinone and pyridoimidazole skeletons as potent human DNA topoisomerase II α (hTopoII α)-catalytically inhibiting anticancer agents were previously explored by us.

Based on the structures of these scaffold-hopped analogs and natural bioactive flavonoids, we considered diaryl substituted pyridopyrimidinone class of molecular framework as potential hTopoII α and tubulin inhibitors. Pharmacodynamics-relevant molecular-diversity feasible synthetic method was developed.

We have developed a new reaction exploring the unique reactivity of 1-aryl-1-cyano quaternary ammonium ylide as a masked C=C=N synthon. The reaction of the ylide with heteroazine-derived imines underwent cascade transformations, distinctive from usual transformations including sigmatropic rearrangements. It provides a new and efficient route to pyridopyrimidin-4-imine/one skeletons. Versatile aryl moieties, available in the aldehyde starting materials, can be easily assembled as 2,3-substitutions in the product-scaffold in a modular fashion via this route. The chemistry of nitrile-stabilized ammonium ylide that involves incorporation of nitrile as a functional/ring-motif into the fused heteroaromatic product skeleton via a set of cascade transformations is unique. The use of such ylide as C=C=N synthon enriches the list of conventional acceptor/donor synthons—synthetic equivalents. Several of the synthesized compounds were found to possess antiproliferative activities in various cell lines. The chemistry aspects, development of the method and biological activities (cellular and enzyme-based) will be presented.



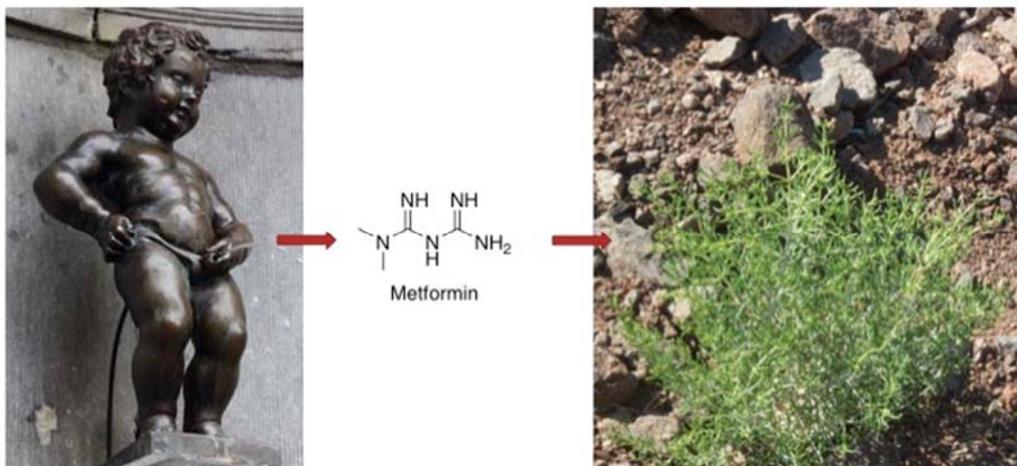
MEDI 217

Discovering drugs from plants or drugs in plants?

John Nielsen, john.nielsen@sund.ku.dk. Department of Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark

A phytochemical investigation of *Seidlitzia rosmarinus* collected along the shoreline of the Gulf of Aqaba in the remote southern desert region of the Sinai peninsula has revealed the presence of the registered drug metformin. However, analysis of the ^{14}C content revealed the drug to be an anthropogenic contaminant. Consequently, natural product researchers should be aware that compounds isolated from plants might originate from environmental contamination rather than biosynthesis. The new natural product *N*-(4-hydroxyphenylethyl)- α -chloroferuloylamide was isolated as a mixture of the *E* and *Z* isomers along with a number of other well-established secondary metabolites.

During this presentation, the importance of natural products in drug discovery will be underlined with important examples from the history of human medicines and so recent accomplishments. However, landmark examples of drugs leaking into the environment and eventually being 'rediscovered' is also provided and critically reviewed.



MEDI 218

Synthesis and evaluation of functionalized benzoboroxoles as potential anti-cancer agents

Subash C. Jonnalagadda, jonnalagadda@rowan.edu. Chemistry and Biochemistry, Rowan University, Glassboro, New Jersey, United States

Benzoboroxoles are cyclic boronic acids that have generated significant attention in the recent years owing to the approval of two drugs tavaborole and crisaborole for the treatment of onychomycosis and atopic dermatitis respectively. We have been working on the development of novel methodologies for the preparation of functionalized benzoboroxoles for the past several years utilizing reactions such as Baylis-Hillman, Passerini, stereoselective allylboration, and reductive amination. Based on these studies, we have been able to identify certain analogs for potential development as anti-tubercular agents and anti-cancer agents. This presentation will focus on our recent efforts in this project involving the synthesis of benzoboroxole conjugates via Click chemistry as well as Barbier allylation.

MEDI 219

Design of Baylis-Hillman template based betulinic acid derivatives as potential anti-cancer agents

Subash C. Jonnalagadda, jonnalagadda@rowan.edu. Chemistry and Biochemistry, Rowan University, Glassboro, New Jersey, United States

Betulin and betulinic acid are triterpene natural products isolated from the bark of birch trees. Betulinic acid shows preferential toxicity towards cancer cells and has been a topic of interest for generating new moieties for drug development. We have recently reported the design of Baylis-Hillman reaction template derived betulinic acid analogs that showed promising cytotoxicity against certain breast and pancreatic cancer cell

lines *in vitro*. This presentation outlines the development of second generation betulinic acid derivatives based on a detailed structure activity relationship assay for further development as potential anti-cancer agents.

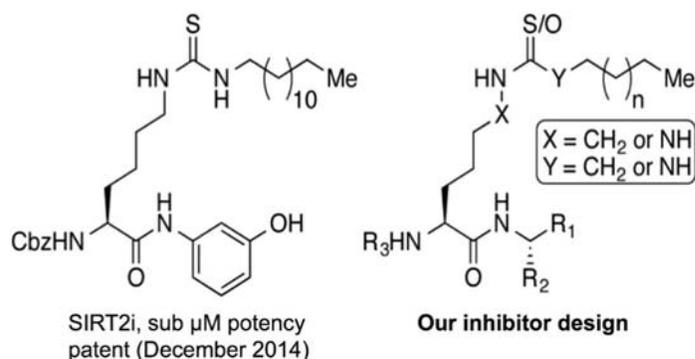
MEDI 220

Potent and selective inhibition of sirtuin 2 deacylation

Alexander Lund Nielsen, alexanderln@sund.ku.dk, Nima Rajabi, Andreas S. Madsen, Christian A. Olsen. Department of Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark

Post-translational modifications are of great importance for regulation of protein function, trafficking, localization, and marking for degradation. The effects and mechanisms of several types of chemical modification to protein side chains have thus been studied extensively, with particular attention dedicated to phosphorylation, ubiquitylation, and acetylation. However, it has become evident that the ϵ -amino group of lysine residues may be decorated with a variety of different acyl groups in addition to acetyl (K_{ac}), such as crotonyl, succinyl, and myristoyl that can be cleaved by a class of enzymes called sirtuins. Sirtuins are NAD^+ -dependent deacylases and the enzyme class comprises seven members, SIRT1-7, in the human genome. The enzymes have different subcellular location and substrate scope. Sirtuins are implicated in a wide range of biological processes related to both gene regulation and metabolism, and possibly provide links between metabolism, longevity, and cancer. Thus, they are important regulatory enzymes with potential as drug targets.

In this present project, we applied both structure- and mechanism-based insight to design novel potent and selective inhibitors of SIRT2. Through an iterative structure-activity profiling, this led to the design of selective inhibitors that are >100-fold as potent as the top candidate found in a recent patent. Our efforts also led to the first-ever full inhibition of demyristoylation activity of SIRT2. Real-time enzymatic assays revealed that kinetics vary greatly depending on the size-, lipophilicity, and warhead of the inhibitors, that quite intriguingly have an influence on substrate selectivity and inhibitor potency. Finally, this work provided important new and highly potent tool compounds for the continuous investigation of sirtuin enzymes.



MEDI 221

Novel nitroxide derivatives combined with low-level laser irradiation for the treatment of acute limb ischemia/reperfusion injury

Xin Yan¹, yanxinmycool@qq.com, Lanrong Bi². (1) chemistry, michigan technological university, Houghton, Michigan, United States (2) Michigan Tech Univ, Houghton, Michigan, United States

In the present study, we have designed and synthesized a series of novel nitroxide derivatives, and examined their anti-inflammatory and analgesic activities. Considering the beneficial effects of low-level laser irradiation, we proposed that a combination therapy of low-level laser irradiation with novel nitroxide derivative might lead to an effective therapeutic strategy for the treatment of acute limb ischemia/reperfusion injury. Herein, the effects of the combined treatment on limb I/R induced tissue damage were evaluated by the measurement of biomedical parameters: MDA, MPO and TNF- α levels. In addition, we also investigated the effects of the combined treatment on remote organ by monitoring the serum AST, ALT, BUN, and Cr levels. Interestingly, when the laser irradiation was employed in combination with an analgesic anti-inflammatory agent (**5j**), the protective effects of the combined treatment against I/R injury were significant. The combined treatment was found to significantly attenuate the structural and functional damage observed in limb I/R. This observation is of clinical interest because it demonstrates that the combination of laser irradiation and an analgesic anti-inflammatory agent may provide an effective therapeutic strategy against reperfusion damage.

MEDI 222

Generalization of a CNS-targeting prodrug strategy for nuclear receptor modulators

Skylar J. Ferrara, sky.ferrara@gmail.com, Thomas S. Scanlan. Physiology and Pharmacology, Oregon Health & Science University, Portland, Oregon, United States

Nuclear receptors have emerged as a class of potentially powerful drug targets for neurodegenerative central nervous system (CNS) diseases. However, blood-brain barrier permeability remains a major impediment for targeted CNS treatment, especially with carboxylic acid-containing drugs, a functional group that is common to many nuclear receptor ligands. Additionally, nuclear receptors are generally expressed in various peripheral tissues associated with adverse effects which can lead to challenges with achieving a sufficient therapeutic index. Herein is described a prodrug strategy which directs the biodistribution of parent drug nuclear receptor modulators into the CNS while masking them as functional receptor ligands in the periphery. We have found that certain amide derivatives of nuclear receptor ligands containing carboxylic acids are good substrates for fatty-acid amide hydrolase (FAAH), an enzyme with enriched expression in the CNS. FAAH cleavage of these prodrugs in the CNS leads to substantial increases in brain exposure, and brain-to-serum ratio increases up to ~100-fold compared to the ratio of the parent drug. Structure-activity relationships, FAAH substrate validation, and comparisons of CNS vs peripheral drug action will also be discussed. Our results demonstrate that this strategy can be generalized to a variety of carboxylic acid-containing drug structures.

MEDI 223

Exploring conformational changes associated with antimicrobial agent, colicin E3 during receptor binding on targeted bacteria

Thushani D. Nilaweera, tdn3ck@virginia.edu, David S. Cafiso. Chemistry, University of Virginia, Charlottesville, Virginia, United States

With the increasing number of drug resistant bacterial strains, it is essential to develop new antibiotics to efficiently fight against such pathogenic strains. Many of these pathogenic bacteria are Gram-negative and contain two membranes (inner and outer), which encapsulate the cellular content and provide protection against harsh environmental conditions and toxic chemicals. Even though the outer membrane (OM) facilitates the uptake of small molecules, the intake of larger molecules, such as essential nutrients including rare metal ions and antibiotics (>600 Da), are mediated by the OM transporters. Bacteriocins are antibiotics produced by some bacteria under stress conditions, targeting similar bacterial species to eliminate the competition for nutrients, including rare minerals essential for survival. Colicin is one class of bacteriocins produced by *Escherichia coli* (*E. coli*) against related *E. coli* strains. This class of bacteriocins is the most widely studied using molecular biological, biochemical and biophysical techniques, and several structural models have been generated using crystallography for colicin bound to their OM receptors and transporters. However, our current knowledge regarding the mechanisms and associated conformational changes that take place during the binding of colicin to the OM receptor and its uptake into the cell is limited.

In our present work, we have combined site directed spin labeling with electron paramagnetic resonance (EPR) spectroscopy to investigate conformational changes

associated with receptor binding step using colicin E3 receptor binding domain (colicin E3R) with its OM receptor, BtuB. Briefly, we have mutated selected positions of colicin E3R into cysteine and expressed, purified and spin labeled these cysteine mutants. Wild type (WT) BtuB, either in live *E. coli* cells or in reconstituted bilayer systems, were used to investigate colicin E3R mutants' binding with BtuB and conformational changes of colicin E3R mutants related to OM receptor binding events. In the future, we are aiming to investigate conformational changes of receptor binding step using spin labeled BtuB at specific extracellular loops, along with spin labeled colicins, to detect distance distributions associated with receptor binding and how receptor bound colicin dynamic changes as to screen for its OM transporter.

MEDI 224

Structure-activity relationship analysis of TNF receptor inhibitors for elucidation of inhibition mechanisms and therapeutic developments

Chih Hung Lo¹, loxxx247@umn.edu, **William Fiers**², **David Thomas**^{3,4}, **Courtney C. Aldrich**², **Jonathan Sachs**¹. (1) *Biomedical Engineering, University of Minnesota, Minneapolis, Minnesota, United States* (2) *Medicinal Chemistry, University of Minnesota, Minneapolis, Minnesota, United States* (3) *Biochemistry, Molecular Biology, and Biophysics, University of Minnesota, Minneapolis, Minnesota, United States* (4) *Photonic Pharma LLC, Minneapolis, Minnesota, United States*

We have employed a structure-based drug design approach to systematically evaluate the structure-activity relationship (SAR) of zafirlukast, a known inhibitor that targets the pre-ligand assembly domain (PLAD) of tumor necrosis factor receptor 1 (TNFR1) and inhibits its function. Receptor-specific inhibition of TNFR1 is a highly sought-after strategy for the treatment of autoimmune diseases such as rheumatoid arthritis. Through performing an innovative FRET-based high-throughput screening, we have recently identified zafirlukast as a small-molecule inhibitor of TNFR1 activation which acts through a novel mechanism of disrupting TNFR1 PLAD-PLAD interaction without ablating native ligand binding. In the current study, we focus on establishing a SAR of zafirlukast by adopting lipophilic ligand efficiency (LLE) and topological polar surface area (TPSA) as metrics to optimize the molecule for improved potency, as well as to investigate the portion of the molecule important for this inhibition mechanism. We have synthesized over 30 analogues of zafirlukast and have managed to improve its activity significantly by 10-fold to a half maximal inhibitory concentration (IC₅₀) of 6 μM, while improving on the drug disposition properties. We are testing two more series of analogues, potentially achieving an IC₅₀ in the nanomolar range. The chemical structures and molecular weights of the analogues were confirmed by NMR and mass spectrometry. In addition, through both experimental observations and computational simulations, we have found that both the sulfonamide and carbamate groups of the molecule are responsible in receptor binding, and the aromatic ring on the sulfonamide group plays a key role in the disruption of PLAD-PLAD interactions. This is a significant discovery not only because our optimized molecule is a novel and potent inhibitor of

TNFR1, but more importantly we are the first to provide information on the chemical structures crucial in disrupting TNF receptor-receptor interaction.

MEDI 225

Scavenging activity of flavonoids present in okra seed extracts against methylglyoxal, a neurotoxin and reactive dicarbonyl species derived from glucose linked to diabetes and neurodegenerative diseases

Bishambar Dayal¹, dayalb77@gmail.com, **Michael A. Lea²**. (1) *Medicine, Rutgers University, Newark, New Jersey, United States* (2) *Microbiology, Rutgers New Jersey Medical School, Newark, New Jersey, United States*

Methylglyoxal, a reactive dicarbonyl species, has been linked in numerous studies to diabetes and neurodegenerative diseases such as Parkinson's. There is a high degree of interest in studying naturally occurring flavonoids which have the capacity to scavenge reactive dicarbonyl species such as methylglyoxal. We will discuss in detail the scavenging activity of flavonoids present in okra seed extract, and also discuss its potential in comparison with well-established diabetes drugs.

MEDI 226

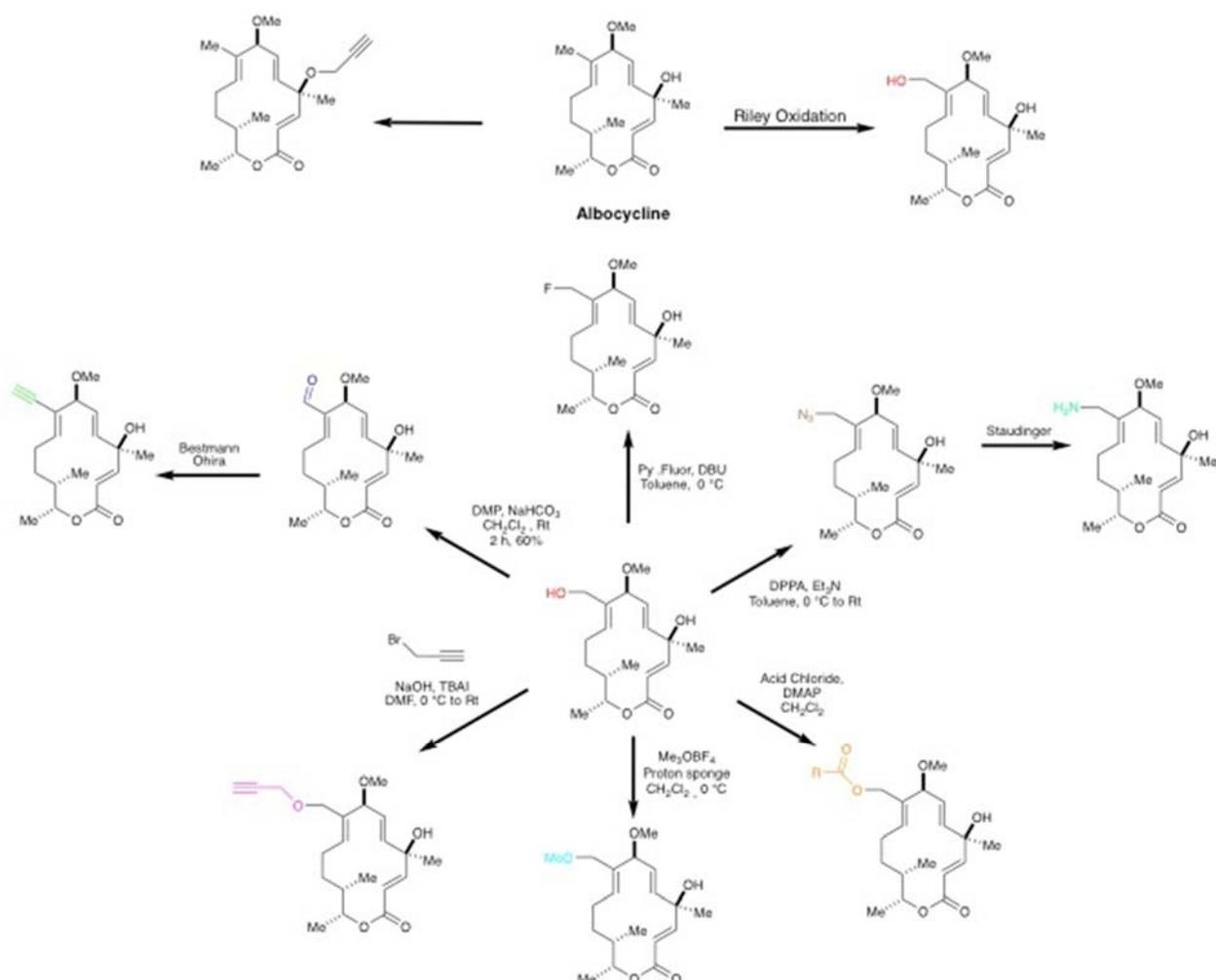
Semi-synthesis of albocycline analogs and biological evaluation for better mechanistic understanding

Samer Daher¹, tuf24815@temple.edu, **Kevin Franklin²**, **Vijay Chatare²**, **Rodrigo B. Andrade²**. (1) *Chemistry, Temple University, Philadelphia, Pennsylvania, United States* (2) *Temple Univ, Philadelphia, Pennsylvania, United States*

Natural products (NPs) or analogs are privileged scaffolds for synthesis of robust antibacterial agents and account for two thirds of all antibiotics used in clinical practice. NPs have inspired novel synthetic methods, which in turn have enhanced and expanded our antibacterial arsenal. We here describe the role of NPs such as albocycline and its analogs as promising antibacterial agents.

Albocycline is a unique NP with potent, narrow-spectrum activity against the "superbugs" such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate (VISA), and -resistant *S. aureus* (VRSA) strains, in addition to being non-toxic to human cells. The first and only report on albocycline synthesis dates back to 1987, carried out by Tanner and Somafi in a total of 40 steps. We, on the other hand, implemented a novel N-sulfinylmetallo dienamine-based approach to synthesize albocycline in 14 steps. Biochemical assays and modular modeling were utilized to show that albocycline is a weak (μM) inhibitor of the *S. aureus* peptidoglycan enzyme MurA but not its homolog, MurZ, nor MurA derived from *Escherichia coli*. Accordingly, we propose that albocycline has an alternative bacterial target. To investigate this further, we used various albocycline analogs, semi-synthesized from albocycline obtained from *Streptomyces maizeus* culture. The minimum inhibitory concentration (MIC) of

these analogs helped validate albocycline's mechanism of action via a consistent structure activity relationship based on functionalizing specific sites on the molecule. In conclusion, we believe that albocycline and its analogs have a tremendous potential in overcoming the serious healthcare challenges posed by multi-drug resistant "superbugs" and show that their synthesis can be achieved in a concise and timely manner.



MEDI 227

Design, synthesis, and molecular modeling of novel 6-substituted pyrido[2,3-*d*]pyrimidines as dihydrofolate reductase inhibitors and potential anti-opportunistic agents

Farhana Islam¹, farhanap40@gmail.com, **David W. Seybert**², **Aleem Gangjee**¹. (1) Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, Pennsylvania, United States (2) Department of Chemistry and Biochemistry, Bayer School of Natural and Environmental Sciences, Duquesne University, Pittsburgh, Pennsylvania, United States

Pneumocystis pneumonia (PCP) is an opportunistic disease caused by the invasion of the lung by the unicellular fungus *Pneumocystis jirovecii* (*pj*). It is a life-threatening pulmonary infection that occurs in immunocompromised individuals and HIV-infected patients. Despite advances of combination antiretroviral therapy (cART), *Pneumocystis pneumonia* continues to occur in HIV-infected patients with late presentation for cART or virological and immunological failure after receiving cART. PCP has also emerged as a concern in patients with non-HIV-related immune deficiencies. Selective dihydrofolate reductase (DHFR) inhibitors, in combination, represent a viable therapeutic approach for the treatment of these infectious diseases. First line treatment of *Pneumocystis pneumonia* (PCP) requires a combination of trimethoprim (TMP)-sulfamethoxazole (SMX), due to the weak inhibitory activity of TMP. The second line treatment involves potent, but non-selective DHFR inhibitors such as trimetrexate (TMQ) and piritrexim (PTX), which cause myelosuppression and have been discontinued. The failure of these two options is due to adverse reactions and resistance to the sulfa drug as well as adverse reactions of second-line agents. Thus there is a substantial unmet clinical need for agents that combine the potency of PTX and selectivity of TMP in single agents. We designed and synthesized a series of 6-substituted pyrido[2,3-*d*]pyrimidines that are selective and potent inhibitors of DHFR derived from *Pneumocystis jirovecii*. Copper-catalyzed Ullmann type chemistry of substituted thiophenols with pivaloyl protected 2-amino-5-iodonicotinonitrile was successfully explored to synthesize these analogs. The synthesis, molecular modeling, and biological evaluation of the new analogs designed to improve selectivity and potency for *pj*DHFR over hDHFR will be presented.

MEDI 228

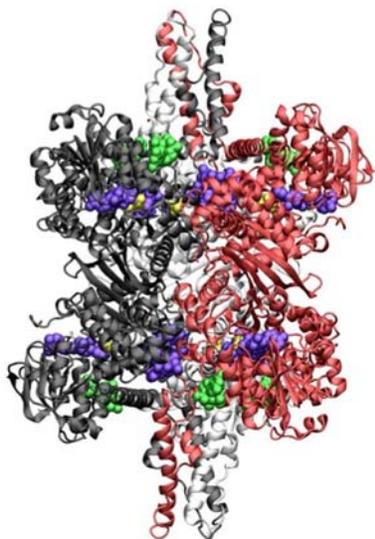
Discovery of a 40-year-old sequence error unveils new understanding of allosteric ligand binding to glutamate dehydrogenase

Omneya Nassar^{1,3}, omneyamn@gmail.com, **Bernard M. Pettitt**^{1,2}, **Thomas Smith**^{2,3}. (1) *Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, Texas, United States* (2) *Biochemistry and Molecular Biology, University of Texas Medical Branch, Galveston, Texas, United States* (3) *UTMB - Galveston, Galveston, Texas, United States*

Overactivating point mutations in glutamate dehydrogenase (GDH) cause children to have the rare disease autosomal dominant hyperinsulinemia/hyperammonemia syndrome (HHS). There are no medications available to treat the disease by directly targeting GDH. Instead, HHS patients are provided with medication for symptomatic treatment.

Mammalian glutamate dehydrogenase can bind 24 ligands simultaneously; making this enzyme one of the most challenging to study. For over 40 years, the incorrect protein sequence for bovine GDH was published on all online protein sequence databases and it was not until recently that we discovered the error and corrected the sequence. Bovine GDH is the standard model used for decades to investigate mammalian GDH

structure and kinetics. Residue 387 is of special importance due to its location at the NADH binding site. Residue 387 was originally identified as asparagine, which was shown crystallographically to interact unfavorably to ligands NADH, ADP and ECG. However, when residue 387 was corrected to the correct amino acid identity, lysine, the thermodynamics and crystallographic refinements improved significantly. Using microsecond molecular dynamic simulations and free energy perturbation techniques, our calculations showed an increased affinity of GDH to NADH by 5 kcal/mol per binding site with the correct sequence.



Bovine glutamate dehydrogenase in the abortive complex bound to 24 ligands: 6 glutamate (yellow), 6 NAD⁺ coenzyme (purple molecule next to yellow glutamate), 6 GTP (green), and 6 NADH molecules (purple); (pdb 3MW9).

MEDI 229

Does β -lapachone isomerize in human body?

Seungil Cho^{1,2}, chosi1@gmail.com, **Bo Kyung Kim**^{1,3}, **Young-Ran Yoon**^{1,4}. (1) School of Medicine, Kyungpook National University, Daegu, Korea (the Republic of) (2) Molecular Diagnostics & Imaging Center, Kyungpook National University, Daegu, Korea (the Republic of) (3) BK21 Plus KNU Bio-Medical Convergence Program for Creative Talent, Kyungpook National University, Daegu, Korea (the Republic of) (4) Kyungpook National University Hospital, Daegu, Korea (the Republic of)

β -Lapachone (3,4-dihydro-2,2-dimethyl-2H-naphthol[1,2-b]pyran-5,6-dione) is a naturally occurring compound found in the bark of a South American Lapacho tree (*Tabebuia avellanedae*). Many in-vitro studies have been performed to show its anticancer and anti-inflammatory effects for several diseases. Now phase II clinical trials have been performed to demonstrate its antitumor activity. It is also known that β -lapachone isomerizes into α -lapachone under hydrochloric acid. If this occurs in

stomach, its bioavailability and efficacy will be significantly reduced. In this study, we first developed a new analytical method to unambiguously determine β -lapachone levels in human plasma using liquid chromatography–tandem mass spectrometry (LC-MS/MS). This analytical method was validated with respect to selectivity, linearity, sensitivity, accuracy, precision, recovery, and stability. Then, we applied it to study the pharmacokinetics and the structural isomerism of b-lapachone in human body.

MEDI 230

Chemical synthesis and applications of a novel fluorescent probe for human complement C3a receptor

Chongyang Wu, chongyang.wu@imb.uq.edu.au, Aline D. de Araujo, Kai-Chen Wu, Robert C. Reid, Thomas Durek, Junxian Lim, David P. Fairlie. Institute for Molecular Bioscience, Division of Chemistry & Structural Biology, Brisbane, Queensland, Australia

Native chemical ligation (NCL) has been used to synthesize full-length human complement protein C3a, specifically modified at the N-terminus by appending diethylenetriaminepentaacetic acid (DTPA) that is a good chelator of europium. The human C3a sequence was divided into three 20-30 residue fragments: DTPA–C3a[1–22]–NHNH₂ (1), Thz–C3a[24–48]–COSR (2), and H–C3a[49–77]–OH (3), which were individually prepared on resin by standard Fmoc–solid phase peptide synthesis (SPPS) using a peptide synthesizer. Full assembly of reduced C3a was accomplished by consecutively joining the three polypeptides in the C- to N- direction. After folding and chelation of Europium, the europium labelled product (Eu–DTPA–hC3a) was obtained. Time-resolved fluorescence analysis has demonstrated that Eu–DTPA–hC3a binds selectively to its cognate G protein-coupled receptor C3aR with full agonist activity and similar potency and selectivity as native C3a in inducing calcium mobilization and phosphorylation of extracellular signal-regulated kinases in HEK293 cells that stably expressed C3aR. The potency of Eu–DTPA–hC3a was further validated by competitive binding experiments and used to measure affinities of potent C3aR-specific agonists (TR16, BR103) and antagonists (SB290157, BR111) via displacement of Eu–DTPA–hC3a from hC3aR. The macromolecular conjugate Eu–DTPA–hC3a is a novel nonradioactive probe suitable for studying ligand–C3aR interactions and discovering high affinity ligands for C3aR. Antagonists of this receptor show potent anti-inflammatory activity via C3aR on human and rodent cells and in animal models of disease.

MEDI 231

Drug repurposing for nontuberculous mycobacteria with assay central

Kimberley M. Zorn¹, kimzorn@gmail.com, Sebastian Murcia³, Alex Clark², Miriam Braunstein³, Sean Ekins¹. (1) Collaborations Pharmaceuticals, Inc., Raleigh, North Carolina, United States (2) Molecular Materials Informatics, Inc., Montreal, Quebec,

Canada (3) Department of Microbiology and Immunology, School of Medicine, University of North Carolina, Chapel Hill, North Carolina, United States

Mycobacterium is broad genus containing well known disease-causing species, such as leprosy and tuberculosis, however nontuberculous infection is also a concern. A lesser known species, *M. abscessus*, is particularly resilient against topical antibiotics; contamination of medical devices can occur, and co-infection is especially dangerous for patients with chronic lung diseases. Another species, *M. smegmatis*, is generally non-pathogenic and fast-growing, making it a common model organism for tuberculosis studies. There is an unmet need for effective treatments for opportunistic mycobacteria, and we have used our software, Assay Central, to try to fill this gap and aid in the identification of molecules for testing and understand differences versus these bacteria. Assay Central can streamline drug discovery and drive discussion between collaborators by deploying a collection of predictive Bayesian models in a self-contained executable. Datasets of structure-activity relationships are collated and stored using the code-management system Git, from which molecular descriptors (extended-connectivity fingerprints) are calculated as contributing to activity at targets of interest. Visualization of molecular features and training data within the executable solidify comprehension while complimenting human intuition to make intelligent decisions. Herein, we present models of *M. abscessus* and *M. smegmatis*, built from published datasets and shared with Assay Central, as well as their utility to repurpose known drugs as lead compounds against *M. abscessus*. At MIC thresholds from 5-16 μM , Receiver Operator Characteristic scores ranged from 0.77-0.87 and Matthews Correlation Coefficient scores ranged from 0.54-0.67. Published data for *M. abscessus* is particularly limited. Furthermore, by testing compounds against *M. smegmatis*, this work aims to provide insight into the mechanism of action from observed differences in compound activity between species, and can effectively drive research for *M. tuberculosis* too.

MEDI 232

Evaluation of butyrophilin (BTN3A1) ligands for gamma delta T cell stimulation

Michael M. Poe, michael.poe@uconn.edu, Chia-Hung C. Hsiao, Andrew J. Wiemer. University of Connecticut, Storrs, Connecticut, United States

Interest in V γ 9V δ 2 T cells is growing and there is an increasing amount of data that suggests these gamma delta ($\gamma\delta$) T cells could be used as an immunotherapeutic agent against various forms of cancer including melanoma, lung, ovarian, and prostate cancer. These specialized T cells are activated following the binding of non-peptidic diphosphate antigens, commonly known as phosphoantigens, to the butyrophilin protein BTN3A1. Natural diphosphate butyrophilin ligands are limited, as isopentenyl diphosphate (IPP) stimulates little effect and the potent *E*-4-hydroxy-3-methyl-but-2-enyl diphosphate (HMBPP) is produced only in organisms that utilize the MEP pathway. Previously, our group developed a phosphonate prodrug related to HMBPP that has overcome the instability and low penetration that has plagued synthetic diphosphate

analogs. Herein, we report ongoing work to improve ligand efficacy and increase data output as we investigate their effectiveness as a potential cancer immunotherapeutic.

MEDI 233

Structure-guided design and SAR studies of hepatitis C virus NS3/4A protease inhibitors incorporating flexible P2 quinoxalines

Akbar Ali¹, akbar.ali@umassmed.edu, Ashley N. Matthew¹, NageswaraRao Desaboini¹, Linah Ruserere¹, Alicia Newton², Christos J. Petropoulos², Wei Huang², Nese Kurt-Yilmaz¹, Celia A. Schiffer¹. (1) Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, Massachusetts, United States (2) Monogram Biosciences, South San Francisco, California, United States

The development of HCV NS3/4A protease inhibitors with pan-genotypic activity is a major milestone in the antiviral drug discovery. The NS3/4A protease inhibitors have become a key component of new all-oral combination therapies. However, despite remarkable improvements in potency, the current protease inhibitors are still susceptible to drug resistance. Moreover, because of their structural similarities, these protease inhibitors exhibit similar resistance profiles, and thus are prone to cross-resistance. We recently developed a substrate envelope guided design strategy for improving the resistance profile of NS3/4A protease inhibitors. This structure-guided strategy, together with our understanding of the mechanisms of drug resistance, led to the design of P1–P3 macrocyclic analogues of grazoprevir that incorporate conformationally flexible P2 quinoxalines and exhibit exceptional potency and resistance profiles. Based on the structural insights, structure-activity relationships were explored focusing on the P2 quinoxaline moiety and P4 capping group to further optimize potency against drug resistant variants and other genotypes. Our findings demonstrate that the substrate envelope model along with incorporating optimal conformational flexibility provides a general strategy for the rational design of NS3/4A PIs with improved potency and resistance profiles.

MEDI 234

Monitoring macrolide-induced changes to membrane properties of living bacteria by using second-harmonic light scattering

Mohammad Sharifian Gh., tue84271@temple.edu, Michael J. Wilhelm, Hai-Lung Dai. Department of Chemistry, Temple University, Philadelphia, Pennsylvania, United States

The world-wide threat of antimicrobial resistance demands continued development of innovative pharmaceutical drugs capable of selectively targeting microbial pathogens by either crossing or increasing the permeability of the bacteria membrane. For example, macrolides form a general class of antibiotic compounds which have been effectively

used in clinical treatments for well over 50 years. There has been considerable interest in characterizing macrolide-membrane interactions over the last decade. In the interest of efficiently optimizing antimicrobial compounds which target the bacteria membrane, it is desirable to develop methodologies capable of monitoring changes to membrane properties in living bacteria. We have previously demonstrated the utility of second-harmonic light scattering (SHS), as a real-time and surface-sensitive technique, for monitoring chemically induced changes to membrane permeability in living bacteria. Here, we present time-resolved SHS to quantify azithromycin (AZM)-induced changes to bacterial membrane permeability in colloidal suspensions of living *Escherichia (E.) coli*. Variations in membrane properties of *E. coli* were monitored through changes in the adsorption and transport rates of an SH-active molecule, malachite green (MG). Our results revealed that regardless of the AZM concentration, instantaneous treatment with AZM has no significant effect on the bacteria membrane permeability. However, 1 hour pretreatment with sub-minimum inhibitory concentrations (MIC) of AZM induced an order-of-magnitude enhancement in the permeability of both the outer membrane and, through facilitation of a new transport mechanism, the cytoplasmic membrane of the bacteria as well. Of significance, there was a dual decay behavior (i.e., fast and slow) observed for cytoplasmic membrane transport events following 1 h exposure to either 75 μM (0.5 \times MIC) or 150 μM (1 \times MIC) AZM. Further, the relative efficiency of the fast transport process was observed to increase with AZM concentration in which the fast decay process accounted for 13% of the 75 μM AZM case and increased to 62% for 150 μM AZM. This suggests that accumulation of increasing concentrations of AZM creates an efficient secondary transport route across the bacteria cytoplasmic membrane. This study illustrates SHS as a novel tool for monitoring antimicrobial-induced changes to membrane properties in living bacteria.

MEDI 235

Synthesis and spectroscopic study of polymer - based nonsteroidal analgesic prodrugs

Hani D. Tabba, hanitabba@hotmail.com. Chemistry, Qatar University, Virginia Beach, Virginia, United States

Drugs with side effects or known for problems associated with their bioavailability, solubility, taste, stability, shelf life time, or improper formulation are changed to derivatives that would reversibly generate the drug during digestion. This approach proved to be successful in solving such problems. These derivatives are known as prodrugs and showed to work effectively in many drugs in the pharmaceuticals market. In this work, several non-steroidal analgesic drugs (e.g. Aspirin, Indomethacin, Ibuprofen, and Voltaren) are hooked to various polymers. The physical and spectroscopic properties are studied.

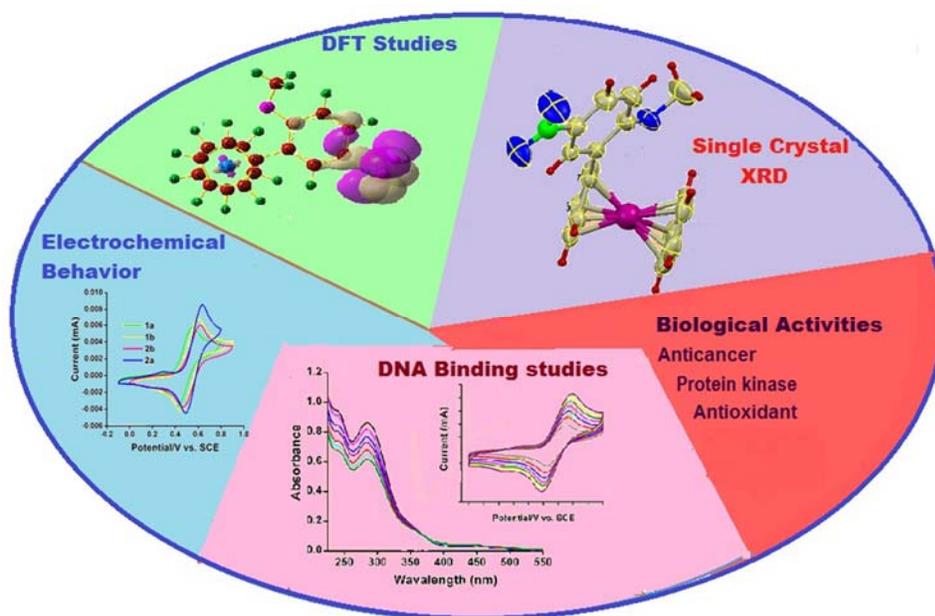
On the other hand, prodrugs resulting from drugs combination could benefit from synergetic activity and higher efficiency.

MEDI 236

Potentially bioactive ferrocene-substituted nitro and amino complexes: Synthesis, structural interpretation, and DFT calculations

Faiza Asghar^{1,2}, faiza994@hotmail.com, **Amin Badshah**³, **Ian S. Butler**². (1) Chemistry, University of Wah, Wah, Pakistan (2) Chemistry, McGill University, Montreal, Quebec, Canada (3) Chemistry, Quaid-i-Azam University, Islamabad, Pakistan

In our search for new antitumor and DNA interacting drugs, ferrocene-modified nitro and aniline compounds were successfully synthesized and characterized by numerous physicochemical and spectroscopic techniques. The desired nitrophenylferrocenes were prepared by the coupling reaction between ferrocene and the diazonium salts of different nitroanilines using a phase transfer catalyst. In the succeeding reactions, these nitro derivatives were reduced to the corresponding anilines using zinc dust/ammonium formate. Mulliken charge distribution and the HOMO/LUMO energies of the optimized structures that were calculated using the DFT/B3LYP method associate well with the experimentally determined redox potential values. The mode and extent of interaction of these complexes with the biomolecule, SS-DNA was examined by cyclic voltammetry, and UV-Vis spectroscopy; the complexes displayed noble binding strengths to DNA. The diffusion coefficients of the compound-DNA adducts for all the complexes are lower than that of the free compound and the small values of the binding site sizes also indicate the dominance of electrostatic interactions. These compounds have also been revealed to be substantial candidates in terms of free radical scavenging, protein kinase inhibition, and cytotoxicity.



MEDI 237

Novel theranostic tools for Alzheimer's disease

Liang Sun¹, liangsun@wustl.edu, Nilantha Bandara^{2,3}, yiran huang¹, Hong-Jun Cho¹, Buck E. Rogers^{2,3}, Liviu M. Mirica¹. (1) Dept of Chemistry Box 1134, Washington University, Saint Louis, Missouri, United States (2) Washington University School of Medicine, Mallinckrodt Institute of Radiology, St. Louis, Missouri, United States (3) Washington University School of Medicine, Radiation Oncology, St. Louis, Missouri, United States

This presentation will focus on the development of bifunctional metal-binding compounds with high affinity for the β -amyloid peptide aggregates as potential PET imaging agents for early diagnosis of Alzheimer's disease. Our group successfully synthesized a series of stilbene and benzothiazole bifunctional compounds with a metal binding ligand part which still have high binding affinity with the amyloid plaques. Some of the bifunctional compounds show good log D value with ⁶⁴Cu binding which means the compounds may penetrate the blood brain barrier. The bio-distribution study on APP and WT mice indicates that the compounds have potential to be used as PET imaging agent for the diagnosis of Alzheimer's Disease.

MEDI 238

Design and antiviral activity evaluation of small molecule compounds against viruses from *Flavivirus* and *Enterovirus* genera

Alexey Orlov^{1,2}, rnase@qsar.chem.msu.ru, Mikhail Drenichev³, Vladimir Oslovsky³, Konstantin Frolov⁴, Anastasia Nikitina^{1,2}, Eugene Khvatov¹, Anastasia Eletskaia^{1,5}, Anastasia Golinec^{1,6}, Sergey N. Mikhailov⁷, Vladimir Palyulin², Galina Karganova¹, Victor Dotsenko^{4,8}, Liubov Kozlovskaya^{1,6}, Dmitry I. Osolodkin^{9,1}. (1) Chumakov FSC R&D IBP RAS, Moscow, Russian Federation (2) Department of Chemistry, Lomonosov Moscow State University, Moscow, Russian Federation (3) Engelhardt Institute of Molecular Biology, RAS, Moscow, Russian Federation (4) Kuban State University, Krasnodar, Russian Federation (5) Department of Fundamental Medicine, Lomonosov Moscow State University, Moscow, Russian Federation (6) Sechenov MMA, Moscow, Russian Federation (7) Institute of Molecular Biology, Moscow, Russian Federation (8) North Caucasus Federal University, Moscow, Russian Federation (9) Department of Chemistry, Lomonosov Moscow State University, Moscow, Russian Federation

In the course of antiviral screening programme we assessed activity of more than 600 compounds against tick-borne encephalitis virus (TBEV), belonging to genus *Flavivirus*, and against a panel of enteroviruses (enterovirus A71, poliovirus, coxsackieviruses A16 and B1). TBEV is an enveloped virus transmitted by ticks, commonly causing deadly encephalitis in northern Eurasia. Enteroviruses are small widespread non-enveloped picornaviruses, causing poliomyelitis and hand, foot and mouth disease. Anti-TBEV activity was observed for several classes of nucleoside analogs and small organic molecules belonging to different chemical classes. Nucleosides bearing large aromatic moieties in the N6 position of adenosine or bulky hydrophobic moieties in 5'-O position were found specifically active against TBEV and mildly cytotoxic. Possible mechanism of action was suggested through time-of-addition experiments and binding

modes of the active compounds were predicted by docking studies to the sites in MTase and RdRp. Phenotypic screening of ten organoselenium and one organosulfur compound classes also revealed a specific inhibition of TBEV reproduction. Seven classes showed micromolar activity while being moderately cytotoxic. The inhibitory activity of these compound series is probably realized by different mechanisms including inhibition of the virus entry process or interfering with the host cell targets, thus preparing the ground for the development of new anti-TBEV compounds classes. We searched for the active compound scaffolds in ViralChEMBL database, containing antiviral compounds extracted from ChEMBL and properly curated, to reveal similar compounds possessing antiviral activity realizing through known mechanisms. Several close analogs were identified that allowed us to suggest possible mechanisms of action for our compounds. These findings lay the foundation for further search of new nucleoside inhibitors of TBEV reproduction.

Replication of enteroviruses was inhibited most efficiently by N6-halobenzyladenosines. Enterovirus A-71 and coxsackievirus A16 species were consistently susceptible to these compounds, whereas for coxsackievirus B1 and poliovirus only fluorination of the benzyl led to acceptable activity. Time-of-addition studies revealed inhibition of the viral replication stage, and possible modes interaction with viral proteins were analysed by docking of the most potent compounds.

MEDI 239

Synthesis and base pairing studies of 5-cyanomethyluridine (cnm⁵U) and 5-cyanouridine (cn⁵U) in RNA duplexes

Song Mao¹, smao2@albany.edu, Jia Sheng². (1) Department of Chemistry The RNA Institute University at Albany, SUNY, Albany, New York, United States (2) Chemistry, SUNY Albany, Albany, New York, United States

5-cyanomethyluridine (cnm⁵U) and 5-cyanouridine (cn⁵U), the two uridine analogues, were synthesized and incorporated into RNA oligonucleotides. The base pairing stability and specificity studies in RNA duplexes indicated that cnm⁵U slightly decreases the duplex stability but retains the base pairing preference. In contrast, cn⁵U dramatically decreases both base pairing stability and specificity between U:A and other non-canonical U:G, U:U and U:C pairs. Our work provides two novel building blocks for constructing RNA based therapeutics. More interestingly, the cn⁵U:G pair shows higher thermal stability than the cn⁵U:A pair in the context of RNA duplex, implying the cn⁵U might slightly prefer to recognize G over A. Although it has not been discovered in the natural RNA systems, our results indicate that the cn⁵U residue might be used by certain biological systems like virus RNA to increase the base pairing diversify and induce higher rates of gene mutation, even though it decreases the overall base pairing stability.

MEDI 240

Synthesis and crystal structure studies of 2'-5'-linked RNA duplexes

Fusheng Shen, *fshen@albany.edu. The RNA Institute, University at Albany, Albany, New York, United States*

The mixed RNA backbone containing both 3'-5' and 2'-5' linkages generated in the RNA chemical replication models has been regarded as a fatal problem in studying the emergence of the RNA World from prebiotic chemistry. However, the very recent finding that the Flavin Mononucleotide (FMN) binding aptamer and a hammerhead ribozyme can still retain considerable functionality in the presence of the certain percentage of 2'-5' linkages suggests that this backbone heterogeneity problem may not be as severe as originally thought. More interestingly, it has been known for a long time that 2'-5' linkages can reduce the melting temperature of RNA duplexes, making it easier to separate the strands. We have previously solved four crystal structures for a 2'-5'-linked CG containing RNA 10mer duplex. In this work, we synthesized a series of new 2'-5'-linked RNA duplexes and systematically explored their thermal stability and structural features. These structures will offer general pictures about how RNA adjusts its structure to accommodate backbone heterogeneity.

MEDI 241

Molecular dynamics simulations of the absorption of dodecaborate hydride clusters by Feraheme medicine

Pavel Rehak, *prehak2@uic.edu. University of Illinois at Chicago, Chicago, Illinois, United States*

Molecular dynamics simulations were used to study the ability of Feraheme (ferumoxytol) to transport dodecaborate hydride complexes, as a novel and safer chemotherapy treatment. We recorded the number of dodecaborate hydride complexes absorbed in the region of glucose-derived polymers of Feraheme and investigated their mutual interactions. We observed strong hydrogen bonding between hydroxyl groups of the polymers and hydride groups of the dodecaborate hydride complexes. We calculated the free energy of the dodecaborate hydride complexes coupled with Feraheme and found that both charge density and charge distribution affect the ability of Feraheme to absorb on the dodecaborate hydride complexes.

MEDI 242

Understanding the effect of arsenic treatment on breast cancer cell lines using gene expression analysis

Lavinia Lorena L. Pruteanu^{1,2}, *llp25@cam.ac.uk, Cornelia Braicu*³, *Dezső Módos*¹, *Anca Jurj*³, *Lajos Raduly*³, *Roxana Cojocneanu-Petric*³, *Alin Moldovan*², *Andreas Bender*⁴, *Ioana Berindan-Neagoe*^{3,2}. (1) *Chemistry, University of Cambridge, Cambridge, United Kingdom* (2) *MedFuture Research Center for Advanced Medicine, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj Napoca, Romania* (3) *Research Center for Functional Genomics, Biomedicine and Translational Medicine,*

*“Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj Napoca, Romania (4)
Chemistry Department, University of Cambridge, Cambridge, United Kingdom*

Triple negative breast cancer (TNBC) is a frequently lethal breast cancer subtype due to faster growth, higher metastatic rate and lack of treatment options. Arsenic derivatives have shown activity *in vitro* against several tumor cell lines, but have not yet been tested widely in TNBC cell lines. In this regard, the purpose of this study was to evaluate the transcriptomic changes induced by arsenic treatment and to evaluate its effects with respect to apoptosis, autophagy, and reduction of cell proliferation.

Illumina G4851C SurePrint G3 Human Gene Exp v3 microarray chip data from 3 samples of 3 breast cancer cell lines (MCF-7 double positive, Hs578 TNBC, MDA-MB-231 TNBC) and normal human mammary epithelial cells (HUMEC) as a control were used to investigate the therapeutic effect of arsenic compared to untreated cells.

After quantile normalization differentially expressed genes were determined using fold change and Benjamini-Hochberg corrected t-tests as implemented in the limma package. In order to predict the pathways/genes involved in arsenic response for each cell line, GSEA (Gene set enrichment analysis) was performed using MolSig database Gene Ontology Biological Processes and Hallmark Gene collections. The difference between the responses of the cell lines to arsenic was explored using Robust Regularized Discriminant Analysis (RDA).

The results showed that arsenic can decrease cell proliferation in the two triple negative cancer cell lines. It downregulated certain gene ontology biological processes such as “DNA replication initiation”, “Centromere complex assembly”, “Centrosome duplication”, “DNA replication dependent nucleosome organization” ($q < 0.15$). Comparing the response to arsenic between the triple negative *versus* HUMEC and the double positive cell lines showed that the triple negative cell lines differed in cell proliferation (G2M checkpoint and E2F pathway), inflammation, mTROC signaling, and apoptosis ($q < 0.15$).

In conclusion, arsenic has a specific proliferation arresting and apoptotic effect on the triple negative malignant Hs578 and MDA-MB-231 cell lines.

MEDI 243

2,3-Difluoro sialic acid analogs as potential bacterial sialidase inhibitors

Wanqing Li, wqli@ucdavis.edu, Abhishek Santra, Hai Yu, Yanhong Li, Teri Slack. Chemistry, UC Davis, Davis, California, United States

Sialic acids (Sia) are common terminal monosaccharides of cell-surface glycoconjugates. They are directly involved in many molecular recognition events including immune regulation, cell-cell interaction, inflammation, cancer metastasis, bacterial and viral infection. Sialidases are exoglycosidases that catalyze the cleavage of terminal sialic acids from oligosaccharides, glycolipids, and glycoproteins. Sialidases

are found in many organisms including bacteria, viruses, fungi and mammals and share a common catalytic domain. Successful sialidase inhibitors targeting influenza A viruses have been developed previously and used as drugs. Here, a library of 2,3-difluoro sialic acid compounds were synthesized and evaluated as bacterial sialidase inhibitors. Inhibition is affected by the C-3 fluorine orientation being axial or equatorial, as well as functional group changes. Effective inhibitors towards bacterial sialidases including *Streptococcus pneumoniae* sialidases SpNanA, *Clostridium perfringens* sialidase and *Arthrobacter ureafaciens* sialidase have been identified with inhibition values typically in low nanomolar range.

MEDI 244

Potent zwitterionic anticancer agent: Selective killing of cancer by targeting cancer redox metabolism

Jie Song¹, jsong7@emory.edu, **Jiaqi Mi**², jmi@augusta.edu, **Lingtao Jin**³, lingtao.jin@emory.edu, **Bill Liang**⁴, **Dean P. Jones**⁴, **Haian Fu**⁵, **Craig L. Hill**⁷, **Shuming Nie**⁶. (1) Department of Chemistry, Department of Biomedical Engineering, Emory University, Atlanta, Georgia, United States (2) Augusta University, Athens, Georgia, United States (3) Winship Cancer Institute, Atlanta, Georgia, United States (4) School of Medicine, Department of Medicine, Emory University, Atlanta, Georgia, United States (5) School of Medicine, Department of Pharmacology, Emory University, Atlanta, Georgia, United States (6) Department of Bioengineering, University of Illinois at Urbana-Champaign, Atlanta, Georgia, United States (7) Department of Chemistry, Emory University, Atlanta, Georgia, United States

Cancer has its unique metabolism. The metabolic difference between cancer and normal healthy cells is expected to offer the novel therapeutic window for cancer therapy. We discovered a nanoscale zwitterionic anticancer agent that selectively kills cancer cells while sparing normal cells. The mechanism study shows that this zwitterion catalytically depletes the cellular reducing metabolic by exploiting the upregulated redox level in cancer. Its potent efficacy has been confirmed by the thorough in vitro and in vivo investigation.

MEDI 245

Prodrug of doxorubicin and biomaterial allow for targeted treatment of soft tissue sarcoma

Kui Wu¹, kwu2@albany.edu, **Maksim Royzen**¹, **Jose Mejia Oneto**², **Nathan Yee**². (1) University at Albany, Albany, New York, United States (2) Shasqi, Inc, San Francisco, California, United States

We will describe a bio-orthogonal chemistry based approach for local tumor control, independent of molecular markers or metabolic activity, that allows tailored multi-drug dosing regimens. The approach addresses the increasing need of developing new

treatments of pediatric sarcomas. The five-year survival rates of patients with this ailment are at 67% and have not improved since the 1990's. There have been no major therapeutic improvements for the remaining third of patients in over 25 years. Meanwhile, only 25% of 120 new cancer drugs approved by the FDA between 1948 and 2002 are used in children. The strategy termed 'catch and release' is based on bio-orthogonal inverse-electron demand Diels-Alder (IEDDA) reaction between tetrazine and *trans*-cyclooctene (TCO). The key element of the proposed design is biocompatible hydrogel, modified with tetrazine (HMT), injected in the vicinity of a local sarcoma tumor. Prodrug of doxorubicin with attenuated activity and minimal side effects, containing a releasable TCO moiety will be systemically injected. When the pro-drug and the hydrogel come in contact, the bio-orthogonal agents react with each other through IEDDA reaction 'catching' the payload. Finally, the resulting intermediate isomerizes spontaneously releasing the active doxorubicin from the hydrogel to perform its therapeutic function locally. *In vitro* data have shown that HMT is stable under simulated physiological conditions and capable of converting multiple doses of pro-drug of doxorubicin into the active anticancer drug. Meanwhile, *in vivo* testing proved that the 'catch and release' strategy is capable of local activation of therapeutically meaningful quantities of doxorubicin to treat sarcoma. Multivalency of HMT allows for the process to be repeated with multiple doses of the systemically administered pro-drugs.

MEDI 246

Polyelectrolytes, potent excipients for protein drugs

Andrew Mancuso^{2,1}, amancuso934@gmail.com, **Nicole Pillarella**¹, **Andrew Sadek**¹, **Mohammad Bazrouk**⁴, **Krishnaswami S. Raja**³. (1) Chemistry, CUNY College of Staten Island, Staten Island, New York, United States (2) PhD Program in Biochemistry, CUNY Graduate Center, New York, New York, United States (3) Dept of Chem 6S 332A, College of Staten Island CUNY, Staten Island, New York, United States (4) Biology, CUNY College of Staten Island, Staten Island, New York, United States

Excipients are commonly employed to increase the stability and/or shelf-life of proteins used in biotechnology and medicine. These excipients are usually essential because the folded and active conformation of the vast majority of proteins are only marginally stable under native conditions. Unfortunately, while proteins are attractive candidates for therapeutics due to their wide range of biological activities and superior specificity, they cannot be incorporated into appropriate delivery systems without irreversibly denaturing and losing their activity, due to the requirement of organic solvents in the preparation of these systems. To counteract this problem, we have applied polyelectrolytes as excipients for protein drugs for their loading into biodegradable polyester based drug delivery systems, which are widely used to their safety, ease of preparation, and diverse range of applications, from nanofibers to implants. Here, we describe the loading of five diverse proteins (hemoglobin, lysozyme, fibrinogen, insulin, and concanavalin A) into multiple polyester based systems (nanofibers, implants, and microspheres) using polyelectrolytes as the excipient. We demonstrate that using polyelectrolytes to prepare protein-polyelectrolytes complexes (PPCs) is capable of

stabilizing all of these proteins against the multiple stresses encountered during loading into a polyester based drug-delivery system, with only negligible losses of protein activity.

MEDI 247

Vitamin B12 derivatives for photopharmaceutical therapy

Jennifer R. Shell¹, jennifer.r.shell@dartmouth.edu, Dillon C. Zites³, Thomas A. Shell², Jason Gunn¹, Brian Pogue⁴. (1) Thayer School of Engineering, Dartmouth College, South Royalton, Vermont, United States (3) Chemistry and Biochemistry, Norwich University, Northfield, Vermont, United States (4) Thayer School of Engineering, Dartmouth College, Lebanon, New Hampshire, United States

There is a dire need to develop more effective treatments for pancreatic ductal adenocarcinoma (PDAC), due to the unique microenvironment of the pancreas tumor, which includes lack of vascularization and high stromal pressure. Current treatment options are limited, ineffective, and suffer from severe side effects due to lack of selectivity for tumor versus healthy tissue. The cobalamin scaffold represents a new selective drug delivery and release platform that allows active receptor mediated uptake of chemotherapeutics into pancreatic tumor cells that yields maximum efficiency while minimizing side effects. A vitamin B12 targeted photopharmaceutical therapy (PPT) platform technology is proposed that allows amplified intracellular uptake and targeted release of active drug. This allows release of active drug only in the area needed, such as a tumor, which avoids the typical side effects seen with chemotherapeutics. This platform is derived from the alkylcobalamin scaffold, which is structurally related to vitamin B12 and is actively transported into cells by transcobalamin receptors (TCbIR). PDAC has enhanced expression of these receptors; therefore, the drug-cobalamin conjugate could be effectively ferried into the tumor via the TCbIR pathway. The cobalamin platform can be used to: **a**) effectively deliver drugs in an inactive form into tumors disguised as vitamin B12 derivatives **b**) release the drug in response to near-infrared (NIR) light at the tumor site **c**) be used in combination with radiotherapy to elicit an enhanced reduction in tumor margins. This work is significant in that it addresses a need for a chemotherapy that is selective for cancer cells, in that it is taken into pancreatic cancer cells utilizing a pathway that is overexpressed (TCbIR), and actively can amplify the internal drug delivery. The PPT technology could be used in combination with radiation therapy, and we will examine Cherenkov-mediated release, as a way to amplify the efficacy of radiotherapy.

MEDI 248

Membrane association controls substrate specificity of lipolytic enzymes

Varnavas Mouchlis, vmouchlis@ucsd.edu, J. Andrew McCammon, Edward A. Dennis. Pharmacology, and Chemistry and Biochemistry, University of California, San Diego, La Jolla, California, United States

Enzymes are exquisitely selective biocatalysts, competent of choosing a unique substrate among many biological compounds. The specificity of an enzyme for a substrate is defined by the level of the reaction rate. Phospholipases A2 (PLA2s), which catalyze the hydrolysis of phospholipids that comprise the membrane bilayer, provide an ideal system for studying substrate specificity. The specificity of a PLA2 enzyme is connected to the three-dimensional structure of its catalytic site, which is complementary to the transition state of the reaction. PLA2s also contain secondary “fingerprint” bonding pockets that increase specificity for a phospholipid species. This study focuses on understanding the allosteric activation mechanism of three human PLA2 enzymes including the cytosolic (cPLA2), calcium-independent (iPLA2) and lipoprotein-associated (Lp-PLA2). cPLA2 is the main arachidonic acid provider for the eicosanoid pathway, while iPLA2 is involved in membrane phospholipid remodeling. Lp-PLA2 was found to associate with LDL and HDL in human plasma to hydrolyze phospholipids containing short-chain and oxidized fatty acids. Hydrogen/deuterium exchange mass spectrometry was used to experimentally identify distinct PLA2 peptide regions that interact with phospholipid vesicles. Molecular dynamics simulations, guided and validated by the experimental data, showed that the active sites of these enzymes are allosterically regulated by membranes. Membrane phospholipids bind to allosteric sites located on the interfacial surface of PLA2s shifting their conformation from the “closed” to the “open” state. This process allows each enzyme to recruit secondary hydrophobic binding pockets that recognize unique types of fatty acids esterified at the sn-2 position of phospholipids. These enzymes are implicated in various chronic inflammatory diseases and understanding their association with membranes, mechanism of action and interactions at the molecular level will allow us to identify potent and selective inhibitors that can be further developed as anti-inflammatory agents.

MEDI 249

Amphiphilic cell-penetrating hybrid cyclic-linear peptides as a drug delivery system

Saghar Mozaffari¹, *mozaf100@mail.chapman.edu*, **Kathy Tavakoli**¹, **Bharti Khungar**², **Rakesh Tiwari**¹, **Keykavous Parang**¹. (1) *Center for Targeted Drug Delivery, Department of Biomedical & Pharmaceutical Sciences, Chapman University School of Pharmacy, Irvine, California, United States* (2) *Department of Chemistry, Birla Institute of Technology & Science, Pilani, India*

The cellular delivery of cell-impermeable and negatively-charged molecules remains a major challenge. The cyclic peptide [WR]₅ containing alternative tryptophan (W) and arginine (R) residues showed significant improvement in the cellular uptake of anti-HIV drugs, doxorubicin, phosphopeptides, and oligonucleotides. We hypothesized that arginine residues on a cyclic ring conjugated with a hydrophobic linear chain of tryptophan residues in a hybrid peptide [R_X]W_Y (X and Y = 5-7) can significantly improve the molecular transporter property versus [WR]₅. Therefore, peptides containing R, W, and lysine (K) residues, namely [R₅K]W₅, [R₅K]R₆, [R₆K]W₅, [R₆K]W₆, [R₅K]W₇, [R₇K]W₅,

and [R₇K]W₇ were synthesized using Fmoc solid-phase chemistry and cyclization. *In vitro* cytotoxicity of the peptides was evaluated by MTS assay using human leukemia (CCRF-CEM), ovarian cancer cell line (SK-OV-3), and normal kidney cell line (LLCPK). The synthesized peptides were not cytotoxic to normal (LLCPK) cells at a concentration of 25 μM. Among all the peptides, [R₅K]W₇ significantly improved the uptake of fluorescent-labeled phosphopeptide (F'-GpYEEI) by 48 fold and the cellular uptake of fluorescent-labeled emtricitabine (F'-FTC) and fluorescent-labeled stavudine (F'-d4T), respectively, by 27, and 36 times in CCRF-CEM cells, respectively, that was higher than that of [WR]₅. The cellular uptake of fluorescent-labeled F'-[R₅K]W₇ was shown to be concentration- and time-dependent. Intracellular uptake of F'-[R₅K]W₇ in CCRF-CEM cells was still observed in the presence of sodium azide, suggesting that the cellular uptake was not completely ATP-dependent. Furthermore, F'-[R₅K]W₇ showed high cellular uptake in the presence of different endocytic inhibitors ruling out clathrin-mediated and caveolae-mediated endocytosis. [R₅K]W₇ was found to be significantly more efficient as a molecular transporter than [WR]₅ and other hybrid peptides, suggesting that this peptide can be used for more efficient delivery of cell-impermeable biomolecules.

MEDI 250

Selective metabolic blackout in hepatocellular carcinoma cells by submicromolar iodoacetate-loaded galactosylated nanoparticles

Asmaa M. Reda, areda@zewailcity.edu.eg. Center for Nanotechnology and Nanomedicine, Zewail City of Science and Technology, Cairo, Egypt

Targeting characteristic metabolic modes to drain bioenergetics in cancer cells has recently gained attention. To increase the potential of this strategy, drugs must be drastic inhibitors of all metabolic pathways in cancer cell subpopulations, and importantly, be targeting malignant cells selectively. We exploited enhanced expression of asialoglycoprotein receptors on human hepatocellular carcinoma HepG2 cell membrane for specific delivery of an effective metabolic inhibitor loaded in nanoparticles conjugated with galactosylated chains as recognition termini. Submicromoles of iodoacetate-loaded nanoparticles (NIA) were sufficient to completely disrupt glycolytic as well as mitochondrial metabolism, causing substantial cytotoxicity of HepG2 cells within 4 h. To identify the mechanism of cell death by NIA, we performed extensive metabolic investigations of mitochondria stress in intact-attached or permeabilized-suspended HepG2 cells as well as on isolated mitochondria. Metabolic, flow cytometric, and molecular studies provided converging evidence that NIA triggers complete cell death through mitochondrial ROS-mediated apoptosis induction concomitant with bioenergetic deprivation in HepG2 and HuH-7 but not in normal WI-38 cells. Imaging studies confirmed lower uptake of NIA by normal cells and their mitochondria relative to cancer cells which highlight the targetability of cancer cell mitochondria by the current combination. Overall, our results revealing the ability of relatively low NIA concentrations to completely disrupt various metabolic pathways that are crucial for

proliferating as well as resilient cancer cells provide a new treatment approach *via* nanoparticle-assisted metabolic interventions.

MEDI 251

Rapid estimation of relative binding affinities of G-protein coupled receptor (GPCR) ligands using precomputed ensembles based free energy approaches

Sirish K. Lakkaraju¹, kaushik@silcsbio.com, *Sunhwan Jo*¹, *Alexander D. Mackerell*^{2,1}. (1) *SilcsBio LLC, Baltimore, Maryland, United States* (2) *Univ. of Maryland, Pharmacy, Baltimore, Maryland, United States*

GPCRs are highly versatile transmembrane sensors and have high therapeutic relevance. Because of the complexities associated with surrounding bilayer and buried binding pockets in the protein, free energy based computational approaches have had limited success with sampling affinity changes for GPCR ligands. We apply two precomputed ensemble-based free energy approaches that effectively sample and efficiently estimate relative affinity changes across such transmembrane systems: Single-Step Free Energy Perturbation (SSFEP) and Site Identification by Ligand Competitive Saturation (SILCS). SSFEP repeatedly reuses pre-computed ensemble of conformations of a parent ligand in explicit solvent and in the protein+bilayer environments to evaluate $\Delta\Delta G$ between the parent and modified ligands. This allows for rapid evaluation of $\Delta\Delta G$ for a library of small functional group substitutions to a parent ligand. In SILCS, the protein+bilayer system is subjected to hybrid Grand-Canonical Monte-Carlo/Molecular Dynamics (GCMC/MD) simulations in the presence of multiple organic solutes that represent different types of functional groups. Affinity patterns of these functional groups, called FragMaps, obtained from the GCMC/MD simulations are then used to rapidly evaluate and rank-order ligands in the GPCR pockets using Ligand Grid Free Energy (LGFE) scoring. Both SSFEP and SILCS correctly predicted direction of affinity changes and rank-ordered known ligands of the b_2 -adrenergic (b_2 AR) GPCR simulated in a bilayer composed of 90% palmitoyl oleoyl phosphatidyl choline (POPC) and 10% cholesterol. For instance, SSFEP correctly predicted the increase in favorability as dopamine was transformed to epinephrine, norepinephrine and their derivatives. SILCS simulations correctly characterized the differences in functional group requirements across active and inactive states of the b_2 AR. Differences in the functional group requirements could be used to distinguish agonists, partial-agonists, antagonists and inverse agonists. Additionally, LGFE scoring could be used to identify growth vectors during optimization of dopamine. Thus, SILCS and SSFEP are attractive strategies that can lead drug-design process for challenging targets such as GPCRs.

MEDI 252

Progress, pitfalls, and best practices for fragment-based drug discovery

Daniel A. Erlanson, erlanson@gmail.com. *Carmot Therapeutics, Inc., San Francisco, California, United States*

Fragment-based drug discovery (FBDD) first captured the imagination of researchers over two decades ago. Since then more than thirty drugs have entered the clinic, two of which have already been approved by the FDA. What did we have to learn to move FBDD from an intriguing idea to a widely-used tool?

Unlike high-throughput techniques that screen millions of drug-sized compounds, FBDD starts with libraries of just a few thousand very small molecules, or fragments. This enables a more thorough exploration of chemical space that can identify better starting points for lead optimization. It also allows greater attention to the physicochemical properties of the fragments and compounds derived from them. However, because the initial fragments are usually such weak binders, artifacts are a serious concern when they go unrecognized. This presentation provides an overview of FBDD and touches on what works, what to avoid, and opportunities for the future.

MEDI 253

Strategizing fragment libraries and screening methods for hit identification against metabolic enzyme targets

Anil Padyana, anil.padyana@agios.com. Biochemistry, Agios Pharmaceuticals, Cambridge, Massachusetts, United States

Many human diseases involve dysregulated states of metabolic enzymes that perturb normal physiology at the cellular level. Understanding and targeting these metabolic outliers using small molecules has proven to be a successful therapeutic strategy. However, the pathogenic nature of the loss of function mutations or complex kinetic profile of dysregulated enzyme states can pose unprecedented challenges to hit identification efforts. Fragment based approaches provide intrinsic advantages in efficiently probing the cryptic druggable pockets. Exploring multiple conformational states by parallel biophysical and biochemical screening methods are key to success in discovering relevant fragment hits. To address these needs we have strategized and implemented a comprehensive fragment library with a fit for purpose design suitable for multiple screening methods. We have successfully used intelligently pooled libraries for high-content ligand observed NMR screening with serial STD, WaterLOGSY, CPMG, DLB acquisitions, surface plasmon resonance (SPR), a variety of mass spectrometry based techniques (affinity chromatography, ultrafiltration) and X-ray crystallography to discover hits to challenging metabolic enzyme targets. Lessons learned from a few case studies will be presented.

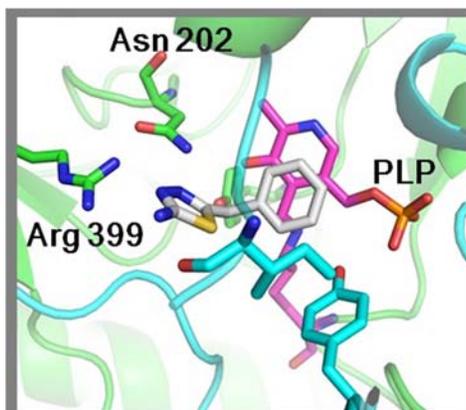
MEDI 254

Fragment-based discovery of KAT II inhibitors via high-throughput chemistry

Mary Harner¹, mary.harner@bms.com, Cullen L. Cavallaro², cullen.cavallaro@bms.com. (1) Biophysics Platform, LDO, Bristol-Myers Squibb,

Princeton, New Jersey, United States (2) Discovery Chemistry, Bristol-Myers Squibb, Princeton, New Jersey, United States

Biophysical screening was employed to identify potential binders to kynurenine amino transferase II (KAT II) from a collection of low molecular weight chemical fragments. Lead exploration was accomplished using parallel synthesis, guided by data from X-ray crystallography, biophysical measurements and, ultimately, an inhibition assay. X-ray data drove the structure-based design and also revealed a unexpected change in binding pose. These efforts led to the successful development of weak biophysical hit, with no measurable KAT II inhibition, into a viable chemical series containing a lead that shows sub-micromolar inhibition of the enzyme.



X-ray structure showing a fragment lead bound to the active site of KAT II.

MEDI 255

Discovery of potent orally bioavailable Factor D inhibitors by exploiting non-validated very weak binding affinity fragments

Anna Vulpetti, anna.vulpetti@novartis.com. Novartis, Basel, Switzerland

Structure-based and fragment-based approaches were applied successfully for identifying structurally distinct hits binding to different sub-pockets and conformations of Factor D, a serine protease of the S1 family involved in the amplification loop of the alternative complement pathway.

Both approaches represented a valuable strategy to tackle this low ligandable target for which HTS of large compound collections in our hands did not deliver any useful chemical starting points.

Two NMR screening efforts were applied against this difficult target: the WaterLOGSY screening of a designed focused target-based library of fragments and the ^{19}F NMR screening of the diverse Novartis library of fluorinated fragments known as LEF (Local Environment of Fluorine). Both methods identified very weak binding affinity fragments which could not be validated by other biophysical techniques. Nevertheless, these initial hits were pursued with chemical modifications and SAR by archive activities with the

aim of improving their solubility and potency. Subsequent optimization by merging the key binding elements of these low affinity fragments interacting at different sub-pockets, as elucidated by crystal structures, has resulted in the generation of potent non-covalent orally bioavailable Factor D inhibitors.

MEDI 256

Fragment-based discovery of an orally bioavailable ERK1/2 inhibitor which reduces the level of phosphorylated ERK

David Norton, david.norton@astx.com. Medicinal Chemistry, Astex Pharmaceuticals, Cambridge, Cambridgeshire, United Kingdom

The RAS-RAF-MEK-ERK signalling cascade is activated through mutations in RAS or RAF in over 30% of cancers. The successful development of inhibitors of BRAF and MEK kinases has led to effective treatment, particularly of melanomas whose tumour growth is driven by activating mutations in BRAF such as V600E. Despite these successes, resistance often emerges after several months. ERK1/2 inhibitors are therefore of key interest as an alternative approach to block this pathway, and several are already in early clinical trials. The tool inhibitor SCH772984 has been shown to reduce the phosphorylation of ERK itself in addition to inhibiting the phosphorylation of downstream substrates such as RSK. We sought to understand the structural link to this pharmacological effect and to develop a series of orally bioavailable ERK inhibitors to assess this profile *in vivo*.

We screened our fragment library by high throughput X-ray crystallography, which provided a selection of hit fragments binding at the hinge of the kinase. One fragment was found to bind in a second pocket also occupied by the inhibitor SCH772984. We postulated that binding in this region of the protein, which is associated with a conformational change in the glycine-rich loop, might correlate with reduced levels of phospho-ERK, and initiated a programme of fragment elaboration to target this binding mode. Structural information from fast turnaround X-ray crystallography experiments was key to optimising the growth of the fragments into potent lead molecules. A key challenge was also to identify a series with suitable oral bioavailability.

The lead compound shows low nanomolar potency in biochemical ERK1/2 assays and an excellent kinome selectivity profile. In BRAF and RAS mutant cell lines, the lead shows low nanomolar cell proliferation IC₅₀ values, while sparing cell lines not driven by the MAPK pathway. The lead exhibits robust anti-tumour activity upon oral dosing in a range of sub-cutaneous xenograft models including the mutant BRAF colorectal line Colo205, providing a promising basis for further optimization towards clinical pERK1/2 modulating ERK1/2 inhibitors.

MEDI 257

Identification of novel CNS active glucosylceramide synthase (GCS) inhibitors for the treatment of neuronopathic lysosomal storage diseases

John P. Leonard, john.leonard@sanofi.com. Rare Disease Science, Sanofi, Waltham, Massachusetts, United States

The Orphan Drug Act of 1983 helped raise public awareness and incentivize the development of drugs to prevent, treat or diagnose diseases occurring in populations of less than 200,000. Since its passing, more than 450 orphan drug approvals have been made in approximately 600 different orphan/rare indications. Enzyme replacement therapy (ERT) for type I gaucher disease was an early success story with the approval of Ceredase and shortly thereafter, Cerezyme in the early 1990's. Over the following decades, the approach has been expanded to 8 additional lysosomal storage diseases (LSD's) with 13 different ERT's currently on the market. However, CNS manifestations of disease that are observed in many LSD's are not impacted by ERT as the proteins do not cross the BBB. Substrate reduction therapy (SRT) is an alternative treatment strategy that targets the synthesis of lipids that traffic to the lysosome. Eliglustat tartrate, a small molecule inhibitor of glucosylceramide synthase was recently approved for the treatment of type I gaucher disease. Given the limited CNS exposure of eliglustat, we sought to identify novel GCS inhibitors with CNS activity that could enable SRT for neuronopathic forms of disease. The starting point for the drug discovery program was a cell based phenotypic screen that was used to identify novel inhibitors of glycosphingolipid synthesis. Subsequent medicinal chemistry efforts focused on the optimization of compounds with CNS exposure and were supported by acute in vivo assays that monitored target engagement and pharmacodynamic activity in plasma and CNS. Lead molecules from a novel series of compounds were potent and selective for GCS inhibition and demonstrated CNS exposure and activity in vivo. Proof of concept for SRT in the CNS was established in models of neuronopathic Gaucher and Sandhoff disease, where GCS inhibition delayed the onset of clinical signs, reduced substrate accumulation and inflammation in the CNS, and significantly prolonged the median lifespan of the mice. Given the positive impact on visceral disease with eliglustat in type I gaucher, it is anticipated that inhibitors with appropriate CNS exposure and activity could address neuronopathic forms of GD that are not served by existing therapies.

MEDI 258

Discovery of sarcomere modulator mavacamten

Johan Oslob, johan.oslob@gmail.com. Chemistry, MyoKardia, Sunnyvale, California, United States

Profile driven goals were used to evaluate compounds that target the abnormal contraction and relaxation characteristic of hypertrophic cardiomyopathy (HCM). Among other things, lipophilicity and polar surface area were important considerations during

the course of this work which culminated in the selection of Mavacamten (formerly MYK-461). Mavacamten is the first direct sarcomere modulator to enter clinical trials for HCM, and may provide patients with a novel treatment option that addresses the underlying biomechanical defect in HCM.

MEDI 259

Discovery and development of avapritinib: A highly targeted therapy for systemic mastocytosis

Kevin J. Wilson, *k.j.wilson.119@gmail.com. Blueprint Medicines, Cambridge, Massachusetts, United States*

Systemic mastocytosis (SM) is a rare myeloid neoplasm in which a KIT Exon 17 mutation is the primary driver of disease, with the D816V mutant accounting for the majority of cases (90-95%). The disease is characterized by abnormal infiltration of mast cells into multiple organs including bone marrow, skin, GI tract, liver and spleen. In advanced forms of the disease (ASM, SM-AHN, MCL), these excess mast cells result in multi-organ dysfunction and reduce overall survival. The indolent subtype (ISM) does not impact overall survival but many patients experience debilitating symptoms, such as itching, flushing, anaphylaxis, syncope, headache and gastric events. Avapritinib (formerly BLU-285) is a potent, highly selective oral inhibitor that targets KIT Exon 17 activation loop mutants – particularly D816V – and is currently in Phase 1 trials for SM. The discovery and preclinical characterization of avapritinib will be described, including the optimization of overall drug-like properties and activity in an in vivo model of disease. Furthermore, recently disclosed data from the dose escalation portion of the Phase 1 trial will be presented. The significant clinical activity observed, with an overall response rate of 72 percent and a disease control rate of 100 percent (as of data cutoff date of October 4, 2017) strongly support the continued evaluation of avapritinib as a targeted therapy for SM.

MEDI 260

Discovery of CFTR correctors for the treatment of cystic fibrosis

Xueqing Wang, *xwa142@yahoo.com. Discovery, Pharmacyclics, an AbbVie Company, Sunnyvale, California, United States*

Cystic fibrosis (CF) is a multisystem disease of the lungs, sinuses, pancreas, and gastrointestinal tract, and is caused by dysfunction or deficiency of the cystic fibrosis transmembrane conductance regulator protein (CFTR), an epithelial anion channel that regulates salt and water balance in tissues and maintains homeostasis of the airway surface liquid layer of the lungs. To address the most prevalent patient population (F508del mutation), two biomolecular modulators are required, correctors to increase CFTR levels at the cell surface, and potentiators to allow the effective opening of the CFTR channel. Despite approved potentiator and potentiator/corrector combo therapies,

there remains high need to develop more potent and efficacious correctors to provide robust clinical efficacy for the large patient population.

As part of a broad AbbVie Galapagos CF collaboration, we have identified a highly potent series of CFTR correctors. In this presentation, we will describe structure activity relationship (SAR) studies that guided the discovery and selection of ABBV/GLPG-2222. This compound was advanced into clinical trials.

MEDI 261

ACH-4471, the first clinically investigated orally administered small-molecule inhibitor of complement factor D for the treatment of rare chronic diseases including C3 glomerulopathy

Jason A. Wiles, jwiles@achillion.com, Venkat R. Gadhachanda, Avinash S. Phadke, Steven D. Podos, Yongqing Huang, Wengang Yang, Hetal Kocinsky, Milind Deshpande, Mingjun Huang. Achillion Pharmaceuticals, New Haven, Connecticut, United States

The complement system, comprising >30 receptors and soluble plasma proteins, plays a vital role in our innate immune defense against invasive microorganisms. The complement components interact via three tightly regulated enzymatic activation cascades—the classical pathway (CP), the lectin pathway (LP), and the alternative pathway (AP)—that converge on the central complement component 3 (C3). The AP is a critical element of the complement system that provides a rapid antibody-independent route for activation and a powerful amplification loop for both the CP and LP. Central to AP activation and amplification, complement factor D (CFD) is a specific serine protease that cleaves its unique substrate, complement factor B in complex with an activated form of C3, to generate the AP C3 convertases C3(H₂O)Bb and C3bBb. Dysregulation of the AP is associated with human diseases such as C3 glomerulopathy (C3G). C3G is a rare disease affecting the glomeruli of the kidney with no approved treatment and 30–50% occurrence of end-stage renal disease within 10 years. The underlying pathophysiology is believed to be AP hyperactivity due to mutations in and/or autoantibodies against complement proteins or complement regulatory proteins. This presentation will outline our innovative efforts to identify small-molecule inhibitors of CFD as a potentially transformative approach to block AP hyperactivity for the treatment of C3G. Topics to be discussed include the general structure–activity relationship of CFD inhibitors, the preclinical profile of our lead candidate ACH-4471, and the early clinical evaluation of ACH-4471, which is advancing in Phase 2 studies for the treatment of C3G and paroxysmal nocturnal hemoglobinuria (PNH).

MEDI 262

Sulfur-halogen intramolecular conformational constraints: Identification of 1,3,4-thiadiazole analogs of LMI070 as SMN2 splicing modulators

Moo Je Sung, mooje.sung@novartis.com. Global Discovery Chemistry, Novartis, Cambridge, Massachusetts, United States

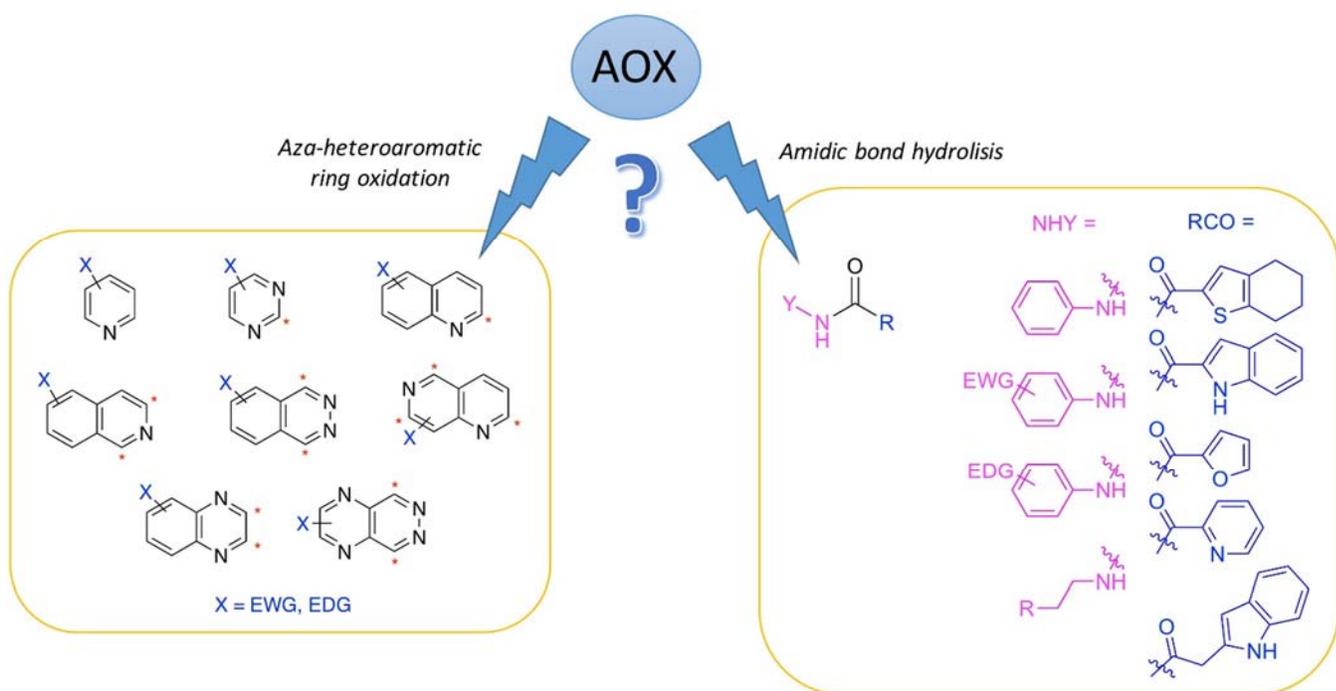
Spinal muscular atrophy (SMA) is a debilitating genetic neurodegenerative disease and is the leading genetic cause of pediatric mortality. SMA is characterized by progressive degeneration of motor neurons, muscle wasting, paralysis, and in severe cases death. SMA is caused by the loss of the survival motor neuron 1 (SMN1) gene. There exists a compensatory gene called survival of motor neuron 2 (SMN2), however, a single nucleotide mutation results in a truncated and unstable SMN protein. The small molecule SMN2 splicing modulator LMI070 has been found to elevate levels of full length SMN protein and extend survival in the SMN-delta-7 mouse model, and the compound is currently in Phase II clinical trials. We will describe our parallel scaffold morphing strategy which led to the discovery of a 1,3,4-thiadiazole as a second scaffold. The thiadiazole provides the opportunity for a planarizing conformational constraint of a biaryl through either a non-bonding sulfur-oxygen interaction, or a sulfur-halogen intramolecular interaction. Taking advantage of sulfur-fluorine and sulfur-chlorine conformational constraints, thiadiazole-containing SMN2 splice modulators have been optimized for in vivo metabolic stability and efficacy.

MEDI 263

Chemical insights into human aldehyde oxidase-mediated metabolism

Susan Lepri, susanlepri@gmail.com, Nicolò Milani, Sara Tortorella, Gabriele Cruciani. Chemistry, Biology and Biotechnology, University of Perugia, Perugia, Perugia, Italy

The early metabolic stability assessment of novel potential drug candidates remains today a major challenge in drug development. Although significant advancements have been made for CYP-mediated metabolism, action mechanism of other non-CYP enzymes remains poorly understood. In particular, Aldehyde Oxidase (AOX) has emerged as a key enzyme responsible for several clinical candidate failures (e.g., carbazeren, GDC-0834). Indeed, AOX has a broad substrate specificity, catalyzing aza-aromatic oxidation and amide hydrolysis, common moieties in drugs. In the present study, we designed a large dataset of potential AOX substrates, covering a diverse chemical domain of commonly used drugs and drug candidates to obtain a sound base for further mechanistic investigation and modeling studies. Thus, more than 300 compounds were synthesized or acquired and tested in human liver cytosol (HLC) for assessing AOX-mediated metabolism. Thus, combining *in vitro* experimental results and DFT calculations, important structure-metabolic stability relationships were identified. As a result, we defined useful guidelines for tuning AOX susceptibility of lead compounds, and developed a new *in silico* model for human AOX-mediated metabolism prediction.

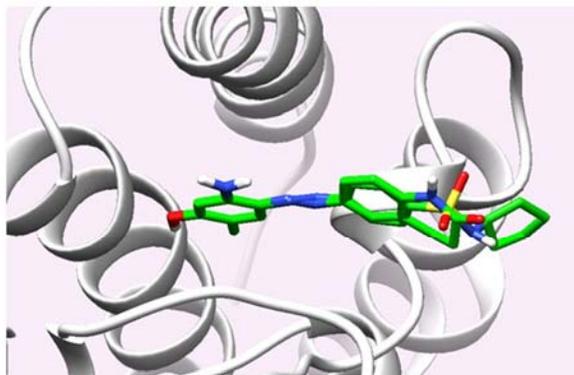


MEDI 264

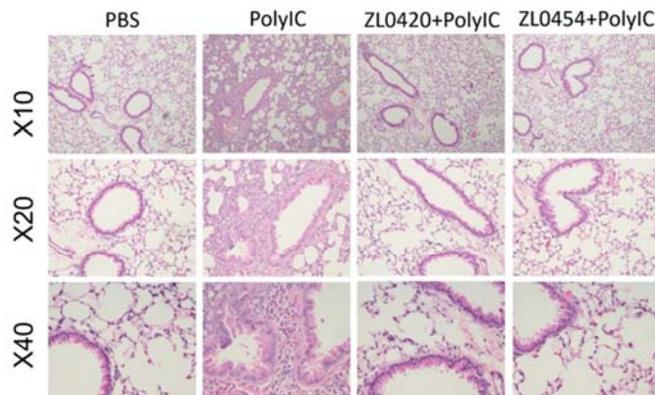
Discovery of potent and selective BRD4 inhibitors capable of blocking TLR3-induced acute airway inflammation

Zhiqing Liu¹, Bing Tian², Haiying Chen¹, Pingyuan Wang¹, Allan R. Brasier², **Jia Zhou¹**, jizhou@utmb.edu. (1) Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, Texas, United States (2) Department of Internal Medicine, University of Texas Medical Branch, Galveston, Texas, United States

A series of diverse small molecules have been designed and synthesized through structure-based drug design by taking advantage of fragment merging and elaboration approaches. Compounds ZL0420 and ZL0454 were identified as potent and specific BRD4 inhibitors with nanomolar binding affinities to bromodomains (BDs) of BRD4 with high selectivity over other BET proteins. Both of them can be well docked into the acetyl-lysine (KAc) binding pocket of BRD4, forming key interactions including the critical hydrogen bonds with Asn140 directly and Tyr97 indirectly via a H₂O molecule. Both ZL0420 and ZL0454 exhibited submicromolar potency of inhibiting the TLR3-dependent innate immune gene program, including ISG54, ISG56, IL-8, and Groβ genes in cultured human small airway epithelial cells (hSAECs). More importantly, they also demonstrated potent efficacy reducing airway inflammation in a mouse model, indicating a proof of concept that BRD4 inhibitors may offer the therapeutic potential to block the viral-induced airway inflammation.



Overlay analysis of BRD4 inhibitors ZL0420 and ZL0454 docked into BRD4 BD1



In vivo efficacy (10 mg/kg) in a mouse model of TLR3-induced airway inflammation

MEDI 265

Discovery of potent BET inhibitors as potential treatments for cancer

Matthew D. Hill¹, matthew.hill@bms.com, **Haiquan Fang**¹, **Derek Norris**¹, **William D. Schmitz**², **Christine Huang**¹, **Richard Westhouse**¹, **Melissa Kramer**¹, **John Morrison**¹, **Ching Kim Tye**¹, **Eric Shields**¹, **Haiying Zhang**¹, **Michael Sinz**¹, **Jean Simmermacher-Mayer**¹, **Francis Lee**¹, **Ashvinikumar V. Gavai**³, **Andrew P. Degnan**². (1) Bristol-Myers Squibb, Wallingford, Connecticut, United States (2) Bristol Myers Squibb, Wallingford, Connecticut, United States (3) Oncology Chemistry, Bristol-Myers Squibb, Princeton Jct, New Jersey, United States

Despite recent advances in cancer treatment, significant unmet need persists. Small molecule approaches remain attractive methods to address many oncologic targets, including the bromodomain and extra-terminal (BET) proteins. We previously disclosed a carboline-containing clinical candidate (BMS-986158) that demonstrated BET-mediated tumor inhibition in preclinical models. Herein, we describe efforts towards a second-generation inhibitor. Deuteration and fluorination strategies were pursued to reduce clearance. Concurrent with these studies, heterocyclic phenyl replacements were employed to drive increases in free fraction and aqueous solubility. This work culminated in the identification of potent BET inhibitors with increased exposure across preclinical species and robust efficacy in a mouse solid-tumor model.

MEDI 266

Development of a YEATS-domain chemical probe

Moses Moustakim¹, moses.moustakim@chem.ox.ac.uk, **Octovia Monteiro**², **James Bennett**², **Charline Giroud**², **Thomas Christott**², **Laura D. Saez**², **Ioanna Panagakou**², **Ling Felce**⁴, **Vicki Gamble**⁴, **Kilian Huber**², **Gillian Farnie**⁴, **Jag Heer**⁵, **Darren Dixon**³, **Paul Brennan**², **Oleg Federov**². (1) Department of Chemistry/Structural Genomics

Consortium, University of Oxford, Oxford, Oxfordshire, United Kingdom (2) Structural Genomics Consortium, University of Oxford, Oxford, Oxfordshire, United Kingdom (3) University of Oxford, Oxford, United Kingdom (4) NDORMS, University of Oxford, Oxford, Oxfordshire, United Kingdom (5) UCB, Slough, Berkshire, United Kingdom

The YEATS domain containing proteins are an emerging class of epigenetic targets in drug discovery. Reported to bind acylated lysine residues, misregulation of these interspecies conserved proteins have been linked to the onset and progression of cancers such as acute myeloid leukaemia (AML). We herein report the discovery and characterisation of the first small molecule chemical probe inhibitor for the closely related YEATS domains of ENL (MLLT1) and AF9 (MLLT3). Our probe molecule is a potent nanomolar inhibitor of ENL/AF9 and displays selectivity over the two other human YEATS domain containing proteins (YEATS2 and GAS41). Evidence of cellular-target engagement of ENL was explored through a NanoBRET displacement assay. Commensurate with recent reports of ENL knockdowns, our probe molecule has been investigated for anti-cancer activity in leukemic cell lines and synergistic effects when dosed in combination with BET bromodomain inhibitors such as (+)-JQ1. Taken together our probe molecule can be used as a novel tool to ENL/AF9 associated biology.

MEDI 267

Development of KDM5 covalent inhibitors as chemical probes

Saleta Vazquez-Rodriguez, *svre77@gmail.com*, Miranda Wright, Paul Brennan. TDI NDM Research Building, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

Histone lysine demethylase (KDMs) are involved in the dynamic regulation of gene expression by reversible regulation of the methylation levels on lysine residues in histone tails. Among the KDMs, the jumonji (JmjC)-domain-containing KDMs (KDM2-7) are Fe(II), 2-OG (α -ketoglutarate) and molecular oxygen-dependent enzymes that employ an oxygenase mechanism to demethylate specific methylation states at various histone sites. KDMs play a critical role in several biological processes such as cell differentiation, inflammation, cancer progression and resistance. Achieving selectivity over the different families of KDMs has been a major challenge. Here we report potent and selective KDM5 covalent inhibitors designed to target a cysteine residue only present in the KDM5 sub-family. *In vitro* assays show that compounds are selective for the KDM5 sub-family, showing potencies in the low nanomolar range, with higher affinity for KDM5A/B. The covalent binding to the targeted proteins was proved by MS. A kinetic approach was studied in order to describe the components of overall inhibitor potency (reversible binding and chemical reactivity), showing a time-dependent decrease of IC₅₀ values for irreversible inhibition. Additional 2-OG competition assays show that compounds were non 2-OG competitive and target engagement assays showed that the compounds inhibited the KDM5 members in cells. Full description of the results will be presented in the meeting.

MEDI 268

Antitubercular drug discovery enabled by Bayesian modeling

Alexander L. Perryman¹, Thomas P. Stratton¹, Jimmy S. Patel¹, Xin Wang¹, Sean Ekins², Joel S. Freundlich^{1,3}, freundjs@rutgers.edu. (1) Department of Pharmacology, Physiology & Neuroscience, Rutgers University, Newark, New Jersey, United States (2) Collaborations Pharmaceuticals, Inc., Raleigh, North Carolina, United States (3) Center for Emerging and Reemerging Pathogens, Department of Medicine, Rutgers University, Newark, New Jersey, United States

In 2016, tuberculosis claimed the lives of 1.7 million people while leading to 10.4 million reported cases. The rise of drug resistance to front-line therapy has necessitated an effort to restock our drug discovery pipeline with molecules that exhibit novel mechanisms of action. Our laboratories have focused on the discovery and optimization of new chemical series as antituberculars that exhibit novel mechanisms of action. To pursue this in a time- and cost-efficient manner, we have employed naïve Bayesian techniques to leverage public data sets and construct models to identify novel antitubercular small molecules and facilitate their optimization toward lead compounds by addressing issues such as metabolic stability, mammalian cell cytotoxicity, and aqueous solubility. This talk will discuss recent efforts in this program and the impact on antitubercular drug discovery.

MEDI 269

Discovery of a highly potent and orally bioavailable selective estrogen receptor degrader (SERD) GNE-149 for ER-positive breast cancer

Jun Liang, liang.jun@gene.com. Genentech, Los Altos Hills, California, United States

Breast cancer is the most common cancer and second leading cause of cancer death in women. Approximately 70% breast cancers are ER-positive. Standard of care therapies include Selective Estrogen Receptor Modulators (SERMs), such as tamoxifen, and aromatase inhibitors. Despite their initial effectiveness, 20-30% of patients eventually relapse and become resistant. Fulvestrant, a Selective Estrogen Receptor Degrader (SERD) with the endogenous estradiol core and a highly lipophilic side-chain, was approved to treat metastatic disease. However, fulvestrant has limited use due to its poor pharmacokinetic and pharmaceutical properties, requiring the drug to be injected intramuscularly.

Herein we report the discovery and optimization that led to the identification of a highly potent SERD with improved pharmacokinetic and pharmaceutical properties. To achieve maximal degradation of ER while maintaining acceptable physiochemical properties, we focused on compounds which carry a basic side-chain. We hypothesized that a SERD with a basic side-chain might be a degrader with the full antagonist profile similar to some SERMs, thus avoiding the partial agonist profile observed for both GDC-0810 and AZD9496 in the uterus of immature rats. Furthermore, compounds were

synthesized with a novel tetrahydrocarboline (THC) core. The THC core lacks a phenol moiety, which was previously believed to be critical for optimal binding with ER. We reasoned that removal of phenol might offer an opportunity to achieve acceptable oral exposure which had been a significant challenge for ER binders containing a basic side-chain. The resulting combination of a THC core with basic side-chains yielded prototype molecules with good potency and excellent oral exposure across preclinical species. Guided by computational modeling and by co-crystal structures, we further optimized *in vitro* potency and ER degradation of the THC analogs, eventually leading to the discovery of GNE-149. GNE-149 showed robust, dose-dependent efficacy in both tamoxifen-sensitive and -resistant xenograft models. Moreover, GNE-149 did not exhibit partial agonist effect in the uterus of immature rats, and was well tolerated up to 100 mg/kg PO QD for 7 days in rats.

MEDI 270

Discovery of a series of selective inhibitors of the sodium-phosphate co-transporter NaPi2a (SLC34A1)

Kevin J. Filipski, kevin.filipski@pfizer.com. Pfizer Worldwide Research & Development, Cambridge, Massachusetts, United States

In the kidney proximal tubule, glomerular-filtered phosphate is in part reabsorbed by the sodium-phosphate co-transporter 2a, or NaPi2a. This is a solute carrier (SLC) transporter encoded by the SLC34A1 gene. A NaPi2a inhibitor is hypothesized to facilitate urinary phosphate excretion and envisioned as a therapy to correct maladaptive mineral and hormonal derangements associated with increased cardiovascular risk in chronic kidney disease – mineral and bone disorder (CKD-MBD). A high-throughput screen was run using SLC34A1-transfected cells whereby the uptake of ³³P-radiolabeled phosphate was detected. A hit from this effort was then optimized to PF-06869206, a useful NaPi2a-selective tool compound with good oral bioavailability. PF-06869206 and its series show excellent selectivity for NaPi2a over the other sodium-phosphate co-transporters, the first known chemical matter to show such selectivity. This compound was used to explore the *in vitro* and *in vivo* pharmacology of selective NaPi2a inhibition including an 8-week study in a rodent model of cardio-renal disease.

MEDI 271

Discovery and application of 3-oxabicyclo[4.1.0]heptane, a non-nitrogen containing morpholine isostere, through predictive quantum mechanical modelling

Heather Hobbs¹, heather.x.hobbs@gsk.com, Gianpaulo Bravi^{1,2}, Ian Campbell¹, Maire Convery¹, Hannah Davies¹, Graham Inglis¹, Sandeep Pal³, Simon Peace¹, Joanna Redmond¹, Declan M. Summers^{4,1}. (1) GlaxoSmithKline, Stevenage, Hertfordshire, United Kingdom (2) Dogmatics, Bishops Stortford, Hertfordshire, United Kingdom (3)

GlaxoSmithKline, Stevenage, United Kingdom (4) Pure and Applied Chemistry,
University of Strathclyde, Hatfield, Hertfordshire, United Kingdom

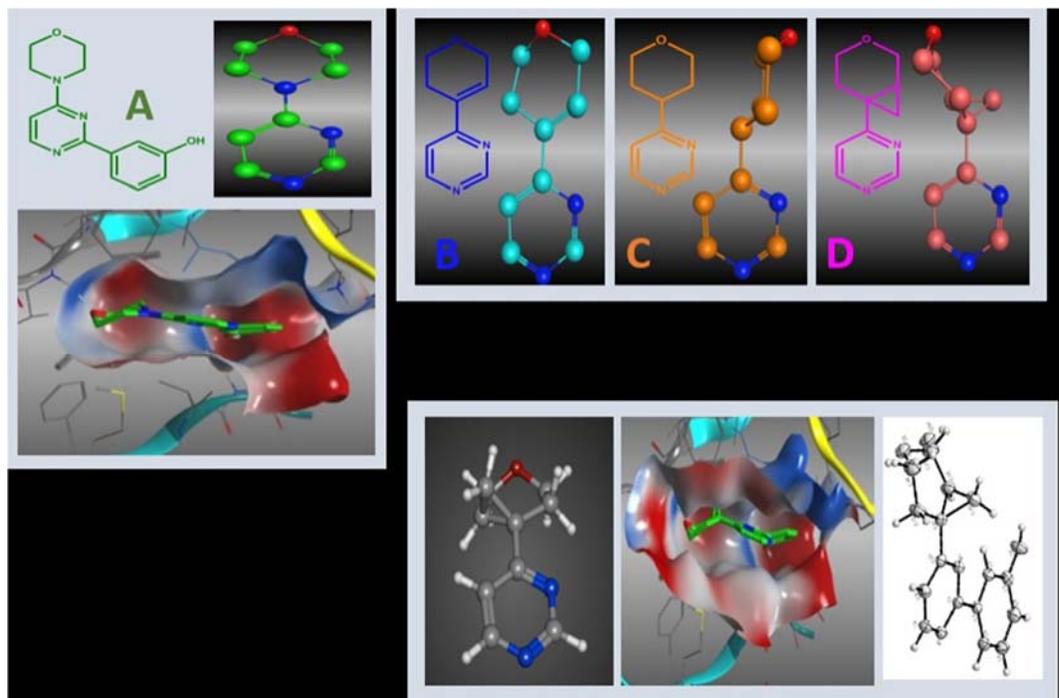
The heteroaromatic morpholine motif is common in the scientific literature and represents a “privileged” motif that confers superior selectivity for inhibitors of lipid and lipid-like kinases¹. Kinase protein binding sites are typically very narrow around the hinge binding region and the co-planarity of the morpholine hinge binder and heteroaromatic core [A] orientate the morpholine oxygen lone pair into favourable direction for hydrogen bonding with the active site (Figure 1)².

Aryl morpholines have the potential to be metabolised *in-vivo* to ames positive aniline; however, carbon linked morpholine replacements for the morpholine are rare and largely limited to dihydropyran³ [B] which is generally considered undesirable due to its reactivity whereas tetrahydropyran [C] adopts an orthogonal geometry and hence is ineffective as a morpholine isostere. Herein we describe the discovery of 3-oxabicyclo[4.1.0]heptane [D] an alternative isostere *via* prospective quantum mechanical molecular modelling.

Basic modelling of molecular mechanics in MOE of morpholine [A], dihydropyran [B], tetrahydropyran [C] and 3-oxabicyclo[4.1.0]heptane [D] are shown (Figure 2).

Rigorous quantum mechanical calculations predicted a *co-planar* conformation for [D]] and hence tool molecules were prepared to test the hypothesis. It was thus discovered that the 3-oxabicyclo[4.1.0]heptane is an active bioisotere for morpholine, furthermore the favourable co-planar conformation was confirmed *via* a ligand-PI3K δ co-crystal structure (Figure 3).

We will describe the discovery of 3-oxabicyclo[4.1.0]heptane, associated risks and benefits and its application in the development of single-digit nanomolar inhibitors of an atypical lipid-like kinase with >1000x selectivity over closely related lipid kinases.



MEDI 272

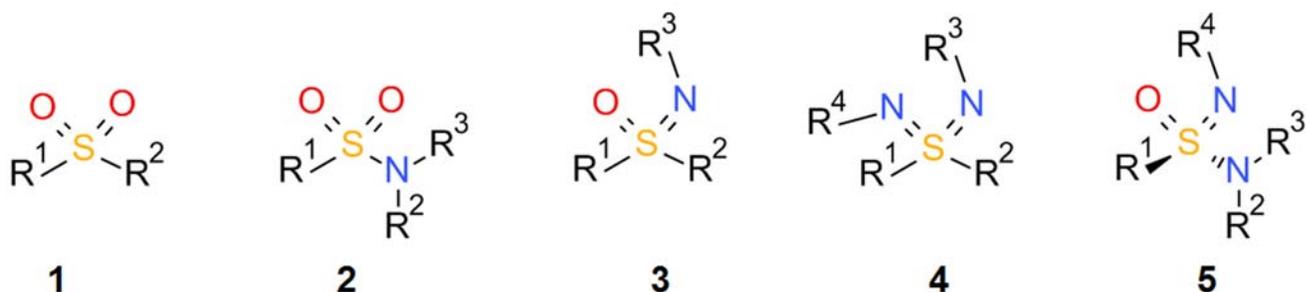
Exploration of novel chemical space by the interplay of drug design and method development: Neglected sulfur (VI) pharmacophores in drug discovery

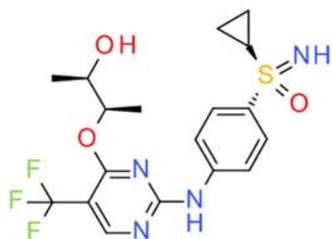
Ulrich T. Luecking¹, ulrich.luecking@bayer.com, Flavia Izzo², Juan Alberto Sirvent¹, Robert A. Stockman², Franz von Nussbaum¹, Marcus Bauser¹, Michael Brands¹. (1) Medicinal Chemistry, Bayer AG, Berlin, Germany (2) School of Chemistry, Nottingham, United Kingdom

Sulfones (**1**) and sulfonamides (**2**) are important pharmacophores found in many drugs on the market. On the other hand, the corresponding aza-analogues, sulfoximines (**3**), sulfondiimines (**4**) and sulfonimidamides (**5**) have received little interest in drug discovery until recently. The infrequent take-up of these sulfur (VI) groups is surprising since they seem to offer very interesting properties, like high stability, favorable PhysChem properties, multiple H-bond acceptor/donor functionalities, and structural diversity. Possible reasons for the neglected use of these functional groups are the lack of commercial availability, limited synthetic methods for their preparation and an incomplete understanding of their medicinal-chemistry-relevant properties.

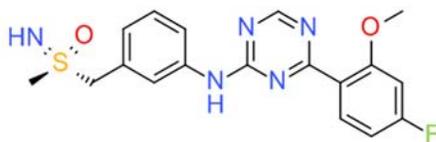
In the identification of CDK inhibitor roniciclib we experienced that the use of the uncommon sulfoximine group can be crucial for overcoming hurdles in lead optimization. This has sparked our interest in neglected sulfur (VI) pharmacophores, which led to additional clinical candidates (atuveclib, BAY 1251152). However, in our drug discovery efforts the syntheses of sulfur (VI) key compounds have often been met with difficulties, including safety concerns. Therefore we have not only readily adopted new synthetic methods to complex drug-like molecules but have also started to develop new synthetic methods for the syntheses of sulfur (VI) groups.

In this presentation we will share the key learnings of various lead optimization efforts leading to multiple sulfur (VI) clinical candidates. In this context we will also highlight the key methods for their preparations. Moreover, we will showcase our latest results for the synthesis and functionalization of =NH sulfonimidamides and the evaluation of their medicinal-chemistry-relevant in vitro properties.

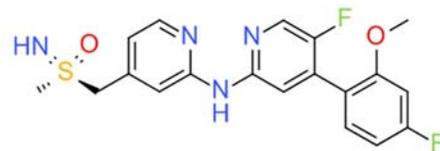




ronniciclib, CDK Inhibitor, Phase II



atuvaciclib, PTEFb Inhibitor, Phase I



BAY 1251152, PTEFb Inhibitor, Phase I

MEDI 273

Assessment of AstraZeneca secondary pharmacology profiling assays and applications to lead optimization efforts

Dean G. Brown, dean.brown@astrazeneca.com. *IMED Biotech Unit, Discovery Sciences, AstraZeneca Pharmaceuticals, Waltham, Massachusetts, United States*

An analysis was completed of ~1300 diverse drug discovery project compounds which were tested against a panel of 125 off-target receptors. For each target, hit-rates were calculated (categories of $IC_{50} < 10 \mu M$ and $IC_{50} < 2 \mu M$), along with the average calculated logD (clogD), molecular weight (MW) and ionization classification of the hit compound sets. These properties were also compared against the inactive compounds for each receptor. Some receptors demonstrated very high hit-rates. For example, 38% of the compounds tested in an adenosine transporter assay demonstrated an $IC_{50} < 10 \mu M$ using a $^3[H]$ nitrobenzylthioinosine binding assay. In comparison, some off-target assays did not demonstrate hits for any of the compounds tested (e.g. GABA-B binding, H_2 cAMP functional assay). Of the 125 targets in the panel, an analysis of the “hits” versus “inactives” demonstrated the vast majority (>90%) of targets favored higher logD, higher MW, and more basic compounds than inactives in each set. Finally, an assessment of off-target profiles of recent clinical candidates which successfully passed Phase 1 safety studies illustrated that most successful Phase 1 clinical candidates only have a small number of off-target hits, but there are significant exceptions to this observation which will be discussed. Overall, this analysis has been useful in building a better understanding of common off-target and secondary pharmacological risks in lead optimization programs, as well as strategies which help to mitigate these risks.

MEDI 274

NKTR-181: Separating euphoria from analgesia in a full MOR agonist

Stephen K. Doberstein¹, sdoberstein@nektar.com, **Neel K. Anand**². (1) *Research and Development, Nektar Therapeutics, San Francisco, California, United States* (2) *Nektar Therapeutics, San Francisco, California, United States*

Mu-opioid receptor agonists that rapidly enter the brain and trigger an immediate surge of dopamine stimulating the reward pathways involved in the reinforcement behaviors

underlying abuse and addiction. We hypothesized that reducing the rate of entry of a drug into the brain by modulating the physiochemical properties of a mu-opioid receptor agonist through application of our polymer conjugation technology, would provide effective analgesia for chronic pain control, but reduce the attractiveness of the drug as a target of abuse, independent of the route of administration.

Following review of existing SAR, we designed, synthesized and evaluated a series of polyethylene glycol (PEG)-morphinan opioid agonist conjugates for their activity, bioavailability, and kinetics of entry into the brain, ultimately selecting NKTR-181 as the first exemplar of this new class of opioid agonists. The structure of NKTR-181 consists of a six-unit PEG chain attached to the morphinan pharmacophore, which results in a reduced rate of entry into the brain compared to conventional opioids.

In pre-clinical models, NKTR-181 demonstrated maximum analgesic activity comparable to that of oxycodone, but was distinguishable from oxycodone by its reduced abuse potential in self-administration and progressive ratio break point models, with behavioral effects similar to those of saline. In a dopamine microdialysis study in rat, brain uptake rates for NKTR-181, following IV administration, were 70-fold slower than for oxycodone, and a delayed and blunted dopamine response to NKTR-181 was observed when compared to oxycodone.

In humans, following oral administration, the difference in the time course between plasma drug exposure and miosis indicated that the half-life of NKTR-181 brain uptake was 17.5-fold longer than that of oxycodone. Recently, NKTR-181 has demonstrated significant clinical efficacy versus placebo in patients with chronic low-back pain, was well tolerated, while demonstrating minimal drug likability, CNS adverse events and withdrawal symptoms.

MEDI 275

Evaluation of opioid antinociceptive tolerance with G-protein signaling biased opioid agonists

Laura M. Bohn¹, lbohn@scripps.edu, Thomas D. Bannister². (1) Molecular Medicine & Neuroscience, The Scripps Research Institute, Jupiter, Florida, United States (2) #3A1, The Scripps Research Institute-Florida, Jupiter, Florida, United States

Early genetic knockout studies support a hypothesis that an agonist that promotes mu opioid receptor (MOR) coupling to G protein pathways without beta-arrestin2 recruitment might be a way to promote antinociception while limiting the side effects associated with opiate narcotic analgesics. Agonists that can stimulate one pathway and avoid another downstream of receptor engagement are referred to as biased agonists. We have developed several selective biased agonists designed to activate MOR-G protein signaling pathways over beta-arrestin2 pathways and have investigated whether divergent signaling in vitro can predict divergent physiologies in mouse models of opioid responsiveness. Our studies show that for such compounds, G protein

signaling is preserved in vivo as well as the antinociceptive properties in mice. However, respiratory suppression is greatly attenuated. A correlation between calculated bias factors, used for ranking compound selection, and the widening of the therapeutic window in vivo will be discussed. Unpublished work examining the chronic administration of these compounds will also be presented.

MEDI 276

NYX-2925 is a novel NMDA receptor-specific spirocyclic- β -lactam that induces rapid and long-lasting analgesia in multiple rat models of neuropathic pain

Roger A. Kroes, *rogerkroes@aptinyx.com*, M. Amin Khan, Nayereh Ghoreishi-Haack, Cassia Cearley, Joseph R. Moskal. Aptinyx, Inc., Evanston, Illinois, United States

N-methyl-D-aspartate receptors (NMDARs) are critical for synaptic plasticity underlying learning and have been shown to play an important role in neuropathic pain. NYX-2925 ((2S, 3R)-3-hydroxy-2-((R)-5-isobutyryl-1-oxo-2,5-diazaspiro[3,4]octan-2-yl)butanamide) is a member of a new class of molecules that mimic the dipyrrolidine-based β -turn motif of rapastinel (formerly GLYX-13) and is both structurally and mechanistically distinct from other known NMDAR modulators. NYX-2925 also has rapid and long-lasting analgesic effects in multiple rat models of neuropathic pain. Mechanistically, NYX-2925 binds to a unique NR2B binding pocket identified by coupling *in silico* modeling algorithms and molecular dynamic simulations with functional validation using site-directed mutagenesis approaches. Thus NYX-2925, along with other members of the platform, comprise a novel toolbox to help dissect the mechanisms of NMDA receptor modulation of neuropathic pain.

MEDI 277

Strategic advances in the identification of small molecule inhibitors of Nav1.7 for the treatment of chronic pain

Benjamin Milgram, *bmilgram@amgen.com*. Amgen Inc., Cambridge, Massachusetts, United States

The voltage-gated sodium channel Nav1.7 serves as a primary driver of action potential firing and neuronal excitability in the pain processing pathway. Genetic evidence supports the role of Nav1.7 in a range of inherited pain syndromes, both gain-of-function and loss-of-function. Consequently, there has been considerable interest in the development of an isoform-selective Nav1.7 inhibitor for the management of chronic neuropathic pain. This presentation will describe the strategic evolution of our program with a focus on the pharmacokinetic-pharmacodynamic relationship across multiple series of small molecule Nav1.7 inhibitors.

MEDI 278

Structure-based drug discovery in a sodium channel: Discovery of chromane arylsulfonamide Nav1.7 inhibitors for the treatment of chronic pain

Steven McKerrall¹, *mckerrall.steven@gene.com*, Philippe Bergeron¹, Brian Safina¹, Daniel F. Ortwine¹, Shannon Shields¹, Lunbin Deng¹, David Hackos¹, Jun Chen¹, Jodie Pang¹, Jae Chang¹, Kwong W. Lai², Wenfeng Liu², Zhiguo Liu², Christoph M. Dehnhardt³, JP Johnson³, Girish Bankar³, Charles Cohen³, Daniel P. Sutherlin¹. (1) Genentech, San Francisco, California, United States (2) Wuxi Apptec, Shanghai, China (3) Xenon Pharmaceuticals, Burnaby, British Columbia, Canada

Chronic pain remains a substantial unmet medical need and this unmet need is a major contributor to the current opioid epidemic in North America. Nav1.7 is one of nine voltage-gated sodium ion channels in the human genome that has been strongly linked to pain sensation through compelling genetic evidence. Specifically in humans both loss- and gain-of-function mutations in SCN9A, the gene that encodes Nav1.7, cause a complete insensitivity to pain or spontaneous pain syndromes respectively. In spite of this strong genetic evidence, development of subtype selective inhibitors with suitable pharmacokinetics and in vivo activity for clinical use has remained challenging. We report the utilization of a crystal structure of a Nav1.7 chimera in the discovery of subtype selective chromane arylsulfonamide Nav1.7 inhibitors. Initial discovery of the scaffold and optimization of the potency, metabolic stability, in vivo pharmacokinetics, and in vivo activity will be discussed.

MEDI 279

Discovery of novel arylsulfonamide Nav1.7 inhibitors: *In vitro-in vivo* correlations, development of multiparameter optimization (MPO) methods, and optimization of selectivity profiles

Anthony J. Roecker¹, *anthony_roecker@merck.com*, Mark E. Layton¹, Michael J. Kelly¹, Joseph E. Pero¹, Thomas J. Greshock¹, Ting Zhang¹, Richard L. Kraus², Yuxing Li², Christopher Daley², Aneta Jovanovska², Becky Klein³, Michelle Clements³, Jixin Wang³, Darrell Henze³, Geoffrey Varty³, Jeanine Ballard⁴, Deping Wang⁵, Fuqiang Zhao⁶, Christopher P. Regan⁷, Hillary Regan⁷, Leo A. Joyce⁸, Edward C. Sherer⁸, Christopher T. John⁹, Xuanjia Peng¹⁰, Xiu Wang¹⁰, Haiyan Sun¹⁰, Andrea K. Houghton², Christopher S. Burgey¹. (1) Medicinal Chemistry, Merck, West Point, Pennsylvania, United States (2) Pharmacology, Merck, West Point, Pennsylvania, United States (3) Neuroscience, Merck, West Point, Pennsylvania, United States (4) Drug Metabolism, Merck, West Point, Pennsylvania, United States (5) Chemistry Modeling & Informatics, Merck, West Point, Pennsylvania, United States (6) Imaging, Merck, West Point, Pennsylvania, United States (7) Safety and Laboratory Animal Resources, Merck, West Point, Pennsylvania, United States (8) Analytical Chemistry, Merck, West Point, Pennsylvania, United States (9) Pharmaceutical Sciences, Merck, West Point, Pennsylvania, United States (10) Wuxi Apptec, Tianjin, China

The voltage-gated sodium channel Nav1.7 continues to be a high profile target for the treatment of various pain afflictions due to its strong human genetic validation. While isoform selective molecules have been discovered and advanced into the clinic, to date, this target has yet to bear fruit in the form of marketed therapeutics for the treatment of pain. This presentation will detail our continued optimization efforts in the arylsulfonamide class of Nav1.7 inhibitors focused on three areas. First, *in vitro* – *in vivo* correlations (IVIVC) between potency in electrophysiology assays and activity in preclinical models of pain as well as a target modulation assay in non-human primates will be discussed. Second, due to significant challenges in achieving good oral bioavailability within the zwitterionic series, a novel multiparameter optimization (MPO) paradigm to prospectively design compounds with acceptable rat oral bioavailability will be presented. Finally, empirical improvements in selectivity profiles will be rationalized through the use of a Nav1.7 homology model that was developed prior to the recent publication of a Nav1.7 x-ray crystal structure. The combination of these approaches culminated in oral agents with excellent Nav1.7 potency, selectivity over homologous Nav1.x channels and activity *in vivo* consistent with Nav1.7 modulation.

MEDI 280

Discovery of selective inhibitors for histone methyltransferases

Jian Jin, jian.jin@mssm.edu. Icahn School of Medicine at Mount Sinai, New York, New York, United States

Histone methyltransferases (HMTs, also known as protein methyltransferases) have been increasingly pursued as potential therapeutic targets. High quality selective inhibitors of HMTs will permit biological and disease hypotheses concerning these enzymes to be tested in cell-based and/or animal models with high confidence. Our laboratory has made significant progress on discovering selective inhibitors of HMTs by pursuing multiple complementary structure-based inhibitor discovery approaches. Our progress on discovering selective inhibitors of GLP, SETD8 and type I PRMTs along with new utilities of our EZH2 inhibitors will be presented.

MEDI 281

Discovery, optimization and biological activity of EED binders allosterically inhibiting the methyltransferase PRC2

Andreas Lingel^{1,3}, andreas.lingel@novartis.com, Ying Huang², Dirksen Bussiere¹, Justin Gu⁴, Ling Li⁴, Wei Qi⁵, Martin Sendzik¹, Youzhen Wang⁶, Zhengtian Yu², Hailong Zhang⁷, Jeff Zhang⁸, Man Zhang⁴, Kehao Zhao⁷, Counde Oyang², En Li⁵. (1) Global Discovery Chemistry, Novartis Institutes for BioMedical Research, Emeryville, California, United States (2) Global Discovery Chemistry, Novartis Institutes for BioMedical Research, Shanghai, China (3) Global Discovery Chemistry, Novartis Institutes for BioMedical Research, Basel, Switzerland (4) Lead Discovery, Novartis Institutes for BioMedical Research, Shanghai, China (5) Cancer Biology, Novartis

Institutes for Biomedical Research, Shanghai, China (6) Oncology, Novartis Institutes for BioMedical Research, Cambridge, Massachusetts, United States (7) Structural Biology, Novartis Institutes for BioMedical Research, Shanghai, China (8) PK Sciences, Novartis Institutes for BioMedical Research, Shanghai, China

Polycomb repressive complex 2 (PRC2) is a multi-subunit methyltransferase involved in epigenetic regulation of development, cell differentiation and growth. PRC2 preferentially methylates lysine 27 of histone 3 (H3K27) which impacts chromatin structure resulting in modulation of gene expression. Aberrant PRC2 activity caused by overexpression or mutations is linked to an increased frequency and poor prognosis of multiple human cancers. Thus, down-regulating PRC2 activity is pursued as a potential approach for cancer treatment, and several first generation inhibitors targeting the catalytic subunit EZH2 entered clinical evaluation as therapeutic agents several years ago. In addition to EZH2, which contains the SET domain responsible for the methyl transfer from the co-factor S-adenosylmethionine to H3K27, PRC2 contains the proteins EED, SUZ12, and RBAP46/48. Since EED was previously shown to allosterically modulate the methyltransferase activity of PRC2, we hypothesized that targeting EED could offer an alternative, potentially orthogonal way to inhibit methyltransferase activity through a new mechanism of action.

In this lecture, an overview of hit finding and triaging activities, structural biology and chemistry optimization of in-house EED inhibitors will be presented. In addition, biological data demonstrating cellular activity and in-vivo efficacy will be discussed.

MEDI 282

Structural rationalization of bioactivity trends that led to identification of the EZH2 development candidate (PF-06821497)

Pei-Pei Kung¹, peipei.kung@pfizer.com, Simon Bergqvist², Patrick Bingham¹, John F. Braganza¹, Alexei Brooun¹, Michael R. Collins¹, Wade Diehl¹, Ya-Li Deng¹, Dinh Dac¹, Connie Fan¹, Valeria Fantin³, Ketan Gajiwala¹, Hovhannes Gukasyan⁴, Wenyue Hu¹, Buwen Huang¹, Robert Kania¹, Wei Liu¹, Susan Kephart¹, Manfred Kraus¹, Cody Krivacic², Robert Kumpf¹, Gary Li⁵, Karen Maegley¹, Indrawan J. McAlpine¹, Lisa Nguyen¹, Sacha Ninkovic¹, Martha A. Ornelas¹, Dan Richter¹, Eugene Rui¹, Michael Ryskin⁶, Stephanie A. Scales¹, Jillian Spangler¹, Al Stewart¹, Scott C. Sutton¹, John Tatlock¹, Cheng-Chung Tsao⁷, Dominique Verhelle², Fen Wang¹, Hui Wang¹, Martin Wythes¹, Shinji Yamazaki¹, Brian Yip², Xiu Yu¹, Luke Zehnder¹, Wei-Guo Zhang², Peter Zhu², JinJiang Zhu¹, Robert Rollins⁷, Shikhar Sharma¹, Martin P. Edwards¹. (1) Pfizer La Jolla, San Diego, California, United States (2) NA, San Diego, California, United States (3) ORIC Pharma, San Francisco, California, United States (4) Allergan, Irvine, California, United States (5) Ignyta, San Diego, California, United States (6) Bank of America, New York, New York, United States (7) Pfizer Pearl River, Pearl River, New York, United States

Cancer genomes are characterized by aberrant patterns of DNA and histone modifications. The epigenetic modifiers in many cancer types often exhibit de-regulated

expression or genetic mutations. The histone methyltransferase EZH2 (enhancer of zeste homolog 2) is the catalytic subunit of the polycomb repressor complex 2 (PRC2). The PRC2 complex is a highly conserved protein complex that regulates gene expression by methylating lysine 27 residues on histone H3 proteins. EZH2 over-expression and gain-of-function mutations have been identified in both hematological malignancies and solid tumors. The discovery of catalytic inhibitors of EZH2 has provided an invaluable tool for further elucidating the role of this enzyme in cancers. Accordingly, we conducted parallel synthesis using a key EZH2 inhibitor pharmacophore that was reported in the literature. Utilizing conformational analysis and property-based design approaches, we identified a development compound, PF-06821497. A co-crystal structure of PF-06821497 together with several co-crystal structures of the inhibitors in complex with the EZH2-EED-SUZ12 three protein complex were obtained during the course of these activities. The design strategies that led to the identification of the development compound and structure-guided rationalizations of observed potency trends will be presented.

MEDI 283

Targeting histone methyltransferases and demethylases

Victor Gehling, *vgehling@gmail.com*. Chemistry, Constellation Pharmaceuticals, Cambridge, Massachusetts, United States

Histone methylation is fundamental to the establishment of the epigenomic landscape in cells. Histone methylation and demethylation, demonstrate significant and multi-functional impact on a variety of important biological processes, including roles in cell-fate, immune-cell programming, and oncology. As such, histone methyltransferases and demethylases are attractive targets for the development of small molecule inhibitors to probe the chromatin signaling network, while affording new therapeutic hypotheses. Here, I will discuss our efforts directed towards targeting histone methyltransferases and histone demethylases.

MEDI 284

Discovery and development of opicapone, a third generation catechol-O-methyltransferase inhibitor

Patricio Soares-da-Silva^{1,2}, *psoares.silva@bial.com*, László Kiss³. (1) Research and Development, BIAL, S. Mamede do Coronado, Portugal (2) MedInUp – Center for Drug Discovery and Innovative Medicines, University Porto, Porto, Portugal

Novel heterocycle-based nitrocatechol catechol-O-methyltransferase (COMT) inhibitors, structurally unrelated to classical “second-generation” predecessors, have been designed from the initial in vitro screening hit BIA 9-693. Replacement of the central pyrazole core with a 1,2,4-oxadiazole ring and definition of the correct 3,5-substitution pattern resulted in a series of leads with increased potency and duration of COMT

inhibition in vivo. 1,2,4-Oxadiazolyl nitrocatechols substituted with a pyridine N-oxide motif were found to present reduced propensity to cause toxicity and were generally endowed with enhanced inhibitory profile over reference compounds tolcapone and entacapone. Based on its promising activity and reduced toxicity risk, opicapone was selected for further pharmacological studies, where it was found to be an extremely potent and purely peripheral inhibitor of COMT and endowed with a truly unprecedented duration of action. Since these characteristics clearly differentiate this compound as having considerably improved biological properties over tolcapone, entacapone and nebicapone, opicapone is presented as a structurally novel, "third-generation" COMT inhibitor. Clinical trial data accessed thus far indicate that opicapone is endowed with superior efficacy and tolerability over its predecessors. Opicapone provides a safe and simplified drug regimen that allows the physician to individually tailor the existing levodopa daily regimen by potentially decreasing the total daily levodopa dose, increasing the dosing interval, and ultimately reducing the levodopa consumption, therefore maximizing its benefit. It is envisaged that opicapone will constitute an improved alternative to older drugs such as tolcapone and entacapone for the adjunctive treatment of late-stage Parkinson's disease patients.

MEDI 285

Spinal muscular atrophy from gene to treatment

Arthur Burghes, *burghes.1@osu.edu*. *Biological Chemistry and Pharmacology, The Ohio State University, Columbus, Ohio, United States*

Spinal Muscular Atrophy (SMA) is an autosomal recessive disorder that is the leading genetic cause of infant death. SMA is caused by loss or mutation of *SMN1* and retention of *SMN2*. The two genes differ by a single nucleotide in exon7 which alters a splice modulator and results in the majority of transcript from *SMN2* lacking exon7. The resulting loss of C terminal amino acids results in a SMN protein that does not efficiently oligomerize and gets rapidly degraded. The reduced levels of SMN results in SMA and the copy number of *SMN2* is inversely correlated with phenotypic severity. We have replicated this situation in mice which have one *Smn* gene by creating transgenic mice containing human *SMN2* and lacking mouse *Smn*. The genetics of SMA with the presence of *SMN2* which produces some SMN protein results in a situation where reintroduction of SMN protein will not result in an immune response against SMN thus allowing a gene therapy approach. In addition, *SMN2* acts as a target for increasing SMN levels using either antisense oligonucleotides or drug compounds to increase exon 7 incorporation and thus produce more SMN protein. Gene therapy, drug compounds and antisense oligonucleotide therapies were all tested in mice both for increasing SMN, affect on survival and in most cases correction of motor neuron phenotypes. A notable feature of obtaining effective treatments is two things first a good target i.e. *SMN2* and second the treatments having a big impact in the model systems. We also created a pig model of SMA and showed correction of this pig model with SMN gene therapy. In both pig and mice early correction of SMN levels was most effective whereas symptomatic resulted in rescue of the motor neurons still present this informed

the clinical trials indicating that the earlier treatment occurred the more effective it would be. Clinical trials have now demonstrated remarkable impact of early treatment in SMA for example in the phase 1 trial of scAA9-SMN 2 type 1 children treated early are walking a milestone never obtained in untreated type 1 SMA. Newborn screening is being implemented and there is still a need for more effective treatments in symptomatic patients potentially by combinatorial therapeutics.

MEDI 286

Small molecule SMN splicing modifiers to treat SMA

Matthew G. Woll¹, woll.matthew@gmail.com, Gary M. Karp¹, Anthony Turpoff¹, Nikolai A. Naryshkin¹, Amal Dakka¹, Jana Narasimhan¹, Vijayalakshmi Gabbeta¹, Marla Weetall¹, Xin Zhao¹, Nicole Risher¹, Josephine Sheedy¹, John Baird¹, Hasane Ratni², Friedrich Metzger², Sergey Paushkin³, Karen S. Chen³. (1) PTC Therapeutics, South Plainfield, New Jersey, United States (2) Roche, Basel, Switzerland (3) SMA Foundation, New York City, New York, United States

Spinal muscular atrophy (SMA) is caused by a genetic defect in the *SMN1* gene, rendering it incapable of producing the survival of motor neuron protein (SMN). In humans a nearly identical copy of the gene (*SMN2*) produces limited SMN protein, due to an alternative splicing event at exon 7 caused by a single nucleotide transition. The amount of SMN protein produced by *SMN2* is insufficient to promote the development and maintenance of neurons and other key tissues. Significant progress in SMA therapeutics has been achieved by designing molecules that increase the inclusion of exon 7 in the *SMN2* mRNA, thus achieving increased levels of SMN protein. We have successfully used this approach to identify orally bioavailable small molecules that selectively stabilize the machinery required to include exon 7 in the splicing process. This approach to increase SMN levels was proven successful in vivo, first in mouse models of SMA and then in humans. Increased SMN levels translated to increased survival time in mice with a severe SMA phenotype. Ongoing clinical trials in SMA patients evaluate the safety and effectiveness of compound mediated increases of SMN levels in humans.

MEDI 287

Spinal muscular atrophy: Advancing small molecule splicing modulators from phenotypic screen to the clinic

Brian Hurley, brian.hurley@novartis.com. Novartis, Cambridge, Massachusetts, United States

Spinal muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disorder, and is the most common lethal monogenic disease of infants and toddlers. SMA is caused by the loss of the survival motor neuron 1 (*SMN1*) gene. A compensatory gene called *SMN2* includes a single nucleotide mutation leading to a mis-spliced RNA

transcript and an unstable truncated SMN protein. Infant SMA patients suffer from degeneration of motor neurons, loss of peripheral and central motor control, and have a reduced life expectancy. Recently, much progress has been made towards disease modifying treatments for SMA. We describe our identification of the pyridazine scaffold from a high throughput screen, and the optimization work leading to the discovery of our clinical candidate LMI070. Additionally, we present the elucidation of its mechanism of action, correcting the splicing defect in the SMN2 gene through stabilization of the spliceosome/pre-mRNA complex. In mouse models, LMI070 increased expression of full length SMN protein in the brain of SMA mice, and extended overall survival. LMI070 is currently being evaluated for efficacy in infant SMA patients, and initial clinical results will be presented.

MEDI 288

Exon skipping therapy for Duchenne muscular dystrophy – it takes more than an antisense oligonucleotide

Annemieke Aartsma-Rus, a.m.rus@lumc.nl. Human Genetics, Leiden University Medical Center, Leiden, Netherlands

Duchenne muscular dystrophy is a severe, progressive muscle-wasting disease caused by the mutations that disrupt the reading frame of the dystrophin gene and abolishing production of functional dystrophin protein. Normally, dystrophin connects the cytoskeleton of muscle fibers to the extracellular matrix, thus providing stability during muscle contraction. Lacking dystrophin, muscle fibers of Duchenne patients are continuously damaged, leading to loss of muscle tissue and function. Interestingly, when mutations maintain the reading frame, internally deleted dystrophins can be produced that are partially functional. These dystrophins are associated with the less severe and less progressive Becker muscular dystrophy.

The aim of the antisense-mediated exon skipping therapy is to allow Duchenne patients to produce Becker-like dystrophins, hoping this will slow down disease progression. Antisense oligonucleotides (ASOs) are small chemically modified RNA or DNA analogs that can manipulate dystrophin pre-mRNA splicing by hiding a target exon from the splicing machinery. This restores the reading frame allowing the production of a partially functional dystrophin, as found in Becker muscular dystrophy patients.

Currently one exon skipping ASO has been approved for Duchenne therapy by the Food and Drug Administration. The presentation will outline the development of this approach through proof-of-concept studies in cell and animal models, preclinical optimization studies and clinical trials, but also discuss the lessons learnt by the field and the requirement for multilateral education of stakeholders (patients, regulators and academics) to develop tools to measure clinical efficacy of the approach.

MEDI 289

Small molecule utrophin modulators for the therapy of Duchenne muscular dystrophy (DMD)

Angela J. Russell^{1,2}, angela.russell@chem.ox.ac.uk, Aini Vuorinen¹, Nicky J. Willis¹, Daniel Conole¹, Maria Chatzopoulou¹, Enrico Emer¹, Isabel Wilkinson¹, Stephen G. Davies¹, Simon Guiraud³, Sarah E. Squire³, Arran Babbs³, Hannah Dugdale³, Ben Edwards³, Sarah Hemming³, Lee Moir³, Kelly Perkins³, Shawn Harriman⁴, Francis Wilson⁵, Graham M. Wynne¹, Jon M. Tinsley⁵, Kay E. Davies³. (1) Chemistry, University of Oxford, Oxford, United Kingdom (2) Pharmacology, University of Oxford, Oxford, United Kingdom (3) Physiology, Anatomy and Genetics, University of Oxford, Oxford, United Kingdom (4) Summit Therapeutics plc, Cambridge, Massachusetts, United States (5) summit plc, Abingdon, United Kingdom

Duchenne Muscular Dystrophy (DMD) is a devastating, X-linked muscle-wasting disease caused by lack of the cytoskeletal protein dystrophin. There is currently no cure for DMD, although various promising approaches (e.g. exon skipping, read through of stop codons, gene therapy) are being developed. By transcriptionally reprogramming the temporal and spatial expression of the dystrophin-related protein utrophin, we aim to develop a pharmacological therapy applicable to all DMD patients by targeting the primary defect and restoring sarcolemmal stability. In partnership with Summit Therapeutics, the 2-aryl benzoxazole utrophin modulator ezutromid (formerly SMT C1100), which demonstrates reduced dystrophic symptoms in the *mdx* mouse, has progressed to human clinical trials. As a potential First-In-Class molecule, ezutromid is currently being evaluated in an open label Phase 2 study in DMD patients. Interim twenty-four week data was made available in January 2018 which excitingly demonstrated a combination of reduced muscle fibre damage and increased levels of utrophin, providing the first evidence of ezutromid target engagement and proof of mechanism.

The successful clinical progression to date of ezutromid provides crucial proof-of-concept for the strategy which is being undertaken, and a comprehensive pipeline of future generation utrophin modulators is being developed. A series of Second Generation Utrophin Modulators which are structurally related to ezutromid, but with improved physicochemical and metabolism profiles have also been evaluated in the *mdx* mouse, and results were published. In parallel, novel utrophin modulator chemotypes have been discovered using an alternative *in vitro* dystrophin null myoblast screening assay where a reporter gene has been directly knocked into a utrophin exon. Multiple new structural classes which significantly increase utrophin expression in both murine and human DMD myoblasts have been identified and are now being optimised. Importantly, our data suggests that some of these small molecules modulate utrophin transcription through an alternative regulatory mechanism to ezutromid. These new compounds exhibit favourable solubility, stability, oral absorption and are well tolerated in the *mdx* mouse. This talk will provide an update on progress of our utrophin modulator drug pipeline, and studies directed towards identifying their mechanism of action.

MEDI 290

Design and synthesis of novel opioid peptidomimetics for potential treatment of cocaine addiction

Deanna Montgomery, *deanna.montgomery14@houghton.edu*, **Jessica P. Anand**, **Nicholas W. Griggs**, **John R. Traynor**, **Henry I. Mosberg**. *University of Michigan, Ann Arbor, Michigan, United States*

Drug misuse, abuse, and addiction are major health concerns, and cocaine is one of the most widely abused illegal drugs. Despite widespread understanding in the medical and research communities that addiction results in physiological changes in the brain, there is currently no FDA-approved pharmacological treatment for cocaine addiction, making this an important unmet medical need. The role of the opioid system in regulating the rewarding properties of drugs of abuse demonstrates potential for opioids to be used in the treatment of addiction. Specifically, it has been demonstrated that KOR (kappa opioid receptor) agonists have the potential to reduce cocaine self-administration in non-human primates. However, KOR activation is associated with negative side effects such as dysphoria which limit the clinical utility of these ligands. It has been suggested that partial MOR (mu opioid receptor) agonism may be able to mitigate dysphoria associated with KOR agonism, increasing the therapeutic potential of a KOR agonist. We report a series of novel MOR partial agonist/KOR agonist ligands based on the dimethyltyrosine-tetrahydroisoquinoline (DMT-Tiq) scaffold. Installation of a 7-benzyl pendant on the tetrahydroisoquinoline aromatic ring introduced strong KOR agonism. A series of small modifications led to the development of several structurally similar MOR partial agonist/KOR agonist compounds with slightly different pharmacological profiles.

MEDI 291

Total syntheses of highly oxidized bioactive natural products

Hang Chu, *hangchu@scripps.edu*. *The Scripps Research Institute, San Diego, California, United States*

Medicinally relevant natural products are found in a variety of therapeutic areas including oncology (Taxol™) and infectious diseases (artemisinin). Despite possessing intriguing biological properties, the widespread utilization of natural products as potential drug candidates is hampered by several development issues, namely low isolation yields and nonrenewable natural resources. The Baran Lab is interested in developing strategies to access useful quantities of densely oxidized natural products, exemplified by thapsigargin and tagetitoxin. The two-phase terpene synthesis logic enabled the successful total synthesis thapsigargin. Currently, a scalable route is under development to access tagetitoxin. Specifically, these routes were designed to bolster the feasibility pertaining to the scalable access of the parent natural products and the production of medicinally relevant analogues.

MEDI 292

Towards the development of an *in vivo* chemical probe for Polycomb chromodomains

Kelsey N. Lamb¹, kelseylamb@unc.edu, **Jacob I. Stuckey**¹, **Sarah N. Dishman**¹, **Jacqueline L. Norris-Drouin**¹, **Stephanie H. Cholensky**¹, **Oliver Bell**², **Sara Musetti**³, **Leaf Huang**³, **Cari A. Sagum**⁴, **Mark T. Bedford**⁴, **Lindsey I. James**⁵, **Stephen V. Frye**⁶. (1) Center for Integrative Chemical Biology and Drug Discovery, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States (2) IMBA- Institute of Molecular Biotechnology, Vienna, Austria (3) Division of Pharmacoengineering and Molecular Pharmaceutics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States (4) Department of Epigenetics and Molecular Carcinogenesis, University of Texas MD Anderson Cancer Center, Smithville, Texas, United States (5) Center for Integrative Chemical Biology and Drug Discovery, UNC Chapel Hill, Chapel Hill, North Carolina, United States (6) Center for Integrative Chemical Biology and Drug Discovery, Division of Chemical Biology and Medicinal Chemistry, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States

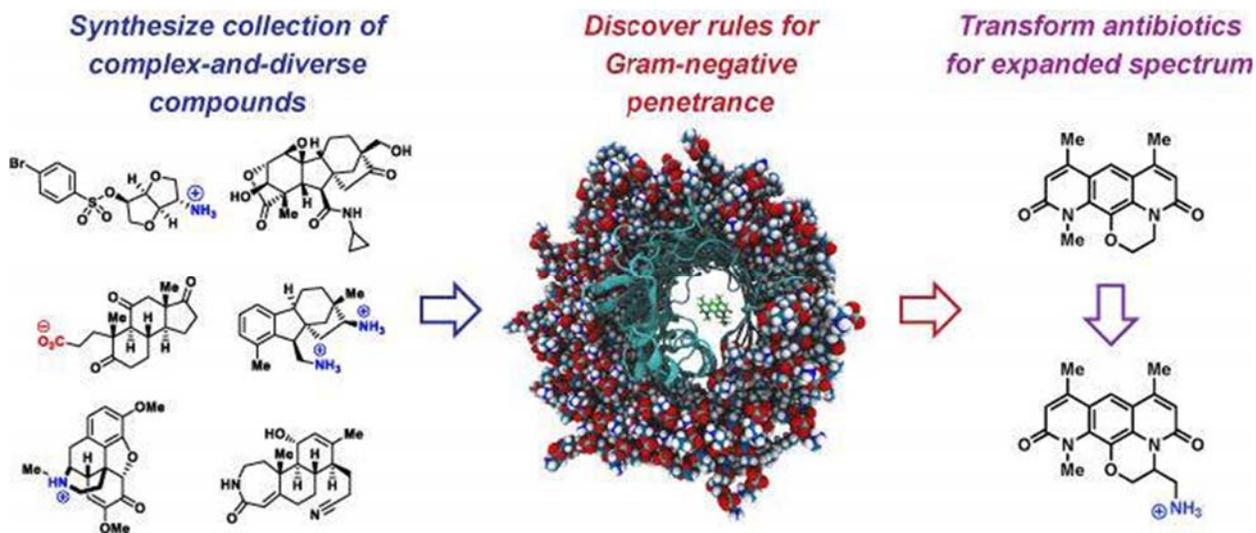
The installation, interpretation, and removal of histone post-translational modifications (PTMs) by distinct classes of proteins represents a crucial mode of chromatin regulation. Lysine methylation (Kme) is one of the most abundant and better studied chromatin modifications, and depending upon its location and degree of methylation, can be implicated in both active and repressed chromatin states. Proteins that interpret this mark are therefore crucial signaling nodes, as they often participate in and recruit multi-subunit protein complexes that elicit varying effects on chromatin structure. Polycomb Repressive Complex 1 (PRC1) is one such complex whose Kme reader function is reliant on the chromodomain of a Chromobox (CBX) subunit (CBX2, -4, -6, -7, and -8). Polycomb-mediated transcriptional repression is essential for establishing and maintaining cellular identity, and deregulation of Polycomb signaling is implicated in many cancers. The development of a peptidomimetic chemical probe for Polycomb chromodomains, UNC3866, is capable of disrupting the surface groove binding mode of the chromodomain, and confirmed that peptide-like ligands are a potent and selective way to target this family of Kme readers. However, UNC3866 displays suboptimal cellular efficacy which has precluded its use as an *in vivo* probe. Here we report our second-generation inhibitor, UNC4976, which was initially found to display much improved efficacy over UNC3866 in a reporter cell line. Additionally, pulldown studies indicate that UNC4976 interacts with intact PRC1 in cell lysates, and chromatin immunoprecipitation (ChIP) experiments demonstrate displacement of CBX7 from chromatin at known sites of PRC1 occupancy. Current efforts are directed towards employing a nanoparticle-based delivery system to increase cellular and *in vivo* activity of UNC4976. We will utilize nanoparticle-formulated compound in a mouse xenograft model to assess the ability of UNC4976 to inhibit tumor growth of an ovarian clear cell adenocarcinoma line that is dependent on CBX7 for progression.

MEDI 293

Development of predictive guidelines for small-molecule accumulation in Gram-negative bacteria

Michelle Richter, michelle.richter12@gmail.com. Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois, United States

The rise in multidrug-resistant bacteria is a major public health concern. In 2017, the WHO published a list of “priority pathogens” that pose the greatest threat to human health. The three pathogens for which new antibiotic development is most critical are all Gram-negative species. Central to the problem of Gram-negative antibiotic discovery is a limited understanding of the physicochemical properties that enable small-molecule accumulation in these species. To address this limitation, we developed predictive guidelines for compound accumulation in *Escherichia coli*. Since the majority of antibacterial drugs are natural products or their derivatives, access to compounds that both possess natural-product-like properties and are easily synthesized is critical to enabling structure-activity relationship studies. We utilized the Complexity-to-Diversity (CtD) method, where we took complex natural products and distorted the ring structures in ≤ 5 synthetic steps, facilitating the rapid synthesis of natural-product-like diverse small molecules. We tested the ability of >180 CtD compounds to accumulate in *E. coli*. Based on this assessment, we developed “eNTRy rules” that state that compounds are most likely to accumulate if they contain a non-sterically encumbered ionizable Nitrogen (primary amines are favored), have low Three-dimensionality, and are relatively Rigid. We applied these guidelines to convert a natural product with Gram-positive antibiotic activity into an antibiotic with activity against Gram-negative pathogens. We anticipate that these findings will aid in the development of antibiotics against Gram-negative bacteria.



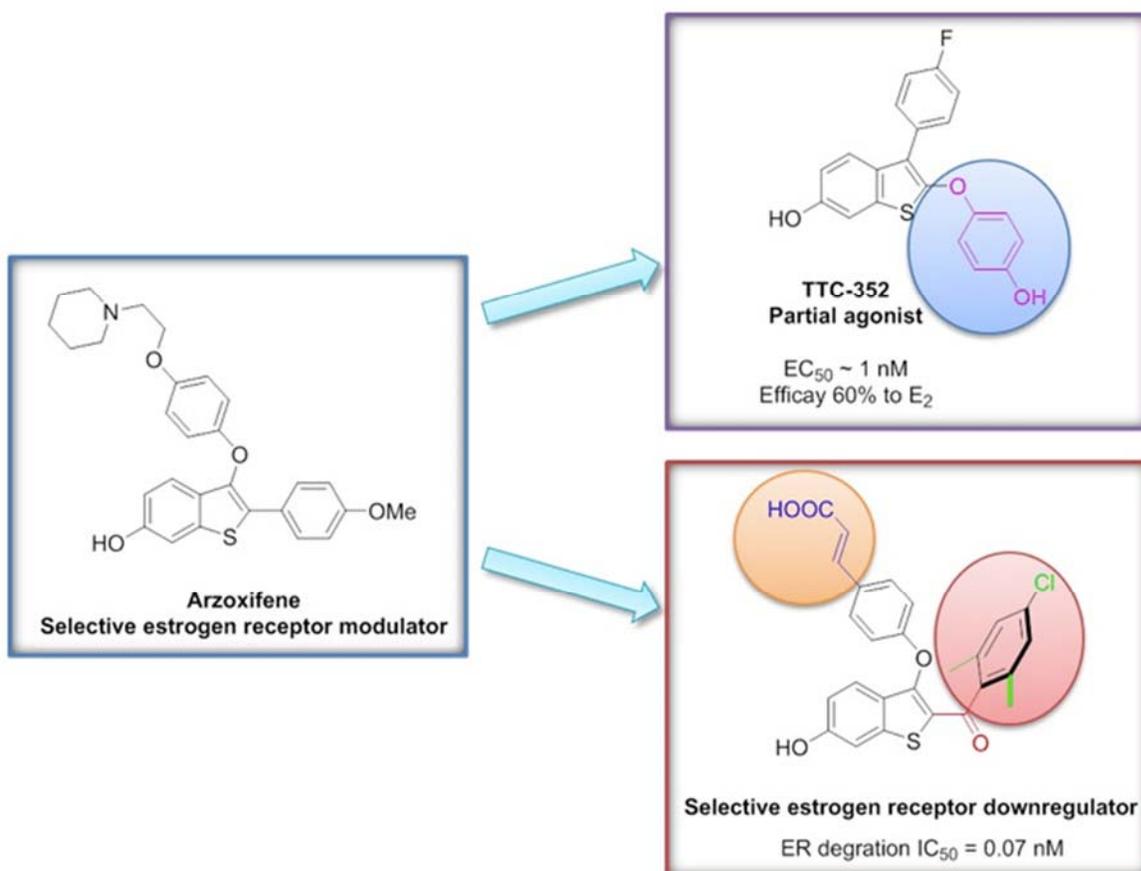
MEDI 294

Novel strategies for treating estrogen receptor positive metastatic breast cancer

Rui Xiong¹, rxiong3@uic.edu, **Jiong Zhao**¹, **Lauren Gutgesell**¹, **Yangfeng Li**¹, **Yunlong Lu**¹, **Carlo Rosales**¹, **Huiping Zhao**², **Debra Tonetti**², **Gregory R. Thatcher**¹. (1) Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy,

University of Illinois at Chicago, Chicago, Illinois, United States (2) Department of Biopharmaceutical Sciences, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois, United States

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer-related death for women in the United States. Up to 70% of breast cancers are estrogen receptor alpha positive (ER α +), wherein deregulated estrogen signaling fuels tumor growth. Antiestrogen therapy such as SERMs (selective estrogen receptor modulators) that block the binding of estradiol (E2) to ER or aromatase inhibitors (AIs) that inhibit estrogen biosynthesis is the first-line therapy for ER+ breast cancers. However, de novo or acquired resistance occurs in 30-50% of all treated patients. We have developed two alternative therapeutic approaches to treatment-resistant breast cancer: 1) design and development of selective human estrogen receptor partial agonists (ShERPAs) that recapitulate the clinical efficacy of estradiol while minimizing serious side effects from full ER activation in gynecological tissues; and 2) design and development of next generation orally-bioavailable selective estrogen receptor downregulators (SERDs), able to ablate ER and block survival of both endocrine-dependent and treatment-resistant ER+ tumors. These two projects have yielded investigational new drugs for metastatic ER+ breast cancer.



MEDI 295

Structure and physicochemical property guided design of small molecule kinase inhibitors and further opportunities

Timothy P. Heffron, theffron@gene.com. MS 232A, Genentech, South San Francisco, California, United States

This presentation will describe the structure and physicochemical property guided design of multiple clinical inhibitors of the PI3K pathway. Considerations for the potential of kinase inhibitors in the treatment of CNS cancers will also be discussed.

MEDI 296

In recognition of those who deserve the Philip S. Portoghese lectureship award but did not receive it

Mark Cushman, cushman@purdue.edu. Department of Medicinal Chemistry and Molecular Pharmacology, and the Purdue Center for Cancer Research, Purdue University, West Lafayette, Indiana, United States

This presentation will highlight the contributions of just a few of the many collaborators, former students, and mentors whose efforts are responsible for the accomplishments of our research group in the areas of organic chemistry, natural products chemistry, chemical biology, molecular biology, and medicinal chemistry. The topics to be discussed may include, but are not necessarily limited to: 1) The Castagnoli-Cushman reaction of Schiff bases with cyclic dicarboxylic acid anhydrides as an approach to the efficient synthesis of natural products, including benzophenanthridine, protoberberine, and 3-arylisquinoline alkaloids, as well as the indenoisoquinoline topoisomerase I poisons indotecan (LMP400), indimitecan (LMP776), and LMP744 that have been in phase I clinical trials in cancer patients at the National Cancer Institute. 2) An update on the clinical status of these three anticancer agents that have been under investigation for chemotherapy in adults with metastatic solid tumors and lymphomas that have relapsed after administration of the usual standard treatments. 3) The application of ab initio quantum mechanics calculations performed at the MP2/6-31G(d) level of theory in medicinal chemistry, especially in the prediction of the DNA binding site specificities and DNA binding site orientations of topoisomerase I poisons. 4) The synthesis of dual and triple inhibitors of topoisomerase I, tyrosyl-DNA phosphodiesterase I, and tyrosyl-DNA phosphodiesterase II as an approach to creating a drug that damages DNA in cancer cells and also inhibits the two phosphodiesterases that repair that damage. 5) The application of sequential palladium catalysis for the discovery of selective Janus kinase inhibitors that offer the prospect of strategically modifying cytokine responses. 6) The construction of aromatase inhibitors that also have selective estrogen receptor modulatory activity as an approach to limiting the unpleasant and damaging side effects of aromatase inhibitors during breast cancer chemotherapy. 7) The design and synthesis of fluorinated substrate and transition state analogues for use as ¹⁹F NMR

mechanistic probes of lumazine synthase and riboflavin synthase, which catalyze the last two steps in the biosynthesis of riboflavin and are rational targets for antimicrobial drug design.

MEDI 297

NCI Chemical Biology Consortium

Barbara Mroczkowski, *mroczkowskib@nih.gov*. National Cancer Institute, Bethesda, Maryland, United States

The National Cancer Institute is working on multiple fronts to discover novel effective therapies for cancer. The Chemical Biology Consortium (CBC) represents a collaborative network of academic, non-profit and private enterprises with a broad range of capabilities to support early stage drug discovery. This platform provides academic researchers and clinicians with preclinical drug discovery expertise and resources to bring new cancer drugs to the clinic. An overview of the CBC will be presented highlighting scientific accomplishments of selected partnerships, focusing on small-molecule based interventions directed at targets that represent specific investigator research interests and CBC center competencies.

MEDI 298

Design and characterization of a chemical fragment library of mercaptophiles

Peter Wipf¹, *pwipf@pitt.edu*, **Taber Maskrey**¹, **Michelle Arkin**², **Donna M. Huryn**³. (1) Univ of Pittsburgh, Pittsburgh, Pennsylvania, United States (2) Pharmaceutical Chemistry, University of California, San Francisco, San Francisco, California, United States (3) University of Pittsburgh, Allentown, New Jersey, United States

Covalent modification of protein targets by reactive yet selective functional group arrays in small organic molecules has evolved from an undesirable property into a rational medicinal chemistry strategy for the development “enzyme knock-out” chemical probes and clinical candidates. Several kinase and proteasome inhibitors with this mode of action have recently been approved by the FDA. This development is inspiring the generation of targeted chemical libraries containing warhead functions, in particular for proteins containing essential cysteine residues. We have previously identified several functional groups, including enones and epoxyketones, that demonstrate a moderate level of reactivity toward thiols, and we have now developed a fragment library of mercaptophiles useful for screening cysteine-containing targets. For the latter, warheads were selected based on our previous work and literature validation for cysteine protease inhibition, and compounds were refined by molecular weight and chemical diversity filters. We used an HPLC assay to probe the reactivity of selected compounds versus model nucleophiles. The library was then assayed in a MS-based tethering screen to identify compounds that selectively alkylated Cys-74 of ATG4b, a

protease involved in multiple steps in the autophagy process, and therefore a potential target for anti-cancer agents.

MEDI 299

Discovery and structure-based optimization of potent, covalent inhibitors of Taspase1

Jeff Neitz¹, jeffrey.neitz@ucsf.edu, **Michelle Arkin**¹, **Alex G. Waterson**², **Lidia Sambucetti**³. (1) *Pharmaceutical Chemistry, University of California, San Francisco, San Francisco, California, United States* (2) *Vanderbilt University, Nashville, Tennessee, United States* (3) *SRI, Palo Alto, California, United States*

Taspase1 is a threonine protease responsible for cleavage of MLL and epigenetic activation of Hox signaling and CyclinE. Knock-down of Taspase1 in a xenograft mouse model of HER-2 driven breast cancer has shown significant delay in tumor genesis. A potent inhibitor of Taspase1 would open a new avenue to selectively treat HER-2 driven breast cancer. This presentation will highlight the collaborative efforts of the CBC team formed around this therapeutic hypothesis to identify small molecule inhibitors of Taspase1. Hits derived from both traditional high-throughput screening and a covalent screen of a proprietary disulfide library will be discussed.

MEDI 300

Discovery, optimization and characterization of allosteric inhibitors of the AAA ATPase p97, an emerging cancer target

Donna M. Huryn¹, huryn@sas.upenn.edu, **Michelle Arkin**², michelle.arkin@ucsf.edu. (1) *University of Pittsburgh, Pittsburgh, Pennsylvania, United States* (2) *UCSF, San Francisco, California, United States*

Through the National Cancer Institute's (NCI's) Chemical Biology Consortium, a team of scientists representing multiple institutions have discovered and developed novel allosteric inhibitors of the AAA ATPase p97 (VCP), an exciting, emerging target in cancer. p97 is a master regulator of protein homeostasis and modulates ubiquitin-dependent degradation as well as membrane fusion activities throughout the cell. These events are directed by a network of protein-protein interactions and ATPase-dependent changes in p97 conformation. The team has designed and optimized allosteric inhibitors that inhibit p97 with biochemical IC₅₀'s in the range of 10-200nM and sub-micromolar cell based activity. We solved the first high-resolution structures of p97 bound to an inhibitor using cryo-electron microscopy, and have developed a binding model of these allosteric inhibitors. By comparing inhibitors of p97 that act through different mechanisms, we aim to develop new experimental therapeutics and can also use these molecules to decipher the complex biological pathways regulated by p97 activity.

MEDI 301

Discovery of novel tricyclic Mcl-1 inhibitors that exhibit selective anti-proliferative activity and *in vivo* efficacy

Taekyu Lee¹, taekyu.lee@vanderbilt.edu, James C. Tarr¹, Bin Zhao¹, Zhiguo Bian¹, Subrata Shaw¹, Johannes Belmar¹, Allison Arnold¹, John L. Sensintaffar¹, William J. Moore², Gordon M. Stott², Melinda Hollingshead², Apurva Srivastava², Craig J. Thomas³, Myrtle M. Davis², Olivia W. Rossanese¹, Edward T. Olejniczak¹, Stephen W. Fesik¹. (1) Biochemistry, Vanderbilt University, Nashville, Tennessee, United States (2) NIH, Washington DC, District of Columbia, United States (3) NIH Chemical Genomics Center, Rockville, Maryland, United States

Myeloid cell leukemia-1 (Mcl-1) is a member of the Bcl-2 family of proteins that regulates apoptosis. Amplification of Mcl-1 is found in various cancers, which causes the evasion of apoptosis and is one of the major resistance mechanisms for many chemotherapies. Targeting Mcl-1 with small molecules is very challenging because Mcl-1 mediates its effects through high affinity interactions with pro-apoptotic BH3 containing proteins, Bak and Bax. Using fragment-based methods and structure-based design, we discovered a novel class of potent Mcl-1 inhibitors. New leads containing a tricyclic indole lactam scaffold exhibit Mcl-1 $K_i < 0.5$ nM with >1000-fold selectivity over Bcl-xL and Bcl-2. They promote apoptosis only in Mcl-1 sensitive cancer cell lines by activating caspases in a dose-dependent manner and exhibit robust efficacy in mice disease models without severe adverse effects. These results provide a strong proof of concept for a selective inhibition of Mcl-1 function as an effective anti-cancer therapy.

MEDI 302

Discovery and characterization of cell active inhibitors of lactate dehydrogenase (LDH) using structure-based design

Alex G. Waterson¹, alex.g.waterson@vanderbilt.edu, **Matthew D. Hall**⁴, hallma@mail.nih.gov, Ganesha Rai⁴, Kyle Brimacombe⁴, Bryan Mott⁴, Daniel J. Urban⁴, Kwangho Kim², Plamen P. Christov³, Alexander P. Lamers³, Ian M. Romaine³, Somnath Jana³, Xin Hu⁴, Shyh-Ming Yang⁴, Tobie D. Lee⁴, Dorian Cheff⁴, Jennifer Kouznetsova⁴, Gloria A. Benavides⁵, Katie Pohida⁴, Eric J. Kuenstner⁴, Diane K. Luci⁴, Christine M. Lucaks⁶, Douglas R. Davies⁶, David Dranow⁶, Hu Zhu⁴, Gary A. Sulikowski², William J. Moore⁷, Gordon M. Stott⁷, Andrew J. Flint⁷, Victor M. Darley-Usmar⁵, Jeffery P. Norenberg⁸, Larry A. Sklar⁸, Leonard M. Neckers⁹, Chi V. Dang¹⁰, Anton Simeonov⁴, Ajit Jadhav⁴, David J. Maloney⁴. (1) Pharmacology, Vanderbilt University, Nashville, Tennessee, United States (2) Chemistry, Vanderbilt University, Nashville, Tennessee, United States (3) Chemical Synthesis Core, Vanderbilt University, Nashville, Tennessee, United States (4) NCATS/NIH, Rockville, Maryland, United States (5) University of Alabama at Birmingham, Birmingham, Alabama, United States (6) Beryllium Discovery Corporation, Bainbridge Island, Washington, United States (7) Leidos Biomedical Research, Fredrick, Maryland, United States (8) University of New

Mexico, Albuquerque, New Mexico, United States (9) National Cancer Institute, Bethesda, Maryland, United States (10) Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania, United States

Lactate Dehydrogenase (LDH) is an enzyme that catalyzes conversion of pyruvate to lactate. The LDH-A gene is upregulated in many cancers, supporting the high glycolytic activity observed in many tumor cells (the Warburg effect). We report the discovery, medicinal chemistry optimization, and biochemical and cellular characterization of a novel series of pyrazole-based inhibitors of human LDH. Utilization of a quantitative high-throughput screening paradigm facilitated hit identification, while structure-based design and multi-parameter optimization enabled the discovery of compounds with potent enzymatic and cell-based inhibition of LDH. Lead compounds exhibit low nM inhibition of LDH, sub-micromolar inhibition of cellular lactate production, and inhibition of glycolysis in multiple cancer cell lines in vitro. Key features leading to cell-based activity included drug-target residence time, measured by kinetic analysis of target binding by SPR, as well as potent target engagement assessed using the cellular thermal shift assay (CETSA). Optimized analogs were found to be metabolically stable in multiple species, producing high plasma and tissue concentrations from multiple dosing regimens, thus enabling the initiation of in vivo pharmacodynamic and efficacy testing.

MEDI 303

MRX-2843, a dual MERTK/FLT3 inhibitor enabled by the NCI Chemical Biology Consortium (CBC) entering Phase 1 clinical trials

*Xiaodong Wang¹, Deborah DeRyckere³, Dmitri Kireev¹, Doug Graham³, H. Shelton Earp², **Stephen V. Frye^{1,2}**, svfrye@email.unc.edu. (1) Center for Integrative Chemical Biology and Drug Discovery, Division of Chemical Biology and Medicinal Chemistry, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States (2) Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina, United States (3) Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, and Department of Pediatrics, Emory University, Atlanta, Georgia, United States*

MERTK belongs to the TYRO3, AXL, and MERTK (TAM) family of receptor tyrosine kinases. Abnormal or ectopic expression of MERTK is observed in many human cancers, including acute lymphoblastic leukemia, acute myeloid leukemia (AML), non-small cell lung cancer, colorectal cancer, prostate cancer, melanoma, and glioblastoma. In this setting MERTK increases cancer cell survival and metastasis, promoting tumorigenesis and chemoresistance. In addition, MERTK's physiologic role in myeloid cells is that of an innate immune checkpoint gene guarding against auto-immunity, a function subverted in tumors to induce an immunosuppressive microenvironment. MERTK kinase inhibition could therefore have a dual anti-cancer role blocking tumor cell survival and chemoresistance and reversing the immunosuppressive phenotype of tumor macrophages and myeloid derived suppressor cells. With NCI CBC NeXT

support, we completed lead optimization of a hit series of potent orally bioavailable MERTK kinase inhibitors discovered through structure-based drug design. The lead compound, MRX-2843, is a picomolar, inhibitor of MERTK with excellent solubility and preclinical pharmacokinetic properties. In addition to the dual potential of targeting of MERTK (tumor cell intrinsic and immunosuppressive microenvironment), MRX-2843 potently inhibits FLT3, including the activated FLT3 mutant proteins with internal tandem duplications (ITD) present in 30% of human adult AMLs, providing a rationale for use in both solid tumors and AML. Phase 1 clinical studies in solid tumor patients have been initiated and subsequent studies are planned in patients with leukemia. The discovery of MRX-2843 as well as lessons learned during the CBC sponsored portion of this project will be described.

MEDI 304

Structure-based drug discovery of G protein-coupled purine receptor ligands

Kenneth A. Jacobson, kennethj@niddk.nih.gov. *Lab of Bioorganic Chemistry, NIDDK, National Institutes of Health, Bethesda, Maryland, United States*

We discover and characterize new receptor ligands to modulate purinergic signaling using chemical, pharmacological, and structural approaches. Purine receptors encompass four G protein-coupled receptors (GPCRs) for adenosine, eight GPCRs activated by nucleotides (P2YRs), and seven ATP-gated P2X ion channels. High-resolution X-ray structures of the adenosine receptors (ARs) and P2YRs, determined through our collaboration with Ray Stevens and colleagues, facilitate the rational design of ligands, either by modification of known agonists and antagonists or by virtual screening (with Jens Carlsson et al.) to discover novel chemotypes. An extrahelical, allosteric P2Y₁R antagonist, diaryl-urea BPTU, displayed both surmountable and insurmountable antagonism. The P2Y₁R interactions of allosteric and orthosteric ligands were predicted using docking and molecular dynamics. We introduced new bitopic A_{2A}AR antagonists and bitopic agonists of the P2Y₆R, which is a potential drug target for inflammation, diabetes and neurodegeneration. Chemical tools for the inflammation-related P2Y₁₄R, such as fluorescent probes, were designed with the aid of molecular modeling based on P2Y₁₂R structures and applied to discovery of novel heterocyclic antagonists. We introduced sterically constrained rings to mimic native ribose in nucleosides and nucleotides, to determine their preferred conformation when bound to P2Y₁R, P2Y₆R or A₃AR. Several of our A₃AR agonists have advanced in clinic trials for treatment of inflammatory diseases and cancer, and other conformationally-locked agonists are being considered for chronic neuropathic pain (collaboration with Daniela Salvemini et al.). A₃AR agonists were designed and screened using an in vivo phenotypic pain model, which reflected both pharmacokinetic and pharmacodynamic parameters. High specificity (>10,000 fold selective) was achieved with the aid of receptor models based on related GPCR structures. A₃AR activation in vivo reduced chronic pain at sites on peripheral neurons, spinal cord, and brain. Thus, purine receptor structures have enabled novel ligand discovery, the elucidation of their biological role and the conceptualization of future therapeutics.

MEDI 305

Application of MD-simulations in GPCR drug design – exemplified by case studies

Christofer Tautermann, *christofer.tautermann@boehringer-ingelheim.com. Medicinal Chemistry, Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany*

Recent years have seen a tremendous progress in the elucidation of experimental structural information for G-protein coupled receptors (GPCRs). Although for the majority of pharmaceutically relevant GPCRs structural information is still accessible only by homology models, the steadily increasing amount of structural information enables the application of structure-based drug design tools for this important class of drug targets. We focus here on the application of molecular dynamics (MD) simulations in GPCR drug discovery programs. Typical application scenarios of MD simulations and their scope and limitations will be described on the basis of selected case studies. First we apply MD to elucidate the SAR and binding modes of CCR3 antagonists, and then we show that binding of orthosteric antagonist to the allosteric site of the M3 receptor already leads to measurable inhibition. Finally, the use of metadynamics for identifying binding sites of allosteric modulators on the CB1 receptor is demonstrated.

MEDI 306

Navigating structural GPCR-ligand interaction space for crafted computer-aided drug design

Chris de Graaf¹, *c.de.graaf@vu.nl*, **Benjamin G. Tehan**¹, **Francesca DeFlorian**¹, **Juan Carlos Mobarec**¹, **Conor C. Scully**¹, **Robert T. Smith**¹, **Giovanni Bottegoni**¹, **Jonathan S. Mason**¹, **Miles Congreve**². (1) *Heptares Therapeutics, Welwyn Garden City, United Kingdom* (2) *Chemistry Department, Heptares Therapeutics Ltd, Welwyn Garden City, United Kingdom*

Novel crystal structures of GPCR-ligand complexes solved at Heptares and elsewhere continue to reveal a diversity of potential ligand binding sites, such as new allosteric binding sites for Class A and Class B GPCRs. This presentation will show how the breakthroughs in GPCR structural biology can be complemented by computational and experimental studies for a more accurate description and prediction of molecular and structural determinants of ligand-receptor binding affinity, kinetics, potency, and selectivity. Integrated cheminformatics workflows will be described that combine structural, pharmacological, and chemical data to explore receptor-ligand interaction space and steer structure-based virtual ligand screening. Orthogonal physics-based (Molecular Dynamics, e.g. Free Energy Perturbation FEP+, WaterMap from Schrödinger) and empirical (e.g. GRID and WaterFLAP from Molecular Discovery) structure-based drug design methods will be presented to target lipophilic hotspots, water networks, and cryptic ligand binding pockets for a variety of GPCR subfamilies.

MEDI 307

Orthosteric and allosteric antagonism of chemokine receptors: Structural insights into compound affinity and selectivity

Kirti K. Chahal¹, Genevieve E. Baker¹, Yi Zheng¹, Andrew Tebben², Tracy M. Handel¹, Irina Kufareva¹, kufareva@gmail.com. (1) Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, San Diego, California, United States (2) Bristol-Myers Squibb, Lawrenceville, New Jersey, United States

The G protein coupled chemokine receptors direct cell migration in development, immunity, and cancer. Two receptors, CCR5 and CXCR4, are also known for their role in HIV infection where they serve as co-receptors for viral entry into host immune cells. Evolved to interact with protein ligands, chemokine receptors typically feature widely open, polar orthosteric binding sites that are challenging targets for small molecule antagonists. Despite decades of efforts, only two small molecules have made it to the clinic thus far: the CCR5 antagonist Maraviroc and the CXCR4 antagonist Plerixafor, for HIV and stem cell mobilization, respectively. CCR2, the receptor that has been actively pursued for autoimmunity and, more recently, for immuno-oncology, has not yielded any clinical candidates thus far. Clinical failures have been attributed to lack of efficacy caused by suboptimal properties of the compounds: poor metabolic stability, high protein binding, inadequate receptor selectivity, or insufficient residence time. Understanding the structural basis of antagonist action at chemokine receptors provides a novel, rational path towards optimization of these properties and, ultimately, development of better clinical candidates.

We were recently successful in determining a crystal structure of CCR2 simultaneously complexed with an orthosteric and allosteric antagonist, and another group crystallized an allosterically inhibited CCR9. The structures revealed the existence of a common druggable site and a novel way of chemokine receptor inhibition: via compound binding at the intracellular cavity. Here we use the CCR2 structure as a launch pad for the development of predictive models of CCR2 complexes with diverse chemotypes of molecules targeting both binding sites. Flexible docking of a wide variety of orthosterics revealed the critical affinity determinants, suggested two distinct structural mechanisms allowing for selectivity over the closely related CCR5, and provided explanation for slow dissociation kinetics, a highly desirable property in anti-CCR2 drug development. Conformational optimization with flexible molecular docking also enabled generation of chemotype-specific models for allosteric antagonists. For both orthosteric and allosteric pocket models, retrospective virtual screening demonstrated high predictive accuracy. Insights into selective and dual targeting of chemokine receptors via allosteric binding site were also obtained.

MEDI 308

Opportunities for advanced computational modeling in GPCR drug discovery

Andrea Bortolato, *andrea.bortolato@schrodinger.com*, Kai Zhu, Kenneth W. Borrelli, Thijs Beuming, Ishita Aloni, Robert Abel. Schrodinger, New York, New York, United States

Approximately 35% of approved drugs act on G protein-coupled receptor (GPCR) targets, which are a large class of membrane-bound signaling receptors with diverse and crucial roles across multiple disease areas. In the last 10 years, GPCR drug discovery has been transformed by great advances in structural biology. Both X-ray and Cryo-EM structures are now available for a diverse set of GPCRs of high pharmaceutical interest. Structure-based drug design for these challenging systems provides various opportunities for advanced computational modeling to significantly improve the efficiency of preclinical drug discovery. Example illustrative applications, including Free Energy Perturbation using FEP+ for ligand potency and selectivity predictions, will be presented to support this view.

MEDI 309

Identifying inter-helical interactions involved in GPCR structure-function and the forces that determine ligand residence time

Alexander Heifetz^{1,2}, *alexander.heifetz@evotec.com*, Andrew Potterton^{2,1}, Inaki Morao¹, Tim James¹, Michelle Southey¹, Dmitri G. Fedorov³, Mike Bodkin¹, Andrea Townsend-Nicholson². (1) Evotec (UK) Ltd, Abingdon, United Kingdom (2) Structural and Molecular Biology, University College London, London, United Kingdom (3) CD-FMat, National Institute of Advanced Industrial Science and Technology (AIST), Ibaraki, Japan

GPCRs comprise the single largest class of proteins against which therapeutic compounds in clinical use have been developed. However, these drugs only target approximately 50 of the 800 GPCRs in the human genome. Expansion of the range of GPCR targets available for the generation of effective therapeutics would provide an enhanced approach to the treatment of cardiovascular, neurological, endocrine and many other disorders.

Today, the key questions in GPCR drug discovery are: 1) What are the structural features responsible for 'gluing' together the seven helices of the GPCR bundle and how do these affect ligand binding, receptor flexibility and activation? 2) What are the forces that most affect the time that small molecules remain bound (residence time, RT) to the target receptor? RT is considered to be one of the most critical properties for the therapeutic efficiency of a drug.

Evotec (UK) Ltd and University College London (UCL) joined forces in the framework of CompBioMed, with the support of the BBSRC, to address these key questions. We integrated a suite of computational and experimental tools designed to address the issues related to GPCR structure and function. We use steered molecular dynamics (SMD) to calculate the forces that affect the residence time of various adenosine

receptor ligands. We have also applied the Fragment Molecular Orbital (FMO) quantum mechanical method for the analysis of 33 GPCR crystal structures to identify the inter-helical tertiary interaction network. FMO offers a considerable computational speed-up over traditional QM methods, especially when combined with DFTB, allowing us to apply our method to the structure of an entire GPCR. This primary analysis revealed a consensus network of >30 inter-TM interactions mediated by 50 topologically equivalent amino acids, providing a proof of concept that a conserved inter-helical interaction network exists and affects GPCR structure-function.

MEDI 310

Lead repurposing for neglected tropical diseases: Strategies for optimization of ADME properties of kinase inhibitor chemotypes

Lori Ferrins¹, *l.ferrins@northeastern.edu*, **Amrita Sharma**², **Kelly A. Bachovchin**¹, **Seema Bag**¹, **Lisbeth Silva**¹, **Dana Klug**¹, **Naimee Mehta**¹, **Jennifer Woodring**¹, **William G. Devine**¹, **Justin Wiedman**², **Kojo Mensa-Wilmot**², **Michael P. Pollastri**¹. (1) *Chemistry and Chemical Biology, Northeastern University, Boston, Massachusetts, United States* (2) *Department of Cellular Biology, University of Georgia, Athens, Georgia, United States*

Lead repurposing for neglected tropical diseases involves identification of approved drugs or clinical candidates as inhibitors of parasite proliferation, and their subsequent fine-tuning to be effective at killing parasitic protozoans. It is a proven method for identifying new anti-parasitic lead compounds, potentially resulting in a shorter overall timeline for drug discovery. Lapatinib is an inhibitor of human EGFR that is currently approved for the treatment of breast cancer and other solid tumors. We reported a series of lapatinib-derived analogs with potent activity against *Trypanosoma brucei* (etiological agent of human African trypanosomiasis), *Trypanosoma cruzi* (causes Chagas disease), *Plasmodium falciparum* (causes malaria) and *Leishmania major* amastigotes (causes leishmaniasis). At the hit-to-lead optimization stage, we produced highly potent compounds that, unfortunately, did not appear worthy of advancing into *in vivo* efficacy models due to (i) poor aqueous solubility, (ii) high plasma protein binding, and (iii) high metabolic clearance. By employing a variety of strategies, we have successfully modulated these properties to arrive at a lead candidate that is more 'drug-like' and orally bioavailable with potent activity against *T. brucei* both *in vitro* and in an *in vivo* mouse model of acute human African trypanosomiasis infection.

MEDI 311

Design of a potent and selective GPR40 agoPAM with low projected human dose

Duane DeMong¹, *ddemong@gmail.com*, **Zhiyong Hu**², **Michael W. Miller**¹, **Robert Orr**², **Adam Weinglass**², **George Eiermann**², **Kaushik Mitra**³, **Juliann Ehrhart**², **Christopher Plummer**², **Helen Chen**², **Harry R. Chobanian**⁴, **Angie R. Angeles**², **Matthew Maddess**⁴,

Eric Ashley⁵, Jerry DiSalvo⁴, Brande Thomas-Fowlkes⁴, Sarah Souza⁴, Boonlert Cheewatrakoolpong⁴, Maria Trujillo⁴, Judith Gorski⁴, Michele Pachanski⁴, Daniel Kosinski⁴, Melissa Kirkland⁴, Joel Mane⁴, Jim Baldassari⁴, Daphne Szeto⁴, Jiyun Xue⁴, Gail Forrest⁴, Koppara Samuel⁴, Richard Tschirret-Guth⁶, Dan Tatosian⁴, Qing Chen⁴, Michael Hafey⁴, Robert Houle⁴, Ann Thomas⁴, Jackie Shang⁴, Tony Pereira⁷, Andrew Howard⁸, Steven L. Colletti⁹. (1) Discovery Chemistry, Merck & Co. Inc., Hanover, Massachusetts, United States (2) Merck, Livingston, New Jersey, United States (3) K15-MW108, Merck and Co., Inc., West Point, Pennsylvania, United States (4) Merck & Co. Inc., Kenilworth, New Jersey, United States (5) Merck & Co. Inc., Rahway, New Jersey, United States (9) Merck Co Inc, Princeton Jct, New Jersey, United States

GPR40 (FFAR1) is a Class A GPCR that is highly expressed in pancreatic b-cells. Exposure to medium and long chain fatty acids, the receptor's natural ligands, enhances glucose-dependent insulin secretion. Partial agonists of GPR40, have been shown to lower plasma glucose levels and improve HbA1c in human clinical trials, with a hypoglycemia incidence similar to that of placebo. More recently, GPR40 full agoPAMs, compounds that are both full agonists and positive allosteric modulators of the native ligands, have been shown in preclinical rat models to decrease plasma glucose to a greater extent than partial agonists. These effects are likely due to a combination of increased pancreatic insulin secretion relative to partial agonists and secretion of GLP-1 in the gut, a phenomenon not observed with partial agonists. We have previously disclosed the discovery of a series of potent biaryl chroman GPR40 agoPAMs. A lead optimization effort was initiated which resulted in the development of compounds with excellent potency and selectivity and a low human dose projection. A select compound from this series was further profiled and this presentation will describe in vivo efficacy studies including a wild type and GPR40 knock out mouse ipGTT to assess on target efficacy and a Goto-Kakizaki rat PK/PD study to evaluate effects on glucose, insulin and incretin levels. Projection of a low human dose based on translation from in vitro potency and in vivo efficacy results will also be discussed.

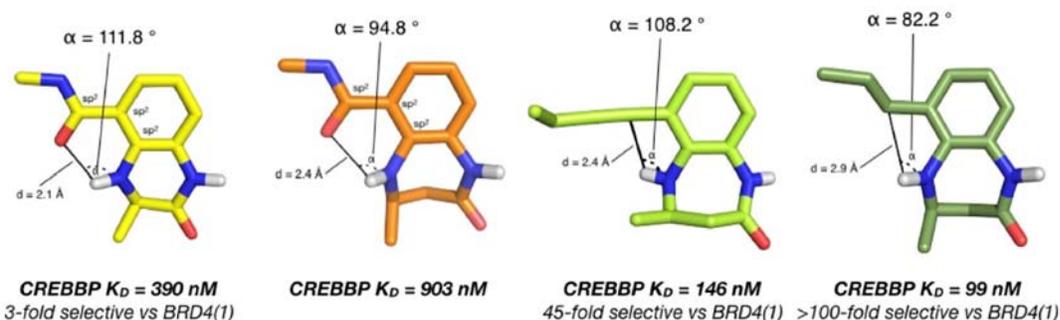
MEDI 312

Harnessing intramolecular hydrogen bonds in the design of potent and selective CREBBP bromodomain ligands

Stuart J. Conway, stuart.conway@chem.ox.ac.uk. Department of Chemistry, University of Oxford, Oxford, United Kingdom

Cyclic AMP response element binding protein (CREB) binding protein (CREBBP or CPB) is a transcriptional co-regulator that interacts with hundreds of protein partners through multiple protein domains. CREBBP contains a bromodomain, which is a protein module that binds to acetylated lysine an 'epigenetic' mark found in numerous proteins, including histones. To understand the role played by the bromodomain in the overall function of CREBBP we have sought to develop potent and selective ligands for the CREBBP bromodomain. These compounds bind to the bromodomain and prevent it from interacting with acetyl-lysine, impairing its function. In initial work, we identified a

series of dihydroquinoxalinone-based ligands in which an intramolecular hydrogen bonds preorganised the ligands into a favourable conformation for binding to the CREBBP bromodomain. When we switched to a closely related benzodiazepinone-based series, we found that this intramolecular hydrogen bond was unfavourable for CREBBP bromodomain binding. By removing this interaction we were able to develop potent and selective CREBBP bromodomain ligands. The structure- and computationally-guided optimisation of these ligands will be presented.



MEDI 313

Identification and *in vivo* evaluation of novel IRAK4 inhibitors in murine models of lupus

John Hynes, john.hynes@bms.com. Bristol-Myers Squibb, Washington Crossing, Pennsylvania, United States

IRAK4 is a member of the IRAK family of serine-threonine kinases which signals downstream of toll-like receptors (TLRs) and IL-1 receptors. TLRs are centrally critical to innate immune system defense due to their ability to recognize molecular patterns associated with various bacterial and viral pathogens. In addition, these pattern recognizing receptors also detect damage-associated molecular pathogens (DAMPs) generated in the course of chronic autoimmune disease states such as lupus. Activation of the TLRs (except TLR3 and to a lesser degree TLR4) by these DAMPs starts a complex signaling cascade of adaptor protein recruitment and IRAK4 activation. Subsequent signaling via downstream kinases leads to NF- κ B activation and cytokine expression. The location of IRAK4 downstream of these innate immune system signaling receptors has resulted in significant interest in therapeutic targeting of IRAK4 in autoimmune diseases. Herein, we present the discovery, SAR, and potency optimization of a pyridine amide series of IRAK4 inhibitors. The structural basis of inhibition will be detailed with X-ray co-crystal structures of select compounds. Additionally, kinase selectivity optimization and *in vivo* efficacy in a murine model of lupus will be presented.

MEDI 314

Discovery of TAK-137 and TAK-653, clinical candidates of α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor potentiators with reduced agonistic activities

Shinji Nakamura, nakamura_shinji@takeda.co.jp, Masashi Toyofuku, Eiji Honda, Toshihiro Imaeda, Akihiro Yokota, Satoshi Sogabe, Akiyoshi Kunugi, Haruhiko Kuno, Yohei Kosugi, Masakuni Kori, Takashi Miki, Haruhide Kimura, Takanobu Kuroita, Tomohiro Kaku. Takeda Pharmaceutical Company Limited, Fujisawa, Kanagawa, Japan

The α -Amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor is a glutamate receptor and it plays an important role in excitatory neurotransmission. In particular, the rapid excitatory signaling *via* AMPA receptors contributes to the induction of synaptic plasticity in neurons, which is thought to be crucial for learning and memory. Therefore, positive modulation of AMPA receptors is an attractive approach to ameliorate cognitive deficits in various neuropsychiatric and neurodegenerative disorders. For over a decade, several AMPA receptor potentiators have been widely investigated as potent cognitive enhancers. However, none of them has been marketed, which might be due to their limited therapeutic window.

In order to develop new chemical series with sufficient therapeutic windows, we have established both a binding assay by using scintillation proximity assay technology and a cellular assay to evaluate agonistic activity using rat primary neurons as a clearly differentiated assay in parallel with a cellular assay using GluA1 expressing CHO cells. The successive high-throughput screening campaign using both binding and cellular assays resulted in the identification of promising hit compounds with unprecedented scaffolds as AMPA receptor potentiators. The hybrid design based on the overlay study of hit compounds led to the identification of a lead compound, which showed potent binding and potent agonistic activity. Further modifications on the compound were guided by its X-ray co-crystal structure in complex with GluA2, culminating in the discovery of **TAK-137** and **TAK-653** as highly potent, orally active, and brain-penetrating AMPA receptor potentiators with reduced agonistic activity.

In this presentation, we will present our strategy for identifying the clinical candidates **TAK-137** and **TAK-653** with optimal profiles in terms of potency, agonistic activity, and brain penetration.

MEDI 315

First class of orally available mono-saccharide galectin-3 inhibitors for treatment of fibrosis (NASH) and cancer

Fredrik Zetterberg, fz@galecto.com. RD, AstraZeneca, Molndal, Sweden

Galectin-3 is a β -D-galactopyranoside specific lectin which is involved in the pathology of fibrosis and cancer. We recently finalized a successful phase I/IIa study with our galectin-3 inhibitor, TD139, which is being developed as an inhaled treatment of

Idiopathic pulmonary fibrosis (IPF). Since genetic depletion or inhibition of galectin-3 reduces fibrosis in other organs such as liver, kidney and heart, there is a need for a systemically available galectin-3 inhibitor. We report here how we developed the first orally available high affinity (nM) galectin-3 inhibitors and the effects of these in PD models of fibrosis and cancer.

Designing small high affinity lectin inhibitors with a natural saccharide as a starting point is a major challenge. In general mono- and disaccharides bind with an affinity in the low μM -mM range due to that the lectin binding sites are shallow and polar. Inhibitors with high polarity also in general have limited oral bioavailability, which indeed is the case for the disaccharide TD139. By introduction of non-natural aromatic substituents to the 1 and 3-position of α -D-galactopyranoside the polar surface area was reduced and lipophilicity increased to result in compounds with PK properties suitable for oral administration. Then high affinity compounds could be achieved by the use of specific interactions, such as fluorine-amide, phenyl-arginine, sulfur- π and halogen bonds.

Further, we have shown that these compounds reduce development of fibrosis in a CCl₄ mouse model and that they also reduce tumor growth and metastasis in a model of Lewis Lung Carcinoma. We are currently in the process of taking candidates of this class to man for development of new treatments of fibrosis (NASH) and cancer.

MEDI 316

Discovery of orally bioavailable non-catechol atropisomer dopamine D₁ agonists with reduced desensitization

Jennifer E. Davoren, jennifer.e.davoren@pfizer.com, David L. Gray, Deane Nason, Anthony Harris, Wenjian Xu, Scot Mente, Jotham W. Coe, rouba kozak. Pfizer, Cambridge, Massachusetts, United States

Selective agonism of dopamine D₁ receptors has been a therapeutic goal for neurological and psychiatric disorders such as Parkinson's and Schizophrenia for nearly 40 years. There have been a number of advancements in understanding the D₁R orthosteric binding site and GPCR signaling cascades, but until recently, leads with good oral pharmacokinetics have remained elusive primarily due to the pharmacokinetic challenges presented by the catechol functionality found in the majority of D₁-selective chemical matter.

Here we disclose the discovery and optimization of a novel series of orally bioavailable, CNS penetrant, non-catechol D₁ selective orthosteric agonists. Lead examples from this series exist as stable atropisomers due to a hindered biaryl bond. In addition, these ligands display evidence of distinct binding to the D₁R orthosteric site that leads to significantly reduced desensitization and recruitment of β -arrestin. Compounds from this series were developed and advanced into clinical studies.

MEDI 317

DRX-065, the deuterated (*R*)-enantiomer of pioglitazone, as a nonalcoholic steatohepatitis (NASH) drug candidate: Preclinical and phase 1 results

Vincent Jacques, vjacques001@gmail.com, *Lex Van der Ploeg*, *Sheila H. Dewitt*. *DeuteRx, Andover, Massachusetts, United States*

Pioglitazone (pio) is a drug approved for the treatment of type 2 diabetes mellitus. Because of its superior efficacy for NASH demonstrated in multiple clinical trials, it is currently the only drug recommended off-label for the treatment of this silent, but highly prevalent liver disease. However, its use is limited due to PPAR γ agonism-related side effects, including weight gain and edema. Pio is a racemic mixture of (*R*)- and (*S*)-enantiomers that rapidly interconvert, which has prevented the characterization of their individual pharmacokinetic and pharmacodynamic properties.

Substituting the hydrogen at the chiral center of pio with deuterium stabilized the enantiomers and allowed their full characterization and evaluation as distinct molecular entities. Herein, we show that, through mitochondrial function modulation, DRX-065, the deuterated (*R*)-enantiomer of pio, is responsible for the NASH efficacy of pio while the (*S*)-enantiomer shows strong PPAR γ agonist activity and the related side effects of weight gain and fluid retention found in the racemate.

The superior efficacy of DRX-065 in rodent models and the observed absence of PPAR γ -driven side effects prompted our advancement of DRX-065 for NASH and adrenomyeloneuropathy (AMN), a rare monogenic CNS disease. Herein, we show that, in a Phase 1 single dose study of 22.5 mg DRX-065 compared to 45 mg Actos[®] (pio), DRX-065 demonstrates good safety and tolerability. Furthermore, dosing of DRX-065 provides selective exposure to the (*R*)-enantiomer and is predicted to have efficacy equivalent to 45 mg pio at a significantly lower dose without the PPAR γ -related side effects of weight gain and edema.

MEDI 318

Discovery of novel potent and selective first in class calpain inhibitors for the potential treatment of neurodegenerative disorders

*Helmut Mack*², helmut.mack@abbvie.com, *Katja Jantos*², *Andreas Kling*², *Charles W. Hutchins*¹, *Wilfried Hornberger*², *Gisela Backfisch*³, *Marjoleen Nijsen*¹. (1) *Discovery, AbbVie Inc, North Chicago, Illinois, United States* (2) *Neuroscience Research, Abbvie Deutschland GmbH & Co. KG, Ludwigshafen, Germany* (3) *Development Sciences, Abbvie Deutschland GmbH & Co. KG, Ludwigshafen, Germany*

Dysregulation of calpain has been observed in various pathophysiological processes like stroke, traumatic brain injury, Alzheimer's, Huntington's, Parkinson's Disease and Multiple Sclerosis. In Alzheimer's Disease hyperactivated calpain leads to synaptic dysfunction, b-amyloid production, tau pathology and neurodegeneration. Inhibition of calpain, either via the natural inhibitor Calpastatin or using low molecular weight calpain

inhibitors, has been shown to ameliorate the pathology in AD-relevant models. Two major challenges in former calpain inhibitor programs have been the selectivity of the inhibitors for calpain versus closely related enzymes like cathepsins and the identification of a drug like warhead interacting with the active site cysteine. Starting from published lead compounds with decent potency but low selectivity and with a poor ADME profile, systematic modification of inhibitor backbone, attached side chains and the active site directed warhead lead to significantly improved inhibitors regarding potency and selectivity, however, species dependent low oral bioavailability remained an issue. Identification of the metabolic hot spot and subsequent dedicated structural modification led to calpain inhibitors with significantly improved oral bioavailability across species, while maintaining the favorable activity and selectivity profile. Advanced lead candidates were identified which featured broad efficacy in AD related preclinical animal models combined with an excellent safety profile in toxicology. The efforts finally led to a clinical candidate with the potential for proof of concept studies in Alzheimer's Disease patients with a first-in-class calpain inhibitor.

MEDI 319

Discovery of the TYK2 selective inhibitor PF-6826647 for the treatment of Crohn's disease, and other autoimmune conditions

Brian S. Gerstenberger², Brian.gerstenberger@pfizer.com, Eric P. Arnold³, Mary Ellen Banker³, Matthew F. Brown³, James D. Clark¹, Alpay Dermenci³, Martin Dowty², Andrew Fensome², Matthew M. Hayward³, Martin Hegen¹, Brett D. Hollingshead⁴, John D. Knafels³, David W. Lin³, Tsung Lin¹, Dafydd Owen², Eddine Saiah², Raman Sharma³, Felix F. Vajdos³, Fabien Vincent³, Stephen W. Wright³, Li Xing², Xiaojing Yang³, Xin Yang³, Liying Zhang². (1) Inflammation and Immunology, Pfizer Inc, Cambridge, Massachusetts, United States (2) Medicine Design, Pfizer Inc, Cambridge, Massachusetts, United States (3) Medicine Design, Pfizer Inc, Groton, Connecticut, United States (4) Drug Safety Research and Development, Pfizer Inc, Cambridge, Massachusetts, United States

Tyrosine kinase 2 (TYK2) is one of the four members of the Janus (JAK) family of kinases, which also includes JAK1, JAK2 and JAK3. JAK kinase hetero-, and to a lesser extent homo, pairs play a key role in signal transduction of cytokines which signal through the JAK- Signal and Transduction of Transcription (STAT) pathway. TYK2 is important in IL-23 and IL-12 signaling where it pairs with JAK2, and Type I interferon signaling where it pairs with JAK1. Genome-wide association studies have associated TYK2 loss of function loci with a number of auto-immune diseases including Crohn's disease, ulcerative colitis, psoriasis, systemic lupus erythematosus, and, rheumatoid arthritis. The pharmacological profile of a selective TYK2 kinase inhibitor provides an opportunity to address a number of auto-immune diseases with a differentiated profile.

In this presentation we describe the discovery of an ATP competitive pyrazolopyrazinyl series of selective TYK2 inhibitors. The target profile and balanced selectivity against JAK2, was established through understanding of PK/PD relationships developed from

our clinical experience. Through a structurally enabled program a scaffold hopping effort lead to several Type 1 kinase hinge designs and a preferred lead template. Further potency optimization involved leveraging P-loop engagement and simulated water thermodynamics. ADME properties in general in the program were favorable, however issues with non-P450 clearance pathways were identified, and a successful solution will be described. This effort led to the identification of PF-06826647 a potent and selective inhibitor of TYK2 which is currently in Phase 1 clinical studies.

MEDI 320

Discovery of AZD5718, a novel 5-lipoxygenase activating protein (FLAP) inhibitor

Malin Lemurell¹, malin.lemurell@astrazeneca.com, Daniel Pettersen¹, Johan Ulander¹, Martin Hayes¹, Carl Whatling¹, Marianne Swanson¹, Johan Broddefalk¹, Hans Emtenas², Eva-Lotte Lindstedt¹. (1) Cardiovascular, Renal and Metabolic diseases IMED Biotech Unit, AstraZeneca, Gothenburg, Sweden (2) Pharmaceutical Sciences IMED Biotech Unit, AstraZeneca, Gothenburg, Sweden

5-lipoxygenase activating protein (FLAP) is essential for the activity of 5-LO, the key first step in leukotriene biosynthesis. AZD5718 is a novel oral FLAP inhibitor aiming to reduce cardiovascular mortality and morbidity in coronary artery disease (CAD) patients by attenuation of proinflammatory and vasoactive leukotriene production.

The recently concluded Phase 1 study demonstrates that AZD5718 is safe & tolerated, with a pharmacokinetics amenable for QD oral dosing. Paired with dose dependent & potent target engagement on both arms of the 5-LO pathway, the Phase 2a study started 2017.

Herein we will disclose the medicinal chemistry discovery and development of AZD5718 which entirely originates from a novel chemical series

MEDI 321

Discovery of LY3154207, a potent and selective dopamine receptor D1 positive allosteric modulator for the treatment of Parkinson's disease dementia

Junliang Hao, haoju@lilly.com, James P. Beck, Joseph H. Krushinski, John M. Schaus, Xu-shan Wang, Beverly Heinz, Robert F. Bruns, David M. Bender, Jeffery W. Cramer, Kjell A. Svensson. Eli Lilly and Company, Indianapolis, Indiana, United States

The dopamine receptor D1 subtype (DRD1) is the most abundant dopamine receptor in the central nervous system, and plays an important role in motor activity, reward, and cognitive functions. Catechol-based DRD1 orthosteric agonists have been extensively studied and are active in many clinically relevant disease models in preclinical species. In particular, these agonists were found to have excellent antiparkinsonian effects in humans and primate models of Parkinson's disease (PD). However, attempts to develop these agonists for clinical use have thus far been largely unsuccessful due to receptor desensitization, poor ADME/PK properties, and dose limiting side effects (e.g.

hypotension). In addition, D1 agonists show a bell-shaped dose response curve on cognitive endpoints. Due to the high degree of structural homology between DRD5 and DRD1 receptors, selective DRD1 agonists have been difficult to design. At Lilly, a positive allosteric modulator (PAM) approach to DRD1 activation has been developed to potentially address the issues associated with the orthosteric agonists. Pure PAMs do not have any direct effects themselves, but indirectly amplify the response to the endogenous agonist when and where the endogenous ligand is released, and thus have the ability to act in a more physiologically relevant way than direct-acting agonists, which activate all accessible receptors for as long as they are present. PAMs also bind to a site distinct from the orthosteric binding site that may have greater structural diversity and thus offer potential to achieve greater subtype selectivity. In this presentation, we will describe the discovery of LY3154207, an orally available, potent and selective DRD1 PAM currently in phase 2 clinical trials for the treatment of Parkinson's disease dementia. Preclinical data supporting its clinical evaluation will be presented.

MEDI 322

Discovery of AMG986, a potent, selective and orally bioavailable APJ agonist for the treatment of heart disease

Paul J. Dransfield⁸, pdransfi@amgen.com, zhihua Ma⁸, Ji Ma¹, Vatee Pattaropong⁸, sujen lai⁸, Matthew R. Kaller⁸, Nobuko Nishimura², ning chen⁸, david kopecky², Dan Horne⁸, kim Hoagland¹, simon hedley¹, Jonathan B. Houze⁸, jeff mihalic², julie heath², yinhong chen¹, Qi Guo¹, xiaoqi chen², Julio C. Medina³, zice fu², jeff deignan⁵, sheldon wang², ted judd², Richard Connors⁴, steve olson⁶, gayathri swaminath⁷, Wes Sutherland¹, Mark fielden¹, Bob Farrell¹, James Harvey⁸. (1) Amgen Inc, S San Fran, California, United States (2) Unknown, West Hills, California, United States (3) unknown, San Carlos, California, United States (4) unknown, Bay area, California, United States (5) Gilead, Foster city, California, United States (6) UCSF, San Francisco, California, United States (7) Merck, South San francisco, California, United States (8) Amgen Discovery Research, Cambridge, Massachusetts, United States

The G protein-coupled receptor, APJ (APLNR), and its endogenous peptidic ligand (apelin) have been implicated in mediating multiple beneficial effects on cardiovascular function. Efforts to employ apelin peptides therapeutically have been hindered by their very short half-lives. This presentation will describe the small molecule drug discovery process from optimizing a small molecule high-throughput screening hit through to the identification of the APJ agonist AMG 986. A phase 1 clinical trial is currently underway evaluating AMG 986 in healthy volunteers and heart failure patients.

MEDI 323

Obstacles to the discovery of novel antibacterials & approaches towards a new strategy

Ruben A. Tommasi, *ruben.tommasi@entasistx.com*. Entasis Therapeutics, Inc, Stow, Massachusetts, United States

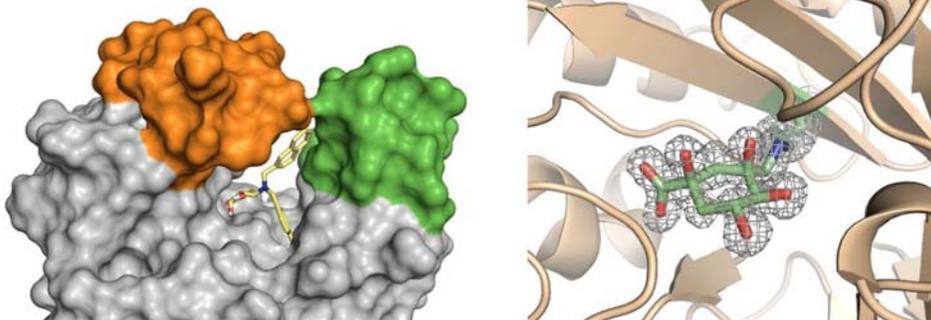
Our understanding of the factors that influence compound accumulation into Gram-negative bacteria is significantly lacking as evidenced by the dearth of new leads arising from large-scale biochemical or target-agnostic phenotypic antibacterial screening efforts. This knowledge gap stems from the historical lack of predictive cellular assays, tools, and models that provide structure-activity relationships to inform optimization of compound accumulation. To address this gap, we developed a sensitive and specific whole-cell approach in *Escherichia coli* called titrable outer membrane protein assay system (TOMAS). We used TOMAS to characterize the structure porin-permeation relationships of the *Pseudomonas aeruginosa* porin OprD and the *Acinetobacter baumannii* porin OmpA. A novel set of carbapenem analogs was used to explore the structure-permeation relationship for permeation through OprD. Our results suggest that small structural modifications, especially the number and nature of charges and hydrogen bonding groups and their position, have dramatic effects on the ability of these molecules to permeate into cells through OprD. We identified OmpA as the porin responsible for the uptake for the β -lactamase inhibitor ETX2514 in *A. baumannii* and have observed comparable results where small structural changes impact the ability of these small molecules to permeate into this serious Gram-negative pathogen. Taken together these results highlight the need to develop a better understanding of structure-permeation relationships.

MEDI 324

Disabling unexplored key enzymes in bacteria to unlock resistance to antibiotics

Concepcion Gonzalez-Bello, *concepcion.gonzalez.bello@usc.es*. CIQUS, Universidad de Santiago de Compostela, Santiago de Compostela, Spain

The emergence of multi-drug resistant bacteria in both community and clinical settings, along with the evident decline in antibiotic research by the major pharmaceutical companies during the last 50 years, has made of resistant infectious diseases one of the most important public health issues of the early 21st century. There is a great interest in the search not only for more effective anti-infective drugs but also to develop novel chemical entities with new mechanisms of action. Our research group is exploring the potential of unexploited essential targets for bacterial viability, which are involved in the aromatic amino acids biosynthesis, as well as in the development of novel scaffolds that target them. Our efforts are also focused in disabling bacterial pathogenicity (capacity to cause infection), which is an attractive choice that is increasingly being explored. Anti-virulence drugs will create an in vivo scenario similar to that achieved by vaccination with a live attenuated strain. The design of the ligands is based on the structure and mechanism of action of these enzymes as well as in the essential motion for catalysis. In this talk, examples of both approaches will be presented.



Binding mode of a *N,N*-dibenzylamino derivative in the active site of shikimate quinase from *M. tuberculosis* (left) and crystal structure of type I dehydroquinase from *S. typhi* covalently modified by an ammonium derivative (right)

MEDI 325

Resetting the antibacterial arms race by enabling a novel Gram negative target

Michael Koehler¹, mkoehler@gene.com, **Hany S. Girgis**¹, **Christopher E. Heise**¹, **Robert I. Higuchi**², **Jeremy Murray**¹, **Tucker C. Roberts**³, **Prasuna Paraselli**², **Lionel Rougé**¹, **Peter A. Smith**¹. (1) Genentech, Inc, South San Francisco, California, United States (2) RQx Pharmaceuticals, Solana Beach, California, United States (3) Aduro Biotech, Berkeley, California, United States

In the nearly one hundred years since the discovery of the first antibiotics, a pattern has firmly established itself. A novel antibacterial agent is introduced, and then resistance to the therapy rapidly emerges, initially in the hospital setting, then spreading to the community. The primary focus of antibacterial drug discovery for the past fifty years has been on circumventing the resistance developed to existing classes of antibiotics. In an effort to change this paradigm, we began reinvestigating molecules with a compelling and essential bacterial target that had been abandoned or unsuccessfully pursued. We identified the arylomycin class of macrocyclic lipopeptides as a promising starting point based on their inhibition of an essential signal peptidase (SPase) in both Gram-positive and -negative bacteria. Reviewing what was known of their activity, spectrum and resistance profile, we began by attempting to capture interactions lost as a result of the missing P1 residue and simultaneously adding functionality to covalently modify the SPase active site serine. Following a period of structure guided optimization, we identified an aminoacetonitrile warhead as optimal. To our great surprise, structures of inhibitors with this warhead in the SPase enzyme revealed an unprecedented covalent interaction with the active site residues which rationalized previously confusing structure/activity relationships. Additional optimization ultimately produced G0775, a potent, broad-spectrum agent active in vitro and in vivo. As would be anticipated for an agent with a novel mode of action, G0775 is unaffected by resistance evolved against therapeutics in current clinical use, and is highly active against 49 strains of multidrug resistant Gram-negative pathogens provided by the CDC. Despite the fact that G0775 inhibits a single bacterial gene product, a moderate

frequency of resistance compatible with use of G0775 as a single agent therapy is observed at a concentration four fold the minimum inhibitory concentration (MIC). Mutant strains of *E.coli* partially resistant to G0775 show single mutations in the binding cleft of the enzyme with modest loss of affinity consistent with their MIC shifts. G0775 has clearly demonstrated the potential of arylomycin-derived Spase inhibitors to be the first new class of Gram-negative active antibiotic introduced in fifty years. If successful, we could once again reset the clock in the ongoing arms race against pathogenic bacteria.

MEDI 326

Systematic conversion of Gram-positive-only compounds into broad-spectrum antibiotics

Paul J. Hergenrother, hergenro@illinois.edu. Univ of Illinois, Urbana, Illinois, United States

The incidence of multi-drug resistant Gram-negative infections has risen sharply in the last decade and is a growing health concern. This problem is exacerbated by the fact that it has been 50 years since the clinical introduction of a new antibacterial class for these pathogens. Central to the problem of Gram-negative antibiotic discovery are the challenges small-molecules face in traversing the Gram-negative outer membrane. This lecture will describe our guidelines, the “eNTRy rules”, for predicting compound accumulation in Gram-negative bacteria. The successful application of the eNTRy rules to the conversion of several different classes of Gram-positive-only compounds into versions that have broad-spectrum antibiotic activity will be discussed.

MEDI 327

Can sideromycins (siderophore-antibiotic conjugates) be effective antibiotics? Challenges and opportunities

Marvin J. Miller, mmiller1@nd.edu. University of Notre Dame, Notre Dame, Indiana, United States

The need for new antibiotics is dire! While bacterial resistance has developed to essentially all of our current antibiotics, few new antibiotics have been developed over the last several decades. A primary cause of drug resistance is the overuse of antibiotics that can result in alteration of microbial permeability, alteration of drug target binding sites, induction of enzymes that destroy antibiotics (ie., beta-lactamases) and even induction of efflux mechanisms. A combination of chemical syntheses, microbiological and biochemical studies demonstrate that the known critical dependence of iron assimilation by microbes for growth and virulence can be exploited for the development of new approaches to antibiotic therapy. Iron recognition and active transport relies on the biosyntheses and use of microbe-selective iron chelating compounds called siderophores. Our studies, and those of others, demonstrate that

siderophores and analogs can be used for iron transport-mediated drug delivery (“Trojan Horse” antibiotics or sideromycins) and induction of iron limitation/starvation (development of new agents to block iron assimilation).

Several examples will illustrate that, aided by chemical syntheses, this approach can generate microbe selective antibiotics. Concerns expressed in the literature about “microbe adaptability” and rapid development of resistance will be reviewed and addressed.

MEDI 328

Microbiome: A key player in modulating infectious diseases and antibiotic resistance

Olga Danilchanka, olga.danilchanka@merck.com. Exploratory Science Center, Merck, Cambridge, Massachusetts, United States

Numerous preclinical and clinical studies have shown that the microbiome is the newly-discovered “organ” that is involved in numerous aspects of fundamental physiology and pathology. Recent discoveries are starting to shed light on the precise mechanisms by which the microbiome regulates both innate and adaptive immune responses. We are beginning to appreciate why and how this regulation affects infectious disease initiation, progression, and treatment response including spread of antibiotic resistance. At the Merck Exploratory Science Center (MESC) in Cambridge we are using a systems biology approach to integrate human and microbiome pathways using well-curated clinical data and preclinical models to identify molecular mechanisms by which the microbiome regulates responses to vaccines and infectious diseases.

MEDI 329

Discovery of a once-weekly NNRTI clinical candidate: A new paradigm for treating HIV-1 infection

Yongxin Han¹, yongxin_han@merck.com, Christopher S. Burgey⁴, Karsten Menzel², Ming-Tain Lai³. (1) Discovery Chemistry, Merck Research Laboratories, Merck & Co., Inc., Boston, Massachusetts, United States (2) PPDM, Merck Research Laboratories, Merck & Co., Inc., West Point, Pennsylvania, United States (3) Discovery Biology, Merck Research Laboratories, Merck & Co., Inc., West Point, Pennsylvania, United States (4) Discovery Chemistry, Merck Research Laboratories, Merck & Co., Inc., West Point, Pennsylvania, United States

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) represent a cornerstone of antiretroviral therapy for the treatment of HIV infected patients. Current market leading NNRTIs are dosed once-daily (QD) as a component of combination therapy. Lifelong adherence to HIV therapy remains a challenge for many patients. Extended duration dosing with forgiving agents is a potential means to address this issue. Towards this goal, we targeted the development of a once-weekly (QW) oral NNRTI. Central to the

success of this approach is the ability to produce an orally bioavailable NNRTI with a long plasma half-life sufficient to enable QW dosing with forgiveness. Our strategy to deliver on this relatively unprecedented objective, along with key elements of the design and optimization effort leading to a clinical candidate, will be presented. The initial clinical data, which support the potential for QW dosing for HIV treatment, will also be discussed. It is envisioned this compound will be a component of a future QW regimen that has the potential to improve adherence and clinical outcome as a new paradigm for the treatment of HIV infection.

MEDI 330

Discovery, structure disclosure, and early clinical development of LY3202626, a low-dose, CNS-penetrant BACE inhibitor

Dustin J. Mergott¹, mergottdu@lilly.com, James E. Audia¹, Mario Barberis¹, James P. Beck¹, Leonard N. Boggs¹, Robert D. Boyer¹, Richard A. Brier¹, Anthony N. Borders¹, Leslie L. Daugherty¹, Robert A. Dean¹, Larry Ereshefsky², Jon A. Erickson¹, Pablo Garcia-Losada¹, Hakop Gevorkyan³, Steven J. Green¹, Erik J. Hembre¹, Michael C. Irizarry¹, Douglas E. James¹, Stanford Jhee², Qun Lin¹, Jose E. Lopez¹, Albert Lo¹, Stephen L. Lowe¹, Brian M. Mathes¹, Patrick C. May¹, David L. McKinzie¹, Scott A. Monk¹, Masako Nakano¹, Warren J. Porter¹, Yuan Shi¹, Stephanie L. Stout¹, David E. Timm¹, Brian Watson¹, Brian A. Willis¹, Leonard L. Winneroski¹, Zhixiang Yang¹, Jennifer A. Zimmer¹. (1) Eli Lilly and Company, Indianapolis, Indiana, United States (2) PAREXEL International, Glendale, California, United States (3) California Clinical Trials, Glendale, California, United States

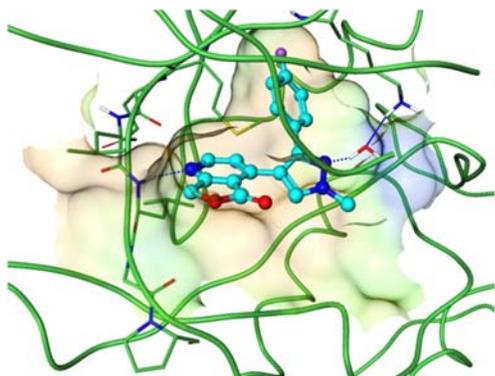
Cerebral deposition of amyloid- β peptide (A β) plays a critical role in Alzheimer's disease (AD) pathogenesis. Owing to its role in the generation of A β , the BACE1 enzyme has been a prime target for designing drugs to prevent or treat AD. However, recent failures of anti-amyloid therapies to slow the progression of AD have caused the field to consider studies in asymptomatic patients with amyloid pathology or combination approaches. Ideally, BACE inhibitors in these studies will maximize target engagement and have excellent safety profiles. This presentation will describe the discovery and early clinical development of LY3202626, a low-dose, CNS-penetrant BACE inhibitor capable of reducing CSF A β by > 90%. This presentation will also include the disclosure of the chemical structure of LY3202626.

MEDI 331

Discovery of PF-05251749 a selective casein kinase 1 (CK1 δ /e) inhibitor for the treatment of circadian rhythm disorders

Travis T. Wager, travis.t.wager@pfizer.com. MS 220-4376, Pfizer Inc, Groton, Connecticut, United States

CK1 delta (CK1 δ) and CK1 epsilon (CK1 ϵ) are closely related members of a family of seven mammalian serine/threonine protein kinases previously known as casein kinases. The CK1 δ and CK1 ϵ isoforms are highly expressed in the suprachiasmatic nucleus (SCN) where they form an essential component of the mammalian biological clock. Selective inhibitors of this class of kinases will provide tools to study the role of circadian clock in CNS disorders such as: bipolar, depression, AD and substance use dependency. A challenge with targeting kinase inhibitors for chronic CNS indications is a seemingly insurmountable task because of the need to achieve good brain penetration for efficacy and high kinome selectivity for safety. Through a combination of structure-based design, computational chemistry, and innovative medicinal chemistry we have identified a series of highly selective, brain penetrant CK1 δ / ϵ inhibitors which demonstrated phase shift in mouse and cynomolgus monkey models of circadian rhythm. These inhibitors also provided excellent therapeutic index in regulatory toxicology studies and in clinical studies. This presentation will highlight the discovery of such compounds as well as general guidelines for targeting kinases for CNS disorders. The safety, tolerability, PK/PD and clinical biomarkers will be discussed.



X-ray co-crystal structure showing the binding of CK1 δ / ϵ inhibitor **PF-05251749** to CK1 δ .

MEDI 332

Discovery of pyrrolidinamides, a novel chemical class for malaria treatment: First time disclosure of the orally bioavailable clinical candidate GSK701

Harshad Rami¹, harshad.rami@gsk.com, **Isabel Castellote**², **Francisco-Javier Gamo**², **John Haselden**², **Felix Calderon Romo**². (1) *Translational Medicine, GSK, Uxbridge, Middlesex, United Kingdom* (2) *Malaria DPU, GSK, Tres Cantos, Madrid, Spain*

Malaria is a major global disease caused by parasites of the genus *Plasmodium*, which are transmitted to people when infected female anopheles mosquitoes feed on human blood. According to the last World Health Organization (WHO) Malaria report, in 2016 there were an estimated of 216 million cases with approximately 445,000 deaths worldwide. Among the different *Plasmodium* species that infects humans, *falciparum* is accountable for nearly 90% of these deaths and children under 5 are particularly susceptible to malaria illness, infection and death. In addition, malaria has a severe

socioeconomic impact in countries where it is endemic because of the persistent and disabling symptoms of the disease. Approximately 25% of the endemic countries incomes are devoted to treating and minimizing the impact of this disease. In the African continent alone the economic burden is estimated at \$12 billion annually.

A current area of global concern in malaria is the emergence of resistance to antimalarial drugs, including the artemisinins (current gold standard treatment). As a consequence, there is an urgent requirement for novel antimalarial drugs with novel mechanism of action that can be deployed to treat the disease.

Pyrrrolidinamides has emerged as a novel potent antimalarial chemical class with activity against resistant strains and potential to deliver a safe, oral new antimalarial medicine. In this session, we will disclose for the first time the structure of GSK701, the first antimalarial clinical candidate belonging to this chemical class. GSK701 is the result of a collaboration between GSK and the Wellcome Trust focused on developing this chemical class discovered from a phenotypic screening of the GSK collection. GSK701 has a physicochemical and safety profile appropriate for oral administration, a robust multi-gram synthetic route and is predicted to be effective against *P. falciparum* malaria with a low dose. The medicinal chemistry strategy, SAR, clinical plans and results of the target identification strategy will be discussed during this presentation.

MEDI 333

Discovery of highly isoform-selective Nav1.6 inhibitors that show potent anticonvulsant activity in mouse models for focal seizures and severe childhood epilepsy

*Thilo Focken*¹, *tfocken@xenon-pharma.com*, *Mike E. Grimwood*¹, *Verner Lofstrand*¹, *Kristen Burford*¹, *Wei Gong*¹, *Qi Jia*¹, *Abid Hasan*¹, *Matthew Taron*¹, *Wei Zhang*¹, *Michael Wilson*¹, *Parisa Tari*¹, *Karen Nelkenbrecher*¹, *Kuldip Khakh*¹, *Samuel J. Goodchild*¹, *Noah Shuart*¹, *Sophia Lin*¹, *Rainbow Kwan*¹, *Luis Sojo*¹, *Robert J. Devita*², *Steven Wesolowski*¹, *Charles Cohen*¹, *JP Johnson*¹, *Christoph M. Dehnhardt*¹, *James R. Empfield*¹. (1) *Xenon Pharmaceuticals Inc, Burnaby, British Columbia, Canada* (2) *RJD Medicinal Chemistry and Drug Discovery Consulting LLC, Westfield, New Jersey, United States*

Voltage-gated sodium channels (Navs) are transmembrane ion channels that play a fundamental role in controlling cellular excitability. Adult Central Nervous System (CNS) neurons primarily express three Navs, Nav1.1, Nav1.2, and Nav1.6. Nav1.1 is the dominant isoform in inhibitory interneurons, whereas Nav1.2 and Nav1.6 are highly expressed in excitatory neurons. An imbalance in the excitatory/inhibitory neurons caused by abnormal expression or function of Nav's contributes to the pathophysiology of epilepsy. For example, patients with loss-of-function mutations in the SCN1A gene encoding Nav1.1 suffer from Early Infantile onset Epileptic Encephalopathy 6 (EIEE6, Dravet Syndrome) while gain-of-function mutations in the SCN8A gene encoding Nav1.6 cause another catastrophic epilepsy, EIEE13.

Non-selective Nav blockers are among the most prescribed antiepileptic drugs. However, they suffer from a narrow therapeutic index, likely due to the high exposure required for efficacy and their lack of selectivity among the Navs. Some EIEE13 patients respond to non-selective Nav inhibitors, presumably due to the block of Nav1.6 which addresses the etiology of the seizures. Seizure control in these patients requires doses higher than is typically used in other epilepsy patients. It is believed that block of Nav1.1 is counter-productive since genetic loss-of-function of this channel leads to seizures. Thus, isoform-selective Nav1.6 inhibitors could provide a more effective treatment for epilepsy with the potential to avoid adverse events arising from non-selective block of other ion channels.

In recent years, a series of heterocyclic aryl sulfonamides has been reported as highly isoform-selective Nav inhibitors, targeting the voltage-sensor domain of Nav channels. Initially, compounds were published with selectivity for the inhibition of Nav1.1/Nav1.3, and later for Nav1.7. We now report on a novel class of aryl sulfonamides with unprecedented isoform selectivity for Nav1.6 over other subtypes. We report on our strategy to optimize potency and CNS penetration of this series. We evaluated the ability of our Nav1.6 inhibitors to prevent seizures in the highly validated maximal electroshock seizure test in mice. In addition, compounds were assessed in a 6 Hz seizure model employing an EIEE13 patient-derived mutation, N1768D, in mice. Compound A showed excellent anticonvulsant activity in the two epilepsy models with EC70's of 0.06-0.07 μ M plasma concentration.

MEDI 334

Synthesis, biological activity and druglikeness profile of new leishmanicidal candidates

Lídia M. Lima^{1,2}, *Imlima23@gmail.com*, *Marina A. Alves*², *Aline C. Queiroz*², *Magna Suzana Alexandre Moreira*², *Sandra E. Haas*², *Eliezer J. Barreiro*^{3,2}. (1) *Biomedical Science Institute, Federal University of Rio de Janeiro, Rio De Janeiro, Brazil* (2) *Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos (INCT-INOVAR), Rio De Janeiro, Rio De Janeiro, Brazil* (3) *UFRJ, LASSBio, Rio de Janeiro RJ, Brazil*

Considering the ability of proteases to catalyze the hydrolysis of peptide bonds, compounds containing amide or amide-mimetic frameworks can be designed as proteolytic inhibitors and be studied as antitrypanosomatid candidates. In this abstract, we describe the synthesis, leishmanicidal activity, druglikeness profile and ADME study of new hydrazide-*N*-acylhydrazone derivatives, containing a new peptide mimetic framework. These derivatives were synthesized in linear four steps process, were characterized and their purity determined by HPLC and elemental analysis. The in vitro leishmanicidal activity against amastigote forms of *L. amazonensis* and *L. braziliensis* were determined, highlighting compounds LASSBio-1705 e LASSBio-1707 e LASSBio-1736. These compounds were evaluated in vivo, in a model of cutaneous leishmaniasis (dose = 30 μ mol/kg/day during 28 days), in BALB/c mice infected with *L. amazonensis*. The aqueous solubility, chemical and plasma stability of LASSBio-1705 e

LASSBio-1707 e LASSBio-1736 were determined. All compounds were very stable at pH =7.4, but only LASSBio-1736 remained stable at pH=2.0. In rat plasma these compounds showed great stability. The Pharmacokinetic profile of LASSBio-1736 in rats by oral (12.6 mg/kg) or i.p. (12.6 mg/kg) administration was determined. In summary we described the discovery of new leishmanicidal lead-candidate (i.e. LASSBio-1736), with high stability in plasma and in pH conditions that mimic gastric and plasma environments. This compound, bearing a new peptide mimetic framework, has great metabolic stability in rats, with half-life of ~28h, and total clearance of ~50mL/Kg/h. However, it showed low oral bioavailability that can be, in part, due its low aqueous solubility (0.85 mM).

MEDI 335

Discovery of 2,4-substituted azaindoles as multi-parasite inhibitors: Utilizing a parasite-hopping approach to drug-discovery

Kelly A. Bachovchin¹, bachovchin.k@husky.neu.edu, **Rosario Diaz**², **Gloria Ceballos**², **Maria Martinez-Martinez**³, **Pilar Manzano-Chinchon**³, **Richard J. Sciotti**⁴, **Miguel Navarro**², **Michael P. Pollastri**¹. (1) Chemistry and Chemical Biology, Northeastern University, Boston, Massachusetts, United States (2) Instituto de Parasitología y Biomedicina “López-Neyra” Consejo Superior de Investigaciones Científicas (CSIC), Granada, Spain (3) Tres Cantos Medicines Development Campus, DDW, GlaxoSmithKline, Tres Cantos, Spain (4) Experimental Therapeutics, Walter Reed Army Institute for Research, Silver Spring, Maryland, United States

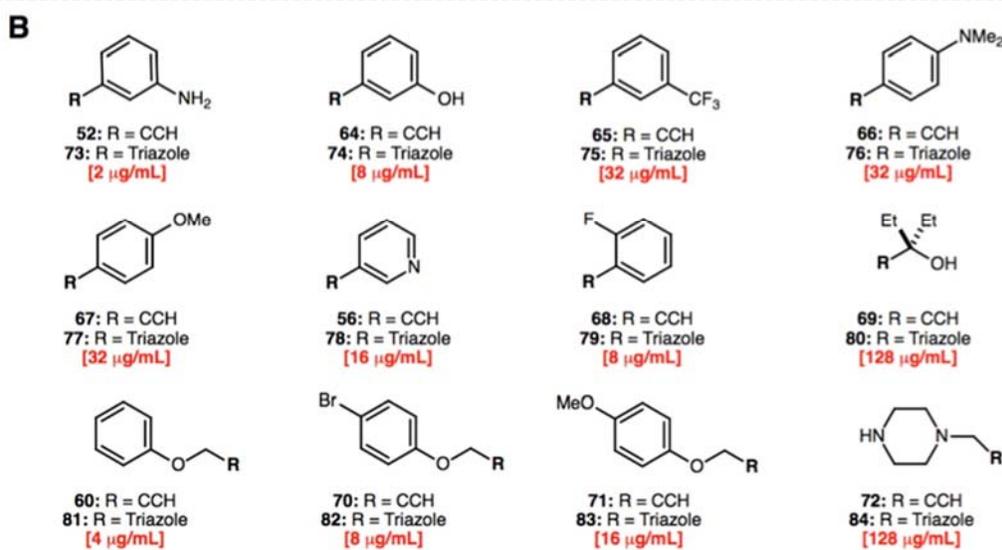
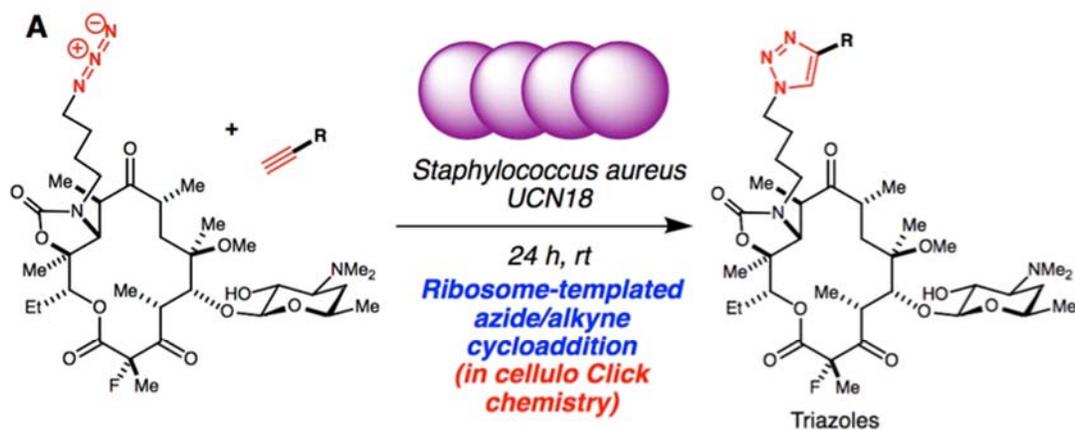
Trypanosoma brucei is the protozoan parasite that causes human African trypanosomiasis (HAT). HAT is a neglected tropical disease (NTD) that burdens millions of people in poor, rural communities of sub-Saharan Africa. In collaboration with the Tres Cantos OpenLab Foundation at GlaxoSmithKline, a high-throughput screen was performed using a library of 42,444 known human kinase inhibitors against *T. brucei*. Potent compounds were further screened in dose response and selectivity assays to narrow down the pool of potential hits. The remaining 797 compounds were analyzed for structural similarity and sorted into clusters. A series of 2,4-substituted azaindoles was chosen to advance into hit-to-lead optimization due to its high potency, fast-acting and cidal nature, and good *in vitro* pharmacokinetic properties. The lead hit from this cluster, NEU-1200, is highly cleared and does not show efficacy *in vivo*. Analogs of NEU-1200 have been synthesized and an understanding of the structure-activity and structure-property relationships has been established. Furthermore, using a parasite hopping approach we have found these compounds to be active against blood and liver stage *Plasmodium falciparum* infections. The improvements in metabolism and potency will be discussed, alongside the preliminary *P. falciparum* data.

MEDI 336

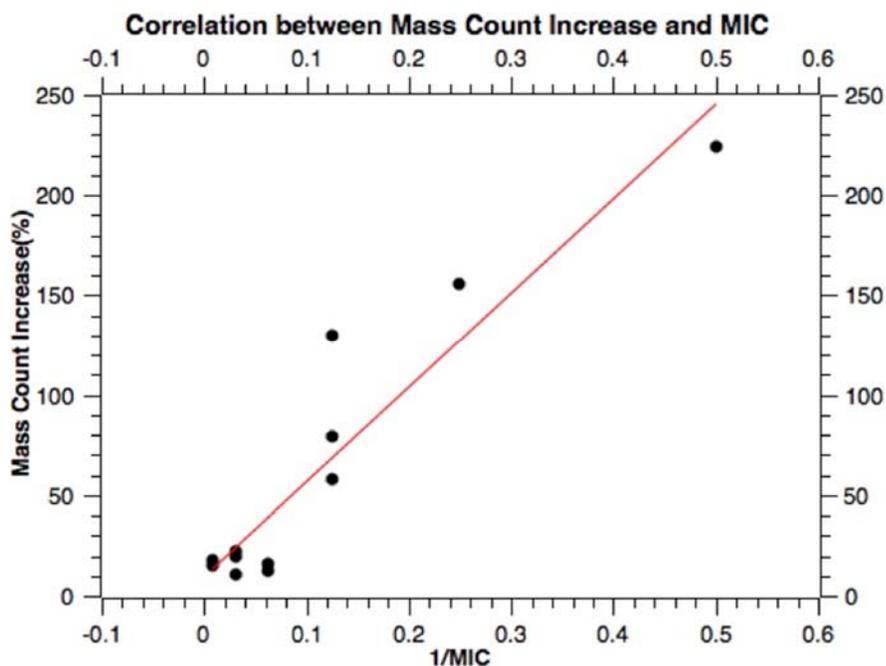
Click chemistry *in cellulo*: Bacterial cell as reaction vessel selectively synthesize macrolide antibiotics

Xiao Jin¹, jinxiao08@gmail.com, Samer Daher¹, Miseon Lee¹, Bettina Buttarò², Rodrigo B. Andrade¹. (1) Chemistry, Temple University, Philadelphia, Pennsylvania, United States (2) Microbiology and Immunology, Temple University, Philadelphia, Pennsylvania, United States

In situ click chemistry has been a practical and influential tool for fragment-based drug design over the past decades. The methodology relies on protein or peptide instead of Cu(I), to catalyze Huisgen [3+2] cycloaddition (click reaction). It is believed that a proper target will catalyze the reaction by binding and orientating azide and alkyne to an optimal position to form a triazole. Similarly, this method could be applicable in the whole cell of a living organism. In this regard, we used the bacterial cell as a reaction vessel, ribosome inside cell as a catalyst to template the click reaction between macrolide azide and various alkynes. The corresponding click products formed are antibiotics, which inhibit the bacterial growth. Therefore, the potency of each *in cellulo* click product can be visualized and assessed directly from a 96-well plate. In addition, the results from LC-MS showed a strong correlation between reciprocal MIC and mass count increase ($r^2=0.88$), which matches with *in situ* click theory. We believed this method could be expanded and implemented as a novel approach for antibiotic drug discovery.



(A) Overview of *in cellulo* click experiments. (B) Structures of alkyne fragments in the library and triazoles derived from *in situ* click experiments with MIC values in square brackets.



Correlation between MIC and mass count percent increase

MEDI 337

Structural requirements for the effective myostatin inhibition of myostatin prodomain–derived peptide derivatives

Kentaro Takayama, ktaka@toyaku.ac.jp, Tomo Asari, Mariko Saitoh, Yoshimi Roppongi, Akari Nakamura, Akihiro Taguchi, Atsuhiko Taniguchi, Yoshio Hayashi. Department of Medicinal Chemistry, Tokyo University of Pharmacy and Life Sciences, Hachioji, Tokyo, Japan

Endogenous mature myostatin negatively regulates skeletal muscle mass. Hence, myostatin is an attractive therapeutic target for muscle atrophic disorders including muscular dystrophy. In 2015, we successfully identified a myostatin inhibitory peptide **1** (23aa, WRQNTRYSRIEAIKIQILSKLRL-NH₂) from an N-terminal region of mouse myostatin prodomain.

Here, we investigated structural requirements for the effective inhibition of peptide **1** and its derivatives. All peptides were prepared by Fmoc-based solid-phase peptide synthesis, and their inhibitory activities were evaluated by the Smad-responsive luciferase reporter assay using HEK293 cells. We identified key residues (N-terminal Trp, rodent-specific Tyr, and all aliphatic residues) required for effective inhibition through Ala-scanning based on **1** with an *in vitro* IC₅₀ of 3.53 ± 0.25 μM and characterized a three-fold more potent inhibitor **2** bearing a 2-naphthyloxyacetyl group instead of N-terminal Trp. We further performed on **1**-based SAR studies focused on all aliphatic amino acids and center Ala residues, discovering a potent derivative **3** (XRQNTRYSRIEWIKIQILSKLRL-NH₂, where X is a 2-naphthyloxyacetyl

group) with an *in vitro* sub-micromolar IC₅₀ of 0.32 ± 0.05 μM. The peptide **3** significantly the *in vivo* weight (up to 20%) of tibialis and gastrocnemius muscles in mice. Recently, we successfully discovered shortened derivatives (16aa) with twice more potent inhibitory activity compared to **3**. These results would be valuable for mid-size peptide-based medicinal chemistry towards the treatment of muscle atrophic disorders.

MEDI 338

Design, synthesis and biological evaluation of a series of novel 2-benzamide-4-(6-oxy-N-methyl-1-naphthamide)-pyridine derivatives as potent fibroblast growth factor receptor (FGFR) inhibitors

Ao Zhang, aozhang@gmail.com. CAS Key Laboratory of Receptor Research, and the State Key Laboratory for Drug Research, Shanghai Institute of Materia Medica, Shanghai, China

The fibroblast growth factor receptors (FGFRs) are a family of highly conserved transmembrane tyrosine kinases (RTKs), which constitute four members (FGFR1-4). Over the past decades, several genomic alterations in the FGF-FGFR axis including activation mutations, gene amplifications, and chromosomal translocations have been identified in a broad spectrum of human tumors as oncogenic drivers, thus offering a new strategy to develop molecular targeted personalized medicine based on the FGFR activation status in cancer patients. On the other hand, it is known that tumor angiogenesis is augmented by cross-talking between FGF ligands, VEGFRs, and inflammatory mediators in tumor stroma, and the synergistic effects of FGFs and VEGFs in tumor angiogenesis have been observed in preclinical studies. Therefore, compared to the previous multi-target FGFR inhibitors with less potency against FGFR, development of selective FGFR/VEGFR2 dual inhibitors with equal or even greater potency against FGFR would be an appealing combination.

Starting from the phase II clinical FGFR inhibitor lincicatinib (**2**), we conducted a medicinal chemistry approach by opening the central quinoline skeleton coupled with a scaffold hopping process thus leading to a series of novel 2-benzamide-4-(6-oxy-N-methyl-1-naphthamide)-pyridine derivatives. Compound **25a** was identified to show selective and equally high potency against FGFR1/2 and VEGFR2 with IC₅₀ values less than 5.0 nM. Significant antiproliferative effects on both FGFR1/2 and VEGFR2 additive cancer cells were observed. In the SNU-16 xenograft model, compound **25a** showed tumor growth inhibition rates of 25.0% and 81.0% at doses of 10 mg/kg and 50 mg/kg, respectively, without obvious body weight loss. In view of the synergistic potential of FGFs and VEGFs in tumor angiogenesis observed in preclinical studies, the FGFR/VEGFR2 dual inhibitor **25a** may achieve better clinical benefits.

MEDI 339

Design and synthesis of vesicular monoamine transporter 2 (VMAT2) inhibitors

John P. Williams¹, jwilliams81018@gmail.com, **Nicole D. Harriott**¹, **Sam R. Hoare**^{2,4}, **Neil J. Ashweek**³, **Jammieson Pires**², **Jun Fan**². (1) Medicinal Chemistry, Neurocrine Biosciences, San Diego, California, United States (2) Pharmacology, Neurocrine Biosciences, San Diego, California, United States (4) Pharmeconomics, Owego, New York, United States

The vesicular monoamine transporters (VMATs) are the central mediators of biogenic amine uptake into presynaptic intracellular vesicles. Dopamine dysregulation is associated with a variety of movement disorders (tics, tremor, myoclonus, chorea, dystonia) and inhibition of VMAT2 would be a potential treatment by reducing the release of dopamine in the synapse. Several approaches were taken to identify inhibitors and the design and synthesis, as well as, the biological characterization of the potential inhibitors will be presented.

MEDI 340

Design and evaluation of immunoproteasome-selective inhibitors for the treatment of autoimmune diseases

Craig E. Stivala, stivala.craig@gene.com. Genentech, South San Francisco, California, United States

The pan-proteasome inhibitor bortezomib has demonstrated clinical efficacy in off label trials in SLE patients. The benefits of this study were accompanied by a number of adverse events that arise from inhibition of the constitutive proteasome. It was postulated that an immunoproteasome-selective inhibitor could sustain clinical efficacy and mitigate the safety liabilities associated with pan-proteasome inhibition. Herein, we disclose our efforts to identify beta 5i selective inhibitors using a ligand-based approach and the effect of these inhibitors in immune cells.

MEDI 341

Peptidomimetics that interact with Rpn-6 as new anti-cancer molecules

Wenzhi Tian, **Darci J. Trader**, dtrader@purdue.edu. Medicinal Chemistry, Purdue University, West Lafayette, Indiana, United States

Inhibition of the proteasome has revolutionized the way hematological cancers are treated, especially multiple myeloma. As with nearly all small molecule therapeutics, resistance does occur and patients require treatment options that have a different mechanism of action. Molecules that interact with subunits of the 19S regulatory particle (19S RP) rather than the active sites in the 20S core particle (20S CP) have been shown to be effective in a variety of cancer cell types. We have recently discovered a suite of peptidomimetics with binding constants in the low micromolar range that interact with Rpn-6 by using a thermal shift assay. Rpn-6 is the main protein responsible for keeping the 19S RP and the 20S CP associated in cells to allow ubiquitin-dependent

degradation to occur. These new molecules have also shown to be toxic in hematological cancers that require significant proteasome activity to survive. Studies are currently on going to determine where the peptidomimetics interact with Rpn-6 to help us rationally design better inhibitors.

MEDI 342

Evolution of efficient purine PI3Kdelta inhibitors with excellent selectivity and physicochemical properties

Joey L. Methot, joey_methot@merck.com, Hua Zhou, Meredith A. McGowan, Neville J. Anthony, Sam Kattar, Matthew Christopher, Yudith Garcia, Abdelghani Achab, Kathryn Lipford, Yongqi Deng, Michael Altman, Xavier Fradera, Charles Lesburg, Thierry Fischmann, Chaomin Li, Stephen Alves, Craig P. Chappell, Renu Jain, Peter Goldenblatt, Armetta Hill, Lynsey Shaffer, Dapeng Chen, Vince Tong, Robbie L. McLeod, Hyun-Hee Lee, Hongshi Yu, Alan Bass, Raymond A. Kemper, Timothy Guzi, Yves Ducharme, Benjamin Wesley Trotter, Sanjiv Shah, Jason Katz. Merck Research Laboratories, Boston, Massachusetts, United States

The role of the lipid kinase PI3Kdelta in B cell function, and its restricted expression in leukocytes, suggest a therapeutic benefit of PI3Kdelta inhibitors for the treatment of allergic, autoimmune and inflammatory diseases. For example, chronic lung inflammation in patients with COPD and severe asthma can lead to overactive signaling of the AKT pathway, which can in turn exacerbate respiratory infections. With the approval of Idelalisib, inhibition of PI3Kdelta is now an established treatment for certain hematological malignancies driven by the AKT pathway, and may be more broadly beneficial in oncology due to the impact on immune cell function in the tumor microenvironment. Our program to discover a potent and selective PI3Kdelta inhibitor involved the optimization of a 6-amino-8-aryl-purine series. Despite promising potency and pharmacokinetic profiles with early lead compounds, safety-related concerns with several non-kinase off-target activities necessitated a series overhaul. Using 3D overlays based on a PI3Kdelta-ligand crystal structure, structure-based redesign of the 6-position selectivity motif led to the discovery of new ligand efficient and highly selective aryl and heterocycloalkyl purines with improved off-target profiles. These purines have excellent physicochemical properties and potency in disease-relevant models, and are well-tolerated. Multipoint optimization, including MetID analyses, gave further improvements in both potency and half-life while maintaining selectivity, rendering PI3Kdelta inhibitors suitable for a low once-daily human dose.

MEDI 343

Discovery of tarantula venom-derived Nav1.7-inhibitory peptide with systemic block of histamine-induced pruritis

Bin Wu, binw@amgen.com. Amgen Inc., Thousand Oaks, California, United States

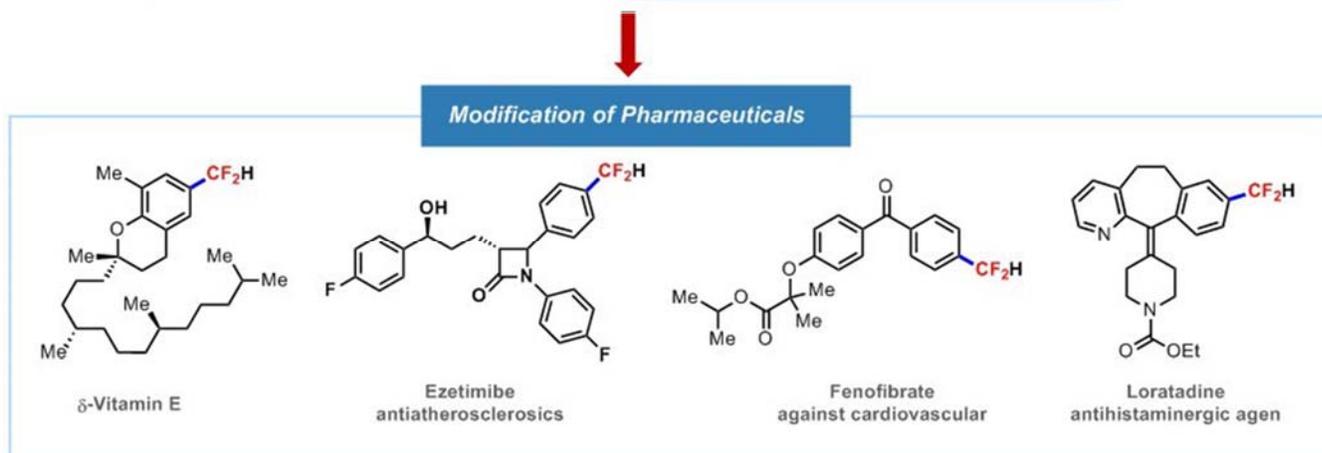
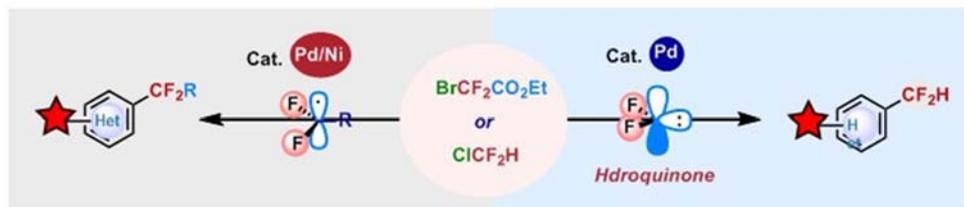
Nav1.7 is a voltage-gated sodium ion channel implicated by human genetic evidence as a therapeutic target for pain. This talk details our efforts in identifying Nav1.7 inhibitors using peptide hits from venom screens. We discovered novel disulfide-rich toxin peptides from tarantula venom containing an inhibitory cystine knot folded motif. Attribute-based positional scans of native residues followed by putative binding face SAR aided by rational molecular docking further improved the potency and selectivity of the native scaffold. Electrophysiology characterization and X-ray crystallography of the lead peptide and its activity in a Nav1.7-dependent in vivo behavior model will be described.

MEDI 344

Catalytic difluoroalkylations through controllable difluorocarbene and radical cross-couplings and their applications in medicinal chemistry

Xingang Zhang, xgzhang@mail.sioc.ac.cn. Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, China

The importance of fluorinated compounds in agrochemicals, pharmaceuticals, and materials science has triggered an explosion of research efforts in developing new and efficient methods to introduce fluorinated functional groups into organic molecules. Although considerable progresses have been achieved in the fluoroalkylation reactions over the past few years, most of them are focused on the use of nucleophilic fluorinated reagents (exg. TMSR_f, R_fML_n) and expensive electrophilic fluorinated reagents (exg. Umemoto reagent, Togni reagent). However, the use of low-cost and widely available fluoroalkyl halides (R_f-X, X = Br, Cl) as starting materials for fluoroalkylations catalyzed by transition-metal has been scarcely studied. Since 2012, we have developed several efficient strategies to catalytically access difluoroalkylated compounds from low-cost and readily available difluoroalkyl halides. Herein, we report the catalytic difluoroalkylations through controllable difluorocarbene and radical cross-couplings (Figure 1). These reactions provide facile routes for applications in medicinal chemistry.



MEDI 345

Developing selective SETD8 inhibitors for treating high-risk neuroblastoma

Anqi Ma¹, *a.m.andrewma@gmail.com*, **Veronica Veschi**², **Wenyu Yu**³, **Nicolas Babault**¹, **Fengling Li**³, **Kyle Butler**¹, **Junyi Wang**⁴, **Minkui Luo**⁴, **Masoud Vedadi**³, **Peter Brown**³, **Cheryl Arrowsmith**³, **Carol Thiele**², **Jian Jin**¹. (1) Icahn School of Medicine at Mount Sinai, New York, New York, United States (2) Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland, United States (3) University of Toronto, Toronto, Ontario, Canada (4) Memorial Sloan Kettering Cancer Center, New York, New York, United States

Neuroblastoma (NB) is an aggressive cancer of immature neuron cells in sympathetic nervous system. Estimated population of NB patients in US is around 20,000 and the patients are mainly in their infancy or childhood. For high-risk (HR) NB patients, the 5-year survival rate is only about 50% using current remedies. Disproportionately to its small patient population, NB accounts for 15% of all cancer related death in children. There is urgent and unmet need to develop effective therapies for NB patients. To understand the roles of epigenetic regulators in HR NB, we performed parallel screenings using siRNA library and small molecule libraries. SETD8 was identified as a druggable target in HR NB. Our selective SETD8 inhibitor, UNC0379, effectively inhibited proliferation of all 8 NB cell lines tested, including 4 high-risk *MYCN* wild type NB cells. UNC0379 demonstrated efficacy *ex vivo* in animal models, reduced tumor size and prolonged survival of mice. We also discovered that high SETD8 level was a poor prognosis of survival for NB patient. Histone methyltransferases (HMTs) belong to the epigenetic “writers” and are the enzymes that catalyze methylation of lysine or arginine residues on either histone tail or non-histone proteins. SETD8 is an HMT responsible for

monomethylation of histone H4 lysine 20 and monomethylation of tumor suppressor p53 at lysine 382 (K382), etc. Overexpression of SETD8 has been found in various types of cancer. Mechanistic studies demonstrated that the inhibitory effect on NB cells was due to the enzymatic inhibition of SETD8, which led to stabilization of p53 by reducing p53K382me1 level and re-activation of the p53 canonical pathway.

After discovery of the first generation covalent SETD8 inhibitor MS453 with IC₅₀ of 0.80 μM in biochemical assay, our medicinal chemistry effort has led to the discovery of MS4138, which is the most potent covalent inhibitor of SETD8 to date with high selectivity over other HMTs (unpublished results). Along with MS4138, we recently discovered other potent SETD8 covalent inhibitors with optimal pharmacokinetics (PK) properties, which made them suitable for *in vivo* animal studies. We are now actively pursuing the cellular and animal studies on these SETD8 covalent inhibitors.

Our studies have shown that SETD8 is an attractive and novel target for treating HR NB. The chemical probes that inhibit SETD8 enzymatic activity are useful tools to help us understand HR NB and develop effective therapy.

MEDI 346

Development of chemical probes for the TRIM33 bromodomain

Larissa See, larissa.see@chem.ox.ac.uk, Amy R. Scolah, Joseph P. Bluck, Jessica K. Reynolds, Angelina R. Sekirnik (née Measures), Stuart J. Conway. Department of Chemistry, University of Oxford, Oxford, United Kingdom

Epigenetic information is encoded in a wide range of histone modifications, which gives rise to the “histone code” and brings an additional level of complexity to the control of gene expression. The proteins involved include “writers”, “erasers”, and “readers”, which install, remove and recognise histone modifications, respectively. Given the implication of epigenetics in diseases, including cancer, epigenetic regulation presents opportunities for the development of novel therapeutics. Understanding the roles of proteins involved in epigenetic regulation is, therefore, important.

TRIM33 is a transcription regulator with E3 ubiquitin ligase activity and has been associated with leukaemia and DNA damage response pathways. It contains a tandem PHD finger-bromodomain cassette, which recognise methylated and acetylated lysine residues on histone proteins, respectively. This project aims to develop ligands for the TRIM33 bromodomain, which can be used as chemical probes to further validate the role of TRIM33.

Initial screening identified a hit TRIM33 bromodomain ligand that has since been validated and used as the starting point for further development. A combination of biological assay techniques and computational studies have been used to guide the investigation of the acetyl-lysine-binding pocket. Iterations of synthesis and testing have led to the development of a binder with an IC₅₀ of 2 μM. Ongoing work is focused on synthesising analogues and further exploring the structure-activity relationships (SAR) around the benzimidazolone core.

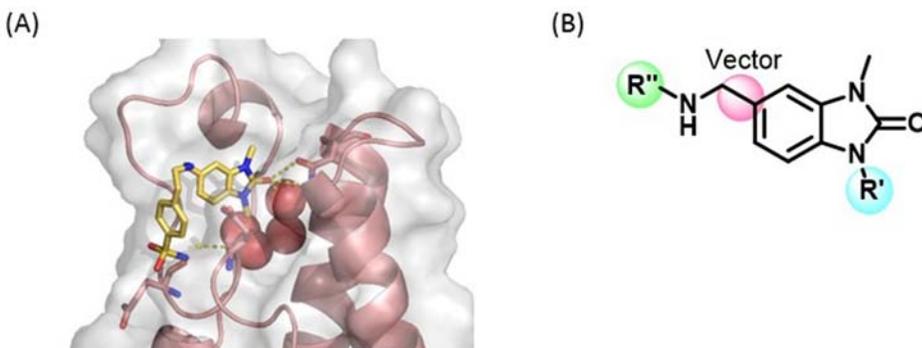


Figure 1. (A) X-ray crystal structure of the TRIM33 bromodomain; (B) Regions of SAR study.

MEDI 347

Synthesis and anti-bacterial activities of derivatives of 2-aminoimidazoles

Reem Alshehry¹, ralshehry@umassd.edu, **Sivappa Rasapalli**². (1) Chemistry, University of Massachusetts- Dartmouth, New Bedford, Massachusetts, United States (2) University of Massachusetts Dartmouth, North Dartmouth, Massachusetts, United States

We have previously developed acyl imidazoles as ant-biofilm inhibitors. In the lead - optimization efforts, we have been involved in the synthesis and screening of hydrazones and oximes of the acylimidazoles and their cyclizations into novel heterocyclic isosters. Synthesis and anti-bacterial screening studies of the library would be presented.

MEDI 348

Hypoxia-activated prodrugs of the KDAC inhibitor panobinostat

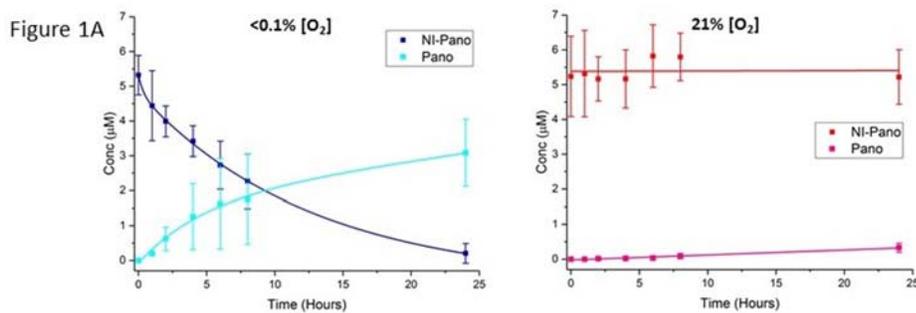
Ewen D. Calder², ewen.calder@chem.ox.ac.uk, **Ishna N. Mistry**¹, **Ester M. Hammond**¹, **Stuart J. Conway**². (1) Department of Oncology, University of Oxford, Oxford, United Kingdom (2) Department of Chemistry, University of Oxford, Oxford, United Kingdom

Hypoxia (conditions of low oxygen) is a common feature of solid tumours and is associated with a more aggressive phenotype and resistance to all modes of cancer therapy. A principle biological response to hypoxia is the stabilisation of hypoxia inducible factor (HIF). HIF-mediated transcription of target genes drives cellular processes linked to metastasis, invasion and angiogenesis, and leads to poor patient prognosis. Lysine deacetylases (KDACs) are a clinically-validated target in cancer treatment. Currently, there are four FDA-approved KDAC inhibitors (KDACi) for the treatment of hematologic malignancies. KDACi affect the stability of HIF and could be efficacious in the treatment of hypoxic tumours. A limitation of KDACi is their lack of tissue specificity, combined with the possibility of broad epigenetic reprogramming, this

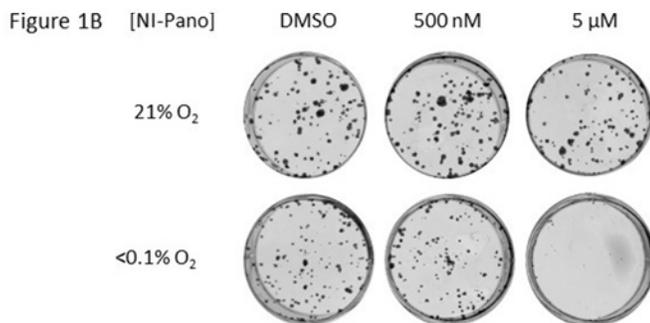
has the potential to cause unwanted off-target effects, and a smaller therapeutic window.

Here, we report the development of a Hypoxia-Activated Prodrug (HAP) derivative of the FDA-approved KDACi, Panobinostat. This approach will increase the therapeutic window and allow new insight into both the role of KDACs in the hypoxic tumour environment and their interactions with the HIF transcription pathway.

The synthesis of four HAP analogues of Panobinostat has been completed. These HAPs have been tested in a bioreduction assay to investigate the rate of release of the KDACi in normoxia and hypoxia (Fig 1A). The most effective HAP releases its cargo in an oxygen concentration-dependent manner in a bioreduction assay and a cellular setting. In colony-survival assays the HAP (5 μM) causes death of an oesophageal cancer cell line (OE21) in a hypoxic environment, while not affecting the same cells at 21% O_2 (Fig 1B). Studies on the cellular stability and rate of release *in vitro* have also been performed. Work is currently progressing toward the use of this compound in mouse xenograft models.



The HAP selectively releases Panobinostat under conditions of Hypoxia.



This translates to an oxygen concentration dependent reduction in cell viability in a colony survival assay.

MEDI 349

Development of a covalent proteasome inhibitor and kinetic analysis of its inhibitory mechanism

Shun Kitahata, *kita1214@eis.hokudai.ac.jp*, Fumika Yakushiji, Satoshi Ichikawa. Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Hokkaido, Japan

Covalent inhibitors are compounds that form a covalent link with a functional group of the target enzyme or protein. Because the reactive functional group of the inhibitors may react with different enzymes and proteins, resulting in dangerous off-target effects, they have rarely been considered as starting points in molecularly targeted drug discovery programs. However, covalent inhibitors have recently been developed as targeted covalent drugs such as afatinib, neratinib, ibuprofen, etc., by gaining selectivity for the protein.

The process to form a covalent complex involves several steps. In the first step, a covalent inhibitor associates with its target protein *via* non-covalent interactions to form an inhibitor-protein complex, defined by the binding affinity K_i . A chemical reaction then takes place between the inhibitor and the protein to form a covalent complex, defined by the reaction rate k_2 . Structure-based drug design using coordinates of a complex structure of a ligand and protein is a valuable approach, which allows us to rationally design inhibitors. However, this method is not always useful for designing covalent inhibitors because an X-ray crystal structure of covalent inhibitor/protein complexes is the reaction product and does not always reflect the association state. Therefore, detailed analysis of each step is necessary in the rational design of covalent inhibitors. The naturally occurring syringolin A irreversibly inhibits proteasome by an oxa-Michael addition of the hydroxy group of the *N*-terminal threonine residue on the $\beta 5$ subunit to the α , β -unsaturated carboxamide moiety embedded in the macrolactam. We performed a systematic structure activity relationship (SAR) study and kinetic analysis of a series of syringolin analogues consisting of macrocycles with different ring sizes. Based on the obtained information, we developed a novel potent proteasome inhibitor. Details of the synthesis and its kinetic analysis of the analogues will be presented.

MEDI 350

Synthesis and evaluation for antibacterial and antibiofilm activities of 2-aminoimidazole derivatives

Sivappa Rasapalli², **Vamshi Krishna Reddy Sammeta**¹, *sammetavamshikrishna@gmail.com*, Zach Murphy³, Sarah Parker¹. (1) Chemistry and Biochemistry, University Of Massachusetts Dartmouth, Newbedford, Massachusetts, United States (2) University of Massachusetts Dartmouth, North Dartmouth, Massachusetts, United States (3) Chemistry and Biochemistry, UMassD, Dartmouth, Massachusetts, United States

Inhibition of biofilm formation is one of the effective ways to combat the multidrug resistance. Marine natural products like Oroidin family containing 2-Aminoimidazole moiety has been shown to exhibit antibiofilm and antibacterial activity. In our research we have developed synthetic analogues of 2-aminoimidazole through formamidine chemistry. These molecules were further modified with different tails to evaluate

whether they can enhance the antibiofilm activity. The molecule with best inhibition activities will be dimerized to check whether dimerization has a role in increasing the activity. SAR of the synthesized analogues will be presented.

MEDI 351

Development of BCL6 protein-protein interaction inhibitors using a fragment-based approach

Brian Linhares^{1,3}, linhares@umich.edu, **Huimin Cheng**², **Wenbo Yu**², **Mariano G. Cardenas**⁴, **Yong Ai**², **Wenjuan Jiang**^{2,5}, **Ari Melnick**⁴, **Alexander D. MacKerell**^{5,2}, **Fengtian Xue**², **Tomasz Cierpicki**^{1,3}. (1) Pathology, University of Michigan, Ann Arbor, Michigan, United States (2) Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, Baltimore, Maryland, United States (3) Biophysics Program, University of Michigan, Ann Arbor, Michigan, United States (4) Department of Hematology & Medical Oncology, Weill Cornell Medical College, New York, New York, United States (5) Computer-Aided Drug Design Center, University of Maryland School of Pharmacy, Baltimore, Maryland, United States

B-Cell Lymphoma protein 6 (BCL6) regulates affinity antibody maturation and governs B-Cell development, via mediation of transcriptional repression complex formation through the BCL6 BTB domain (BCL6^{BTB}). Constitutively overexpressed BCL6 is an oncogenic driver in numerous subtypes of Diffuse Large B-Cell Lymphomas (DLBCLs), and has been demonstrated to recapitulate lymphomagenesis in mouse models consistent with the malignant phenotype of BCL6-dependent DLBCLs. BCL6 has thus been promoted as a target for therapeutic intervention in treatment of BCL6-dependent DLBCLs. Here we report the identification and optimization of a novel class of inhibitors of BCL6-co-repressor Protein-Protein Interactions (PPIs). By screening an in-house library of fragment-like, small molecules by protein-observed solution-NMR spectroscopy, we found a hit, 7CC5, which binds BCL6^{BTB} with low-mM affinity. As a ligand of BCL6^{BTB}, 7CC5 represents a novel scaffold. We determined the crystal structure of BCL6^{BTB} in complex with 7CC5 and revealed that this compound binds to a well-defined pocket of BCL6^{BTB} that is occupied in BCL6-co-repressor PPIs. The binding mode of 7CC5 suggested that the fragment could be extended to an adjacent pocket that is a hot spot in BCL6 co-repressor PPIs. Subsequently, we performed extensive medicinal chemistry optimization of 7CC5. To rank binding of various series of 7CC5 analogues, we quantified chemical shift perturbations of selected amide proton resonances on ¹H-¹⁵N HSQC spectra of BCL6^{BTB} in the presence of individual compounds. This guided design and development of more potent BCL6^{BTB} ligands. Our efforts yielded small-molecule inhibitors that demonstrate mid- μ M affinity for BCL6, and we determined crystal structures of the most potent compounds in complex with BCL6^{BTB}. These inhibitors represent an improvement in potency from the fragment hit by two orders of magnitude. As a novel inhibitor scaffold, this class of compounds may hold potential as a chemical probe, and may aid in further inhibitor development.

MEDI 352

Synthesis and ^{19}F NMR-based screening of a library of diverse and three-dimensional fluorinated fragments

Nikolaj Andersen, *nisten@kemi.dtu.dk*, Mads Clausen. Technical University of Denmark, Kgs Lyngby, Denmark

Fluorine ligand-based NMR spectroscopy has emerged as a powerful screening tool for fragment-based drug discovery (FBDD). Compared to ^1H NMR-based methods, ^{19}F NMR screening offers several key advantages including increased sensitivity and simplicity. When using ^1H NMR, screening cocktails are typically limited to five compounds due to spectral overlap of signals and interference from solvents, buffers, or detergents. However, with fluorine the spectral range is much broader (~ 200 ppm) and as fluorinated molecules normally give rise to only one signal ^{19}F NMR-based screening facilitates screening cocktails of up to 40 compounds. Unfortunately, the use of ^{19}F NMR for screening in FBDD is currently limited by the limited availability and relatively low diversity of commercially available fluorinated fragments.

Thus, to further investigate and contribute to the usefulness of ^{19}F NMR-based screening in FBDD and at the same time developing new fragment scaffolds, we set out to synthesize a small and diverse library of fluorinated fragments. Based on a reagent-based diversity oriented synthetic strategy, we have constructed a highly three-dimensional library starting from similar and commercially available trifluoromethylated starting materials (Figure 1). Together with already existing fluorinated fragments, the fragments are screened against multiple targets using ^{19}F NMR-based methods. We here present the synthesis of the fluorinated fragment library and the latest results from ^{19}F NMR screening assays.

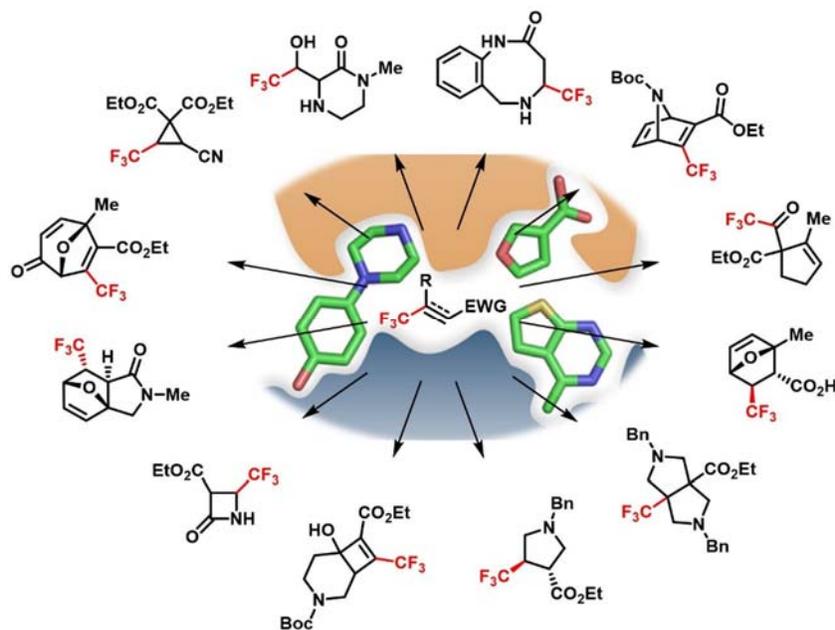


Figure 1: Scaffold overview of the fluorinated fragment library synthesized from reagent-based diversity oriented synthesis starting from similar β -trifluoromethyl α,β -unsaturated compounds. Scaffolds are then further rearranged and/or decorated to increase library diversity.

MEDI 353

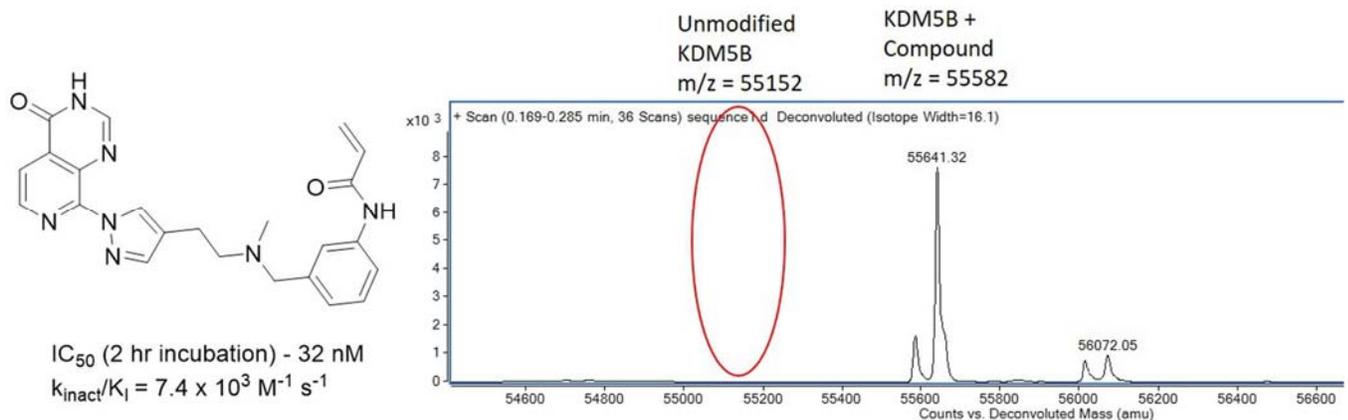
Development of 8-pyridopyrimidinone-based covalent inhibitors of KDM5B

Miranda Wright¹, miranda.wright@st-hildas.ox.ac.uk, **Saleta Vazquez-Rodriguez**², **Paul Brennan**³, **Akane Kawamura**¹. (1) University of Oxford, Oxford, United Kingdom (2) Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom (3) TDI NDMRB, University of Oxford, Oxford, United Kingdom

Lysine demethylases (KDMs) catalyse the removal of methyl modifications on histone tails which regulates gene expression. Over twenty KDMs have been discovered and linked to tumour growth and stem cell differentiation. JmjC-domain containing KDMs require 2-oxoglutarate (2-OG) and molecular oxygen as cosubstrates and Fe(II) as a cofactor to function. Current inhibitors of JmjC-KDMs are generally limited to metal-chelating scaffolds which inhibit enzymatic activity through chelation to the active site Fe(II) and compete with 2-OG. The main challenges have been achieving cellular activity and selectivity between KDMs due to similarity in their active sites.

The aim of this project was to design and synthesise irreversible inhibitors of KDM5B to reduce competition with cellular 2-OG. Cysteine 480 in KDM5B is not conserved across KDM5 subfamily and across other KDM families so targeting this cysteine could result in a selective covalent inhibitor. The designed compounds incorporated a core scaffold, 8-pyridopyrimidinone and different cysteine-selective electrophiles such as acrylamide and chloroacetamide in order to fine-tune the covalent reactivity.

The synthesised inhibitors were confirmed to bind covalently to KDM5B and were very potent against KDM5B (<50 nM) in biochemical assays. Clickable analogues of the most potent inhibitor were also synthesised for use in pull-down assays to determine target engagement of the compounds with KDM5B in the cell.



Covalent inhibitor of KDM5B and MS showing covalent binding

MEDI 354

Structure-based design of extracellular FLT3 inhibitors: First-in-class preclinical candidates for the treatment of neuropathic pain

Cyril Rivat³, Chamroen Sar³, Jean-Philippe LEYRIS^{3,2}, Corinne Sonrier^{3,2}, Yann Philipson¹, Martine Schmitt¹, Pierre Sokoloff², Jean Valmier³, **Didier Rognan¹**, rognan@unistra.fr. (1) Laboratoire d'Innovation Thérapeutique - UMR7200, CNRS, Illkirch, France (2) BIODOL Therapeutics, Montpellier, France (3) Institut des Neurosciences, Montpellier, France

The Fms-like tyrosine kinase 3 receptor (FLT3) has long been known to be expressed in hematopoietic stem cells and progenitor cells, to play a role in cell proliferation, differentiation and survival of lymphocytes. However, FLT3 and its cytokine ligand FL are also expressed in or at the vicinity of primary sensory neurons in dorsal root ganglia (DRG). Upon nerve lesion, activation of FLT3 expressed at the surface of primary sensory neurons potentiates rapidly-acting ion channels (e.g. TRP channels) and induces long-term modifications in DRG, to produce hyperexcitability of sensory neurons and NP symptoms. Secondly, stimulated FLT3 promotes activation of microglial cells in the dorsal spinal cord (DSC) via cytokines, such as CSF1, to mediate central sensitization and pain chronification. The role of FLT3 in NP could be demonstrated across various models of NP, using various means to inhibit FLT3 function: gene deletion, acute gene downregulation by siRNA, neuron-delivered shRNA, demonstrating FLT3 as a novel therapeutic target for NP (Rivat et al. Nat Commun, 2018).

To identify highly selective FLT3 inhibitors, we targeted the unique extracellular domain to which the FL ligand binds. A first *in silico* screening campaign led to the discovery of BDT0001 as the first extracellular FLT3 inhibitor. Beside allosterically inhibiting the binding of extracellular FL to the FLT3 receptor, the compound prevents FL-induced FLT3 phosphorylation. Importantly, BDT001 selectively blocks FL-mediated TRPV1 sensitization to capsaicin in DRG neurons, inhibits FL-induced mechanical hyperalgesia in mice, and completely reverses neuropathic pain for two days after a single 5 mg/kg

intraperitoneal administration. BDT001 displays a unique pharmacological profile that surpasses that of standards of care, such as pregabalin.

MEDI 355

Wnt signaling pathway inhibitors for non-alcoholic fatty liver diseases (NAFLD)

Fengtian Xue¹, *fengtian.x@gmail.com*, **Yong Ai**¹, **Yingjun Li**¹, **Yan Shu**², **Wei Yang**¹. (1) *University of Maryland, Baltimore, Maryland, United States* (2) *Pharmaceutical Sciences, University of Maryland, Baltimore, Maryland, United States*

Dysregulation of the Wnt/ β -catenin signaling pathway pathway has been well recognized as a pathogenic mechanism for an array of diseases including NAFLD. Using pyrvinium as a template, we have designed, synthesized and tested a novel class of triazole-based new inhibitors, of which, **YW1128** inhibits Wnt/ β -catenin signaling activity with significantly improved potency (IC₅₀ 6.8 nM). Moreover, this new inhibitor indicated promising efficacy *in vitro* and *in vivo*, is nontoxic in mice. Our preliminary results have also indicated a connection between downregulation of the Wnt/ β -catenin pathway and the activation of AMP-activated protein kinase (AMPK). The mechanism of action by new inhibitors was determined *in vitro* and *in vivo*. Moreover, we have performed the proteomic strategy thermos protein profiling (TPP) to identify the protein target of selected new inhibitors.

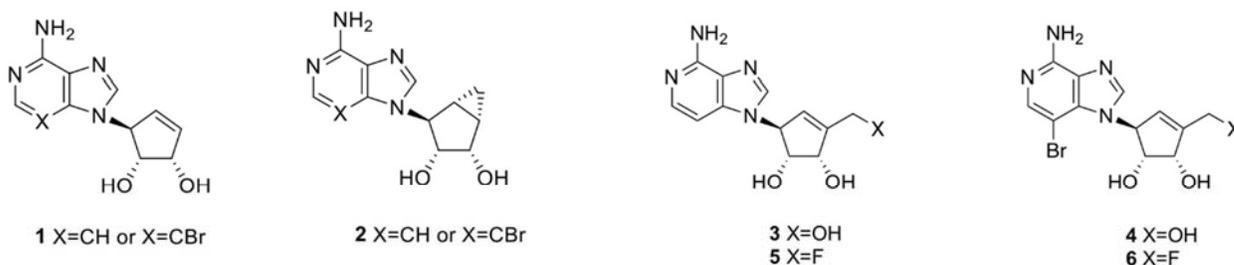
MEDI 356

Study of L-neplanocin analogues: Synthesis and antiviral property

Qi Chen, *qi.chen@sru.edu*, **Nichole Miller**, **Alexander Smith**, **Gabriel Imhoff**. *Chemistry Department, Slippery Rock University of Pennsylvania, Slippery Rock, Pennsylvania, United States*

Previous studies have shown that L- like carbocyclic nucleosides, such as L- isoneplanocin analogues, possess broad spectrum antiviral activities, including Ebola, norovirus, vaccinia, HBV, HCMV, measles and Dengue and further studies have also suggested their antiviral property may be caused by inhibiting viral replication through an unknown mechanism different with their naturally occurring D-counterparts. It is noteworthy that replacing the nitrogen atom with a CH or a CBr group at the N-3 position has significant impacts on their biological properties. Our recent study has also found that L-like, N-3 modified C-4' truncated (DHODA) (**1**) and 4',6'-methanocarba (MC) (**2**) Neplanocin analogues are potent antiviral agents and especially effective against norovirus by adopting different conformations. Following the lead, we have designed and synthesized L-3-deazaneplanocin (**3**) and L-3-deaza-3-bromoneplanocin (**4**) with newly developed synthetic method. Since the hydroxyl group on the C-5' plays an essential role for many viral RNA polymerase inhibitors, 5'-F analogues (**5**, **6**) are important in this work to further explore the mechanism of antiviral activity for L-

neplanocin analogues. Recent antiviral activities data are also included and more viral activities are forthcoming.



3 Tacaribe virus $EC_{50}=1.3 \mu\text{g/mL}$;
Pichinde virus $EC_{50}=0.9 \mu\text{g/mL}$.

MEDI 357

Design, synthesis and biological evaluation of D3 antagonists with an aryl linker motif

Pierpaolo Cordone^{1,2}, *pcordone29@gmail.com*, **Bryant Muniz**¹, **Emilio Gallicchio**^{3,2}, **Rajat K. Pal**^{3,2}, **Thomas P. Kurtzman**⁴, **Wayne W. Harding**^{1,2}. (1) Chemistry, Hunter College, Brooklyn, New York, United States (2) The Graduate Center, New York, New York, United States (3) Chemistry, Brooklyn College, Brooklyn, New York, United States (4) Chemistry, Lehman College, CUNY, New York, New York, United States

The dopamine D3 receptor (D3R) is involved in the craving response in drug addictions. Molecules which block D3R (D3R antagonists) are very valuable as potential therapeutics to treat substance abuse disorders. Poor pharmacokinetic properties and sub-optimal selectivity especially versus the closely related D2 receptor (D2R), have limited the clinical availability and utility of D3 antagonists. We have employed a progressive combination of *in silico* docking, synthesis and bioassays towards the discovery of novel, selective and potent D3R antagonists. The ligand design was based on a classical D3R pharmacophore comprising an amine-containing “head” moiety, a hydrocarbon linker “body” and an arylamide “tail” region. A tetrahydroisoquinoline motif representing the “head” portion was retained in all the analogues, with variations in an aryl linker moiety and the arylamide “tail” region. After docking at the D3R crystal structure, the top ranked analogues (based on Glide scores) were synthesized. Thereafter, the synthesized molecules were subjected to binding assays at dopamine receptors (D1R-D5R) *in vitro*. A number of selective D3R antagonists with moderate affinity were identified and this has provided important clues for future optimization. Results on our *in silico* studies as well as the synthesis and biological evaluation of the analogues will be presented.

MEDI 358

4-Fluoropiperidine amides as fatty acid synthase inhibitors

Craig A. Zifcsak, *craig.zifcsak@tevapharm.com*, Nadine C. Becknell, Arup K. Ghose, Thelma S. Angeles, Mark A. Ator, Lisa D. Aimone, Sheila J. Miknyoczki, Pawel Dobrzanski, Bruce A. Ruggeri, Robert L. Hudkins. Specialty Research & Development, Teva Branded Pharmaceutical Products R&D, Inc., West Chester, Pennsylvania, United States

Fatty acid synthase (FASN) catalyzes the production of the fatty acid palmitate from malonyl CoA and acetyl CoA. This complex cycle of condensation reactions is conducted on a single multifunctional polypeptide chain that catalyzes 7 distinct transformations. High FASN overexpression in premalignant, invasive and metastatic lesions is associated with poor prognosis and disease recurrence in a variety of solid human tumors. Due to the dependence of cancer cells on the lipid products formed from palmitate, FASN is an attractive target for development of antitumor drugs with potentially favorable therapeutic indices across multiple tumor types. Reported here is the optimization of a series of 4-benzyl-4-fluoropiperidine amide ketoreductase (KR)-domain FASN inhibitors. A member of this series, 1-[4-fluoro-4-[[4-(8-methyl-7-quinolyl)phenyl]methyl]-1-piperidyl]propan-1-one, demonstrated excellent potency, pharmacokinetics and robust oral in vivo antitumor efficacy and tolerability in human xenograft models.

MEDI 359

Optimization of aryl sulfonamides as CNS penetrant, isoform-selective Nav1.6 inhibitors with efficacy in mouse models of epilepsy

Kristen Burford¹, *kburford@xenon-pharma.com*, Thilo Focken¹, Jean-Christophe Andrez¹, Mike E. Grimwood¹, Alla Zenova¹, Matthew Taron¹, Wei Gong¹, Shannon Decker¹, Sultan Chowdhury¹, Noah Shuart¹, Parisa Tari¹, Rainbow Kwan¹, Luis Sojo¹, Robert J. Devita², Charles Cohen¹, JP Johnson¹, Steven S. Wesolowski¹, James R. Empfield¹, Christoph M. Dehnhardt¹. (1) Xenon Pharmaceuticals, Vancouver, British Columbia, Canada (2) RJD Medicinal Chemistry and Drug Discovery Consulting LLC, Westfield, New Jersey, United States

The development of alternative antiepileptic drugs is needed as many patients remain untreated or often suffer from undesired side effects of the currently available therapeutics. Unselective sodium channel blockers have long been used as anticonvulsants; however, isoform selective inhibition of Nav1.6, while sparing Nav1.1, may offer a more effective and better tolerated approach to treatment. This presentation will describe the design, synthesis, and biological activity of a series of CNS penetrant aryl sulfonamides that inhibit Nav1.6 with isoform selectivity. Optimization focused on improving Nav1.6 potency, isoform selectivity over Nav1.1, and stability in human liver microsomes, while reducing P-gp efflux in order to increase CNS penetrance. These

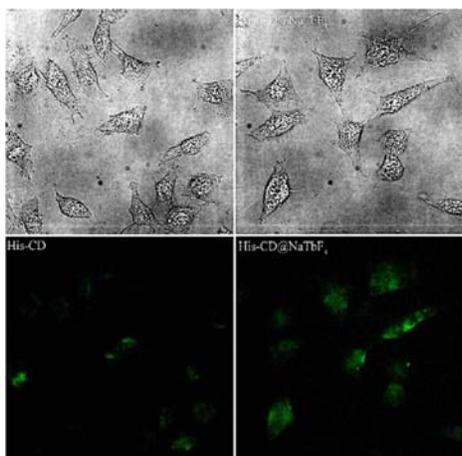
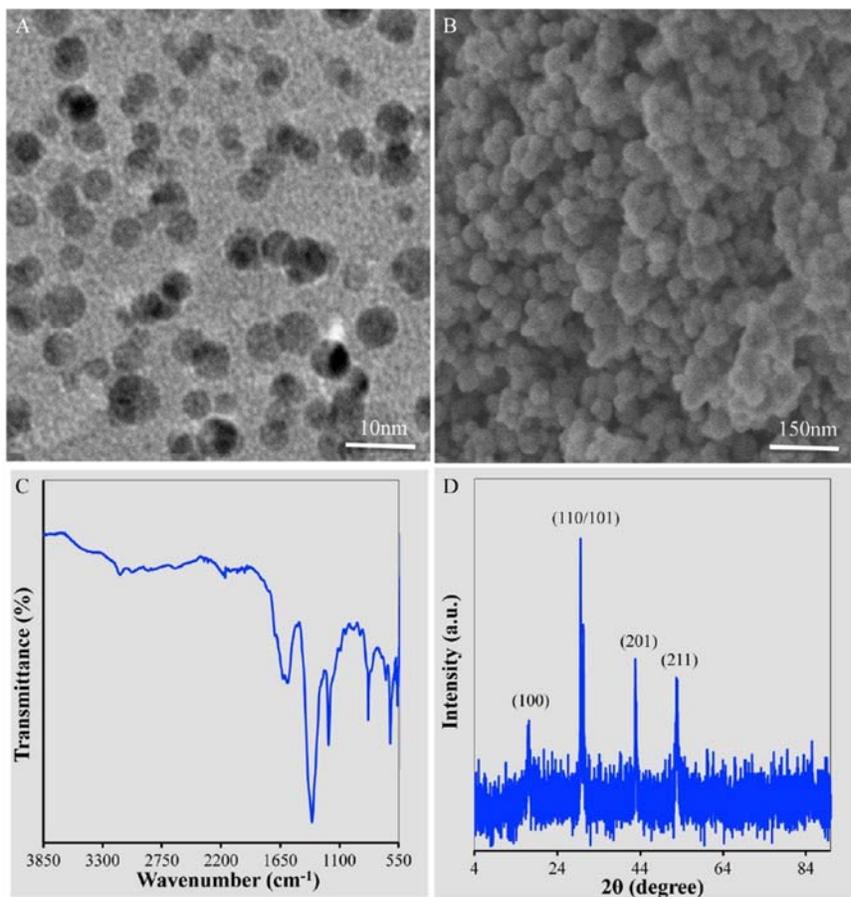
efforts ultimately led to the development of a brain penetrant tool compound that reduced seizure activity in a dose-dependent manner in an epilepsy model in mice, establishing an important proof-of-concept that state-dependent, selective Nav1.6 inhibitors provide efficacy in an *in vivo* model.

MEDI 360

Carbon dot@NaTbF₄ for imaging and *in vivo* drug delivery

Ruiyi Li, jessicamegy@qq.com. Jiangnan University, Wuxi, Jiangsu, China

Carbon dots and rare earth fluorides are important and different characteristic luminescent materials. Their combination may lead to unusual properties and related applications. A carbon dot@NaTbF₄ composite was synthesized by hydrothermal reaction using a histidine functionalized carbon dots as the stabilizer. The study shows that the NaTbF₄ is a hexagonal crystal, the carbon dots are covalently coated on the surface of NaTbF₄ crystals and the particle size is only in the range of 4-6 nm. The small size and the rich of hydrophilic groups make the composite is easy to disperse in water. The formed dispersion offers an excellent stability. The absorption spectra of NaTbF₄ and the emission spectra of carbon point are greatly overlapped. The distance between His-CD and NaTbF₄ is very short. Thus, their combination induces a highly effective fluorescence resonance energy transfer. Compared with single carbon dots, the increase in the fluorescence intensity for carbon dot@NaTbF₄ is more than 7 times. The composite material has been successfully applied to the Hela cell imaging. This material was also applied as the nano carrier and delivered the DOX into the cells after endocytosis. Our results figure out that this composite material is a considerable promise for Imaging and *in vivo* drug delivery.



MEDI 361

Synthesis and evaluation of ^{18}F -radiolabeled anticancer agents as tracers of nucleic acid metabolism

Alice K. King, alice.king1005@googlemail.com, Andreas Doepner, David Turton, Daniela M. Ciobota, Gabriela Kramer-Marek, Graham Smith. Radiotherapy and Imaging, Institute of Cancer Research, London, United Kingdom

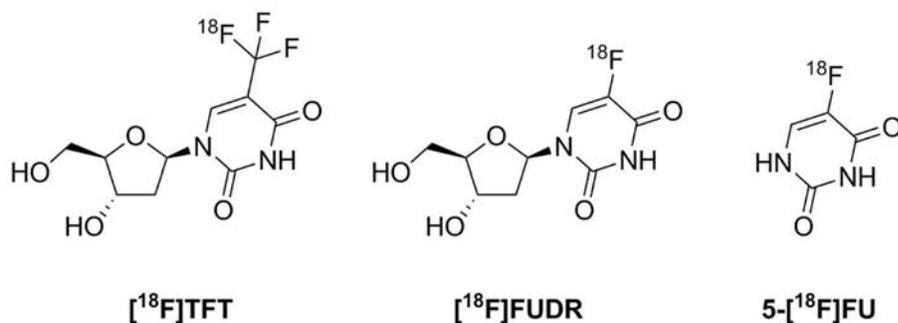
Trifluridine (TFT), floxuridine (FUDR) and 5-fluorouracil (5-FU) are nucleic acid-derived anticancer agents that disrupt DNA synthesis pathways. However, their effectiveness is difficult to predict due to inter-individual differences in nucleic acid metabolism. The intrinsic presence of fluorine in these compounds creates an opportunity to probe their pharmacokinetic properties using positron emission tomography (PET).

Using an automated ^{18}F -trifluoromethylation procedure, we have developed the first radiosynthesis of [^{18}F]TFT. Furthermore, we present an alternative route to non-radioactive TFT from an iodinated nucleoside precursor. Biodistribution and PET-imaging data were obtained using a HCT116 xenograft model in mice, and the tumors were clearly identifiable 60 minutes post-injection. *In vivo* metabolite analysis of selected tissues revealed the presence of parent [^{18}F]TFT, together with known [^{18}F]TFT metabolites.

Our preliminary data also suggest that uracil and uridine precursors that are iodinated at the 5-position can be ^{18}F -fluorinated using [^{18}F]fluoride; subsequently we have used this method to radiolabel [^{18}F]FUDR and 5- ^{18}F]FU analogues. An investigation is underway to elucidate the reaction mechanism.

In a clinical setting, [^{18}F]TFT, [^{18}F]FUDR and 5- ^{18}F]FU may provide useful predictions of treatment response for the development of personalized treatment plans. We present improved methods to access these radiotracers, enabling more thorough research into their role as PET imaging agents.

Figure 1. Radiolabeled derivatives of TFT, FUDR and 5-FU.



MEDI 362

First asymmetric synthesis of dihydro-thieno-indol scaffold, the alkylation subunit of NMS-P528, a new highly promising agent for ADC generation

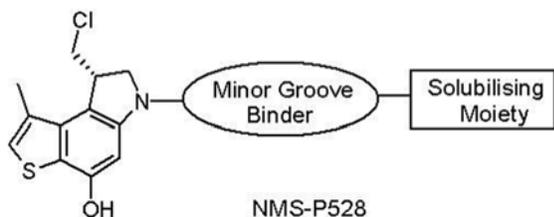
Paolo Orsini¹, paolo.orsini@nervianoms.com, Michele Caruso¹, Ilaria Candiani², Nicoletta Colombo¹, Matteo D'Anello¹, Riccardo Frigerio², Fabio Gasparri¹, Daniela Ramella², Barbara Valsasina¹, Daniele Donati¹. (1) Oncology, Nerviano Medical Sciences S.r.l., Nerviano (MI), Italy (2) NerPharMa S.r.l., Nerviano (MI), Italy

Traditional cancer chemotherapy widely used in clinic is often accompanied by systemic toxicity to the patient with narrow therapeutic windows. Approaches aimed at selectively delivering the drug to the site of action are of great relevance.

A wide spectrum of carriers can be used for targeting drugs and, among them, antibody-drug conjugates (ADCs) are increasingly employed in different oncology settings. At present there are more than sixty ADCs in clinical evaluation and more than 60% of the antibodies result to be conjugated to auristatin or maytansine, two well-known tubulin binding agents. New toxins with a different mechanism of action in cells, possibly acting also on not proliferating cells are therefore strongly needed.

Duocarmycins are DNA minor groove alkylating agents and several semisynthetic derivatives evaluated in early clinical trials resulted highly toxic. Their use as warheads for antibody conjugation besides their high cytotoxic potency show tendency to induce antibody aggregation once conjugated.

In this context we approached a new proprietary class of alkylating agents, the thienoindole derivatives, with the aim to obtain new and highly potent toxins with the proper physico-chemical profile suitable for the generation of non-aggregating ADCs. The synthesis of several derivatives for this novel chemical series led to the identification of potent cytotoxic compounds and, among them, NMS-P528 was selected for the physicochemical properties highly compatible with the development as antibody payloads. The desired compound was initially obtained as pure enantiomer after preparative chiral HPLC purification. Once defined the structure, extensive research studies have been completed for the design of a new and efficient stereoselective method allowing us the preparation of the desired compound on 100g scale. Herein we describe the selection process of NMS-P528 and compare the synthetic routes for the total synthesis of our lead drug compound, which is proposed as a licensing opportunity for conjugation with tumor-targeting antibodies.



MEDI 363

Design and synthesis of potent DNA alkylating indolino-benzodiazepine compounds (BIAs) linked with a DNA binding moiety for use in antibody-drug conjugates (ADCs)

Emily E. Reid, emily.reid@immunogen.com, **Katie E. Archer**, katie.archer@immunogen.com, Manami Shizuka, Molly A. McShea, Erin K. Maloney, Olga Ab, Leanne Lanieri, Alan Wilhelm, Jose F. Ponte, Nicholas C. Yoder, Ravi V. Chari, Michael L. Miller. Immunogen Inc, Waltham, Massachusetts, United States

A new class of DNA alkylating effector molecules (termed BIAs), in which an indolino-benzodiazepine (IGN) monomer subunit is connected to a bis-aryl moiety with affinity for the DNA binding pocket, have been designed and synthesized. Structure activity relationship (SAR) studies identified a series of BIAs that met our requirement of high *in vitro* potency for tumor-specific delivery in the form of ADCs. Potency was enhanced by modifying substituents on the bis-aryl moiety with increased binding affinity to DNA. Selected BIAs were further modified to incorporate functionalities that allow linkage to an antibody and ADCs were prepared.

MEDI 364

Imidazo[1,2-*b*]pyridazines as potent glycogen synthase kinase-3 β inhibitors for the potential treatment of Alzheimer's disease

*Richard A. Hartz*¹, richard.hartz@bms.com, *Vijay Ahuja*¹, *Prasanna Sivaprakasam*¹, *Catherine Burton*¹, *Hong Xiao*¹, *Carol Krause*¹, *Wendy Clarke*¹, *Kevin Kish*², *Hal Lewis*², *John E. Macor*¹, *Gene M. Dubowchik*¹. (1) Bristol-Myers Squibb, Wallingford, Connecticut, United States (2) Bristol-Myers Squibb, Princeton, New Jersey, United States

Glycogen synthase kinase-3 (GSK-3) is a proline-directed serine/threonine kinase whose activity has been implicated in a variety of diseases, including neurodegenerative disease as well as bipolar disorder, cancer, and diabetes. Evidence suggests that GSK-3 β may play a role in the production of abnormal hyperphosphorylated microtubule-associated protein tau, which is present in the neurofibrillary tangles that are the hallmark of Alzheimer's disease. Inhibitors of GSK-3 β appear to hold promise as disease modifying therapeutic agents for the treatment of Alzheimer's disease. A series of imidazo[1,2-*b*]pyridazine derivatives was identified as GSK-3 β inhibitors. Structure-activity relationship (SAR) studies led to the identification of a sub-nanomolar, brain penetrant GSK-3 β inhibitor that was effective at lowering levels of phosphorylated tau in a triple-transgenic mouse Alzheimer's disease model.

MEDI 365

Embrace the sulfonamide! The unusual pathway from the identification to the optimization of PERK inhibitors

Davide Carenzi, davide.carenzi@nervianoms.com, *Elena Casale*, *Marina Fasolini*, *Ilaria Motto*, *Italo Beria*, *Marco Silvagni*, *Claudia Perrera*, *Barbara Valsasina*, *Daniele Donati*, *Eduard R. Felder*, *Arturo Galvani*, *Antonella Isacchi*, *Maurizio Pulici*. Oncology, Nerviano Medical Sciences srl, Nerviano, Italy

The HTS campaign performed on our proprietary chemical collection in search for PERK inhibitors returned, among others, a series of N-(3-thiazolo[5,4-*b*]pyridin-2-yl-phenyl)-benzenesulfonamides. Subsequent expansion identified compound 1 as a lead (IC₅₀ = 0.27 μ M). In co-crystallization with PERK (Δ loop) kinase domain the compound

structure revealed that the pyridine ring establishes hydrogen bonding with the enzyme hinge region, the distal benzene ring occupies the kinase back pocket, and the sulfonamide group makes key interactions with the DFG sequence.

Incidentally, a weak cross reactivity vs. PERK was observed for a class of N-[3-(4-pyridin-4-yl-1H-pyrazol-3-yl)-phenyl]-benzenesulfonamides under development for a different kinase inhibition program. A focused effort in this class rapidly increased PERK inhibition, leading to compound 2 (IC₅₀ = 0.056 μM). We noticed that the common sulfonamide feature of the two series superimposes well in the PERK co-crystals, while the pyridine ring faces the kinase hinge backbone with an improved directionality in the second series. Further elaboration of this series did not significantly ameliorate the potency, while confirming the predominant role of the sulfonamide. We therefore opted for a permutation strategy of the hinge-binding moiety in the next stage of optimization. Probing a series of heterocyclic rings led to the identification of a novel prototype benzenesulfonamide class, currently under further exploration within the PERK inhibition program.

MEDI 366

***N*-(2,4-difluoro-3-((6-(2-fluoropyridin-3-yl)quinazolin-4-yl)amino)phenyl)propane-1-sulfonamide (DRF-0529) as a novel RAF kinase inhibitor**

Shao-Zheng Peng, szpeng@dcb.org.tw, *Chu-Bin Liao, Mann-Yan Kuo, Shih-Chieh Yen, Hung-Jyun Huang, Ju-Ying Yang, Yen-Hsi Liu, Sian-Yi Ciou. Institute of pharmaceuticals, Development center for biotechnology, New Taipei city, Taiwan*

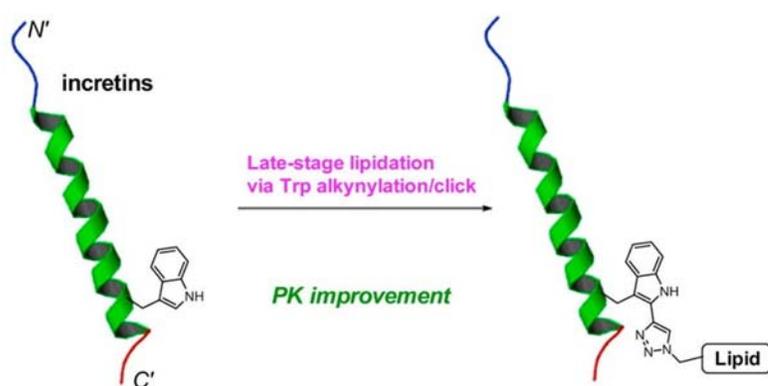
The oncogenic mutations of BRAF which occur most frequently in V600E, leading to constitutive activation of the MAPK signaling pathway, are common in a variety of human cancers. Recently, drugs targeting RAF kinase have been approved as an effective treatment for human malignancies that rely on this target for their growth. Thus, suppressing RAF kinase activity is a clinically meaningful approach to treat cancer patients harboring RAF driven oncogene. In this study, we introduced a novel compound DRF-0529 possessed good potency for RAF kinases, selective cytotoxicity against cancer cells harboring BRAF V600 mutation, and dose-dependent inhibition of phosphorylation of RAF downstream effectors MEK and ERK in BRAF^{V600E} positive melanoma cell. Moreover, DRF-0529 was oral active in mouse xenograft model without observed toxicity. Hence, DRF-0529 proved to be active as RAF inhibitor.

MEDI 367

Improving peptide pharmacokinetics through tryptophan late-stage lipidation

Chunhui Huang¹, chunhuijun@gmail.com, *Huaibing He*², *Vijay Bhasker Gangula Reddy*², *Ravi P. Nargund*³, *Songnian Lin*³, *Anandan Palani*³. (1) *Discovery Chemistry Modalities, MRL, Merck & Co. Inc, Boston, Massachusetts, United States* (2) *PPDM, MRL, Merck & Co. Inc, Kenilworth, New Jersey, United States* (3) *MRL, Merck & Co. Inc, Kenilworth, New Jersey, United States*

Peptide drugs have a range of favorable features such as superior efficacy, high selectivity and low toxicity, but suffer from their poor pharmacokinetics due to proteolytic instability and fast clearance. The late-stage functionalization of fully elaborated, drug-like peptides would be ideal to speed up the drug discovery process. Current chemistry toolbox for peptide late-stage functionalization (LSF) is very limited, especially for both chemo- and regioselective modifications. We investigated a mild, tryptophan C2-selective functionalization method for native peptides, including glucagon, GLP-1, oxyntomodulin (OXM), parathyroid hormone (PTH), etc. This novel transformation offers an orthogonal synthetic handle, which can be coupled with a fatty acid lipid to enhance the physicochemical, pharmacological and even biological properties of peptides. As a proof-of-concept, we showcased that the lipidation of glucagon peptide can substantially extend in vivo half-life from < 5 min to 7 hours in rats.



MEDI 368

Discovery of new oxindoles derivative as potent and selective AMPK activators

Oliver Venier, olivier.venier@sanofi-aventis.com, **Claudie Namane**, **Eykmar Fett**, **Eric Nicolai**, **Patrick Mougenot**, **Pascal Paul**, **Bruno Cornet**, **Philippe Chamiot-Clerc**. Sanofi R&D, Chilly-Mazarin, France

A novel class of AMPK activators containing an oxindole core has been discovered. Chemical optimization has led to potent and selective activator of human AMPK with an appropriate ADME profile.

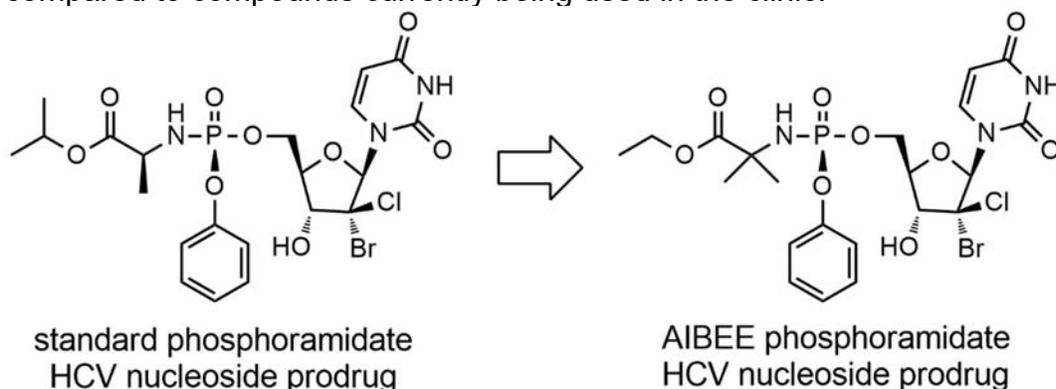
MEDI 369

Discovery of 2-aminoisobutyric acid ethyl ester (AIBEE) phosphoramidate prodrugs that deliver high levels of the active triphosphate of nucleoside HCV inhibitors in human hepatocytes and in dog liver biopsy studies

John T. Randolph, john.randolph@abbvie.com, **Tongmei Li**, **Allan C. Krueger**, **Howard R. Heyman**, **Hui-Ju Chen**, **Dan Bow**, **Cecilia Van Handel**, **Vincent Peterkin**, **Robert A. Carr**, **DeAnne Stolarik**, **Tatyana Dekhtyar**, **Michelle Irvin**, **Preethi Krishnan**, **Rolf Wagner**,

David A. DeGoey. Research and Development, AbbVie, Inc., North Chicago, Illinois, United States

A research effort focused on synthesis of novel 2'-dihalogenated nucleosides has identified 2'-a-bromo-2'-b-chloro-uridine as a potent inhibitor of HCV NS5B polymerase. The standard 5'-phosphoramidate prodrug of this nucleoside, which has the alanine isopropyl ester that has been utilized to deliver several nucleoside HCV inhibitors that have been studied in the clinic, is a potent, pan-genotypic inhibitor in replicon assays. However, pharmacokinetic studies in dog revealed low levels of the active nucleoside triphosphate were present in the liver following oral administration of this compound. We synthesized new prodrugs of this nucleoside and evaluated their potential to deliver the triphosphate metabolite in human hepatocytes. Promising analogs were then tested in the dog liver biopsy study. This method identified a 2-aminoisobutyric acid ethyl ester (AIBEE) phosphoramidate prodrug that provided >10-fold improvement in triphosphate levels in dog liver at both 4 and 24 hours following oral dosing in comparison to the standard phosphoramidate prodrug. Further studies revealed that the AIBEE phosphoramidate can be used to provide high liver triphosphate levels for other nucleoside HCV inhibitors, and thus may provide HCV inhibitors with increased efficacy compared to compounds currently being used in the clinic.



MEDI 370

Design, synthesis and biological evaluation of novel 4-phenylisoquinolinone BET bromodomain inhibitors

Michael Bennett¹, Yiqin Wu⁴, Amogh Bloor¹, Jennifer Matuszkiewicz⁴, Shawn O'Connell⁴, Lihong Shi⁴, Ryan Stansfield³, Joselyn Del Rosario³, James Veal¹, David Hosfield², Jiangchun Xu⁵, Stephen Kaldor¹, Jeffrey Stafford¹, **Juan M. Betancort¹**, juan.m.betancort@gmail.com. (1) Medicinal Chemistry, Celgene Quantice Research, Celgene Corporation, San Diego, California, United States (2) Ben May Department for Cancer Research, University of Chicago, Chicago, Illinois, United States (3) DMPK, Celgene Quantice Research, Celgene Corporation, San Diego, California, United States (4) Structural & Chemical Biology, Celgene Quantice Research, Celgene Corporation, San Diego, California, United States (5) Drug Discovery Operations, Celgene Quantice Research, Celgene Corporation, San Diego, California, United States

Bromodomains have been targeted in drug discovery for their roles in cancer, inflammation and various other diseases with several inhibitors of the bromodomain and extra-terminal (BET) sub-family advancing into clinical studies. There continues to be a need for novel agents with differentiated profiles and physicochemical properties that translate into improved biological activity. This communication describes our efforts on the discovery and characterization of a novel series of BET bromodomain inhibitors. Screening of a focused library based on the bromodomain pharmacophore followed by structure guided SAR exploration resulted in >10,000-fold potency improvement for the BRD4-BD1 bromodomain. Lead compounds exhibited excellent potencies in both biochemical and cellular assays in MYC-dependent cell lines as well as adequate exposure levels *in vivo* that supported their evaluation in mouse cancer models.

MEDI 371

Anti-filarial activity of natural neurolenin D and synthetic neurolenin derivatives

Lizette Perez-Perez¹, lizette.perez1@outlook.com, **Steven A. Williams**², **Kevin M. Shea**³. (1) Biological Sciences, Smith College, NORTHAMPTON, Massachusetts, United States (2) Biological Sciences and Biochemistry, Smith College, Northampton, Massachusetts, United States (3) Chemistry, Smith College, Northampton, Massachusetts, United States

Lymphatic filariasis (LF) is a neglected tropical disease that threatens 52 countries and over 1 billion people. There are drugs available to treat LF; however, they are ineffective against adult worms, potentially toxic when people have other infections, and prolonged administration has led to emerging drug resistance. Thus, there is an urgent need to develop a novel, safe and affordable drug that is able to kill adult worms without causing side effects. Our work has focused on studying the bioactivity of neurolenin D, available from *Neurolaena lobata*, and synthetic analogs against the lymphatic filarial parasite *B. pahangi*. These analogs were created by modifications of the neurolenin scaffold including esterification at the reactive secondary alcohol position. Their bioactivity was measured *in vitro* against male and female adult nematodes by adding one dose (3µg/mL) of the respective drug and then monitoring nematode mortality over a period of 100 hours. Interestingly, the activity of neurolenin analogs varies between male and female nematodes, indicating the presence of some mechanism resulting in gender selectivity. The bioactivity of neurolenin D and the most promising analogs will be further tested by means of RNAseq analysis comparing untreated and treated *B. pahangi* male and female adults. Studying the effect of the drugs on the transcriptome will provide us with information on the mechanism of action of these compounds. These results will provide further useful data on neurolenin and its analogues as promising alternatives for the treatment of LF and perhaps other neglected tropical diseases caused by nematode parasites.

MEDI 372

Identifying compounds that restore normal cellular function in Frontotemporal dementia caused by progranulin haploinsufficiency

Maria Telpoukhovskaia^{1,4}, maria.telpoukhovskaia@gmail.com, Kai Liu², Faten Sayed^{1,4}, Jon Iker Etchegaray^{1,4}, Yungui Zhou^{1,4}, David Le^{1,4}, Min Xie¹, Matthew S. Bogyo³, Sheng Ding², Li Gan^{1,4}. (1) Neurological Disease, Gladstone Institutes, San Francisco, California, United States (2) Cardiovascular Disease, Gladstone Institutes, San Francisco, California, United States (3) Stanford Univ, Palo Alto, California, United States (4) Neurology, University of California, San Francisco, San Francisco, California, United States

Frontotemporal dementia (FTD) affects an estimated 50,000 Americans and is the second leading cause of dementia in people under 65 years of age. Of the hereditary cases of FTD, about a quarter are caused by a mutation in the gene *granulin*. This gene codes for the protein progranulin (PGRN) that is involved in many cellular processes. People with *granulin* mutation have half of PGRN protein, and thus have impaired cellular function, eventually resulting in neurodegeneration, changes in personality, and social behavior.

Like other neurodegenerative diseases, FTD resulting from PGRN haploinsufficiency has no cure. Our approach to treatment is to identify a compound that has the same function as progranulin. To identify progranulin mimetics, we utilize RASL-seq (RNA-mediated oligonucleotide Annealing, Selection, and Ligation with Next-Generation sequencing) technology to establish effect of thousands of compounds on gene expression in brain cells that model the disease.

Here, we present data from a multiplex screen of 1,400 bioactive compounds. Using this assay, we established a transcriptional difference (mRNA levels) between normal mouse microglia brain cells and those with progranulin genetically removed. After addition of compounds, we analyzed gene expression profiles and ranked compounds by their effectiveness in shifting cells toward normal function. The top 50 compounds were selected for testing in cellular activity assays to further narrow down best candidates that can replace PGRN. We test lysosomal activity using fluorescent agent BMV109, as well as cellular inflammatory response to endotoxins. Top five compound hits from these assays are further examined for structure-activity relationships (SAR) in order to modify and improve their activity.

The ultimate goal of this project is to identify compound hits and develop them into lead compounds for curing Frontotemporal dementia.

MEDI 373

Metal-free and mild approach to 1,3,4-oxadiazol-2(3H)-ones via oxidative C-C bond cleavage using molecular oxygen

Bumhee Lim¹, hiliboom@snu.ac.kr, Seunggun Park¹, Jae Hyun Park¹, Jonsik Gam², Sanghee Kim¹, Jung Woon Yang³, Jeeyeon Lee¹. (1) College of Pharmacy, Seoul

National Universtisy, Seoul, Korea (the Republic of) (2) Department of Medicinal Bioscience, College of Interdisciplinary & Creative Studies, Konyang University, Nonsan, Korea (the Republic of) (3) Department of Energy Science, Sungkyunkwan University, Suwon, Korea (the Republic of)

Molecular oxygen, which is a critical component of many biological systems in nature, is considered as an ideal oxidant from a green chemistry perspective. Accordingly, metal-free and mild conditions using molecular oxygen are highly desirable. In particular, the direct cleavage of C(CO)-C(alkyl) or 1,2-dicarbonyl units under metal-free conditions is still challenging.

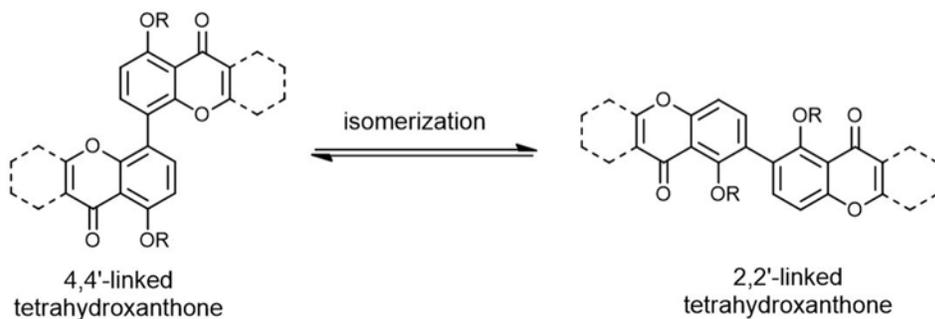
Herein, we described the metal-free and mild synthesis of 1,3,4-oxadiazol-2(3*H*)-ones via the aerobic oxidative cleavage of the C-C bonds of 1,3,4-oxadiazin-5(6*H*)-ones using molecular oxygen. 1,3,4-Oxadiazin-5(6*H*)-ones and 1,3,4-oxadiazol-2(3*H*)-ones, *N,O*-containing five or six-membered heterocycles, have drawn substantial attention as prominent scaffolds found in numerous biologically active molecules. The novel transformation of six to five-membered ring, promoted by the electron-withdrawing *p*-substituents on the phenyl group at the α -carbonyl position, features a tandem reaction consisting of oxidative hydroxylation and C-C bond cleavage using molecular oxygen. The method utilizes K_2CO_3 in CH_3CN without any oxidants, transition metals, or additives, enabling the tunable synthesis of 1,3,4-oxadiazin-5(6*H*)-ones, 1,3,4-oxadiazol-2(3*H*)-ones, and α -ketoamides under mild aerobic conditions.

MEDI 374

Design and synthesis of dimeric tetrahydroxanones as anticancer agents

Rameez Ali, ramyzali@gmail.com, Gary A. Bradshaw, Alexandria N. Leveille, Anita E. Mattson. Chemistry and Biochemistry, Worcester Polytechnic Institute, Worcester, Massachusetts, United States

Phomoxanthone A is a naturally occurring dimeric tetrahydroxanthone that shows impressive anticancer activities in both cisplatin-sensitive (sens) and cisplatin resistant (cisR) cell lines. A major challenge in the identification of structural features responsible for this remarkable activity is the lack of an efficient and a generalized method to synthesize a variety of tetrahydroxanthone analogs. It is plausible for 4,4'-linked tetrahydroxanthone dimers to isomerize to give 2,2'-linked dimers, raising questions about the more potent linkage. We have developed a general approach to synthesize both 2,2'- and 4,4'-tetrahydroxanthone dimers. This approach has allowed us to prepare analogs for a comprehensive structure-activity relationship (SAR) study that probes the more potent dimer linkage and identify the primary pharmacophore in phomoxanthone A.

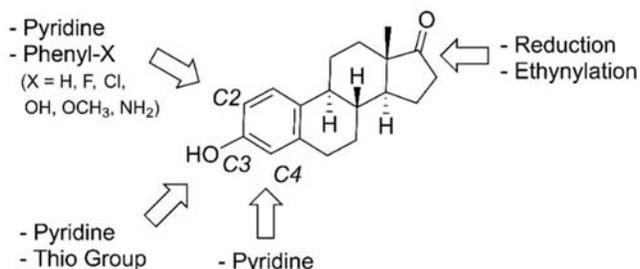


MEDI 375

Four series of estrane derivatives as selective inhibitors of cytochrome P450 (CYP 1B1): Design, synthesis and evaluation

Donald Poirier^{1,2}, donald.poirier@crchul.ulaval.ca, **Raphaël Dutour**^{1,2}, **Jenny Roy**¹, **René Maltais**¹, **Francisco Cortés-Benitez**¹. (1) Laboratory of Medicinal Chemistry, CHU de Québec - Research Center, Québec, Québec, Canada (2) Université Laval, Québec, Québec, Canada

Cytochrome P450 (CYP) 1B1 is an attractive therapeutic target and CYP1B1 inhibitors could be a promising strategy within a context of multitherapies for the treatment of cancers. The structure-activity relationship results obtained from a screening of a library of steroid derivatives have oriented our work towards the chemical synthesis of four series of estrane derivatives: twelve estrone (E1) and 17 β -estradiol (E2) derivatives bearing a 3- or 4-pyridinyl group at C2, C3 or C4 of the steroid nucleus (Series 1), eight estrane derivatives with different sulfur groups at C3 (Series 2), nineteen E1 and E2 derivatives bearing distinct aryl moieties at C2 (Series 3) and four D-ring derivatives (Series 4). The CYP1B1 and CYP1A1 inhibitory activities of these four series of compounds were assessed using the ethoxyresorufin-O-deethylase (EROD) assay and compared to that of α -naphthoflavone (ANF), a known non-steroidal CYP1B1 inhibitor. From the first three series, we observed that the E2 derivatives (17 β -OH) were more active than their oxidized analogs at C17 (E1 derivatives), thus highlighting the key role of the 17 β -OH to interact with CYP1B1. The most potent CYP1B1 inhibitors were obtained with Series 3, and among these compounds, the 2-(4-fluoro-phenyl)-E2 (**13b**) is particularly interesting with IC₅₀ value of 0.24 μ M for CYP1B1 and a selectivity index (SI) of 16 over CYP1A1. Also, the addition of an ethynyl group at C17 α as D-ring modification improved the metabolic stability as well as the SI.



MEDI 376

REAL database a comprehensive database of synthetically feasible molecules: An update

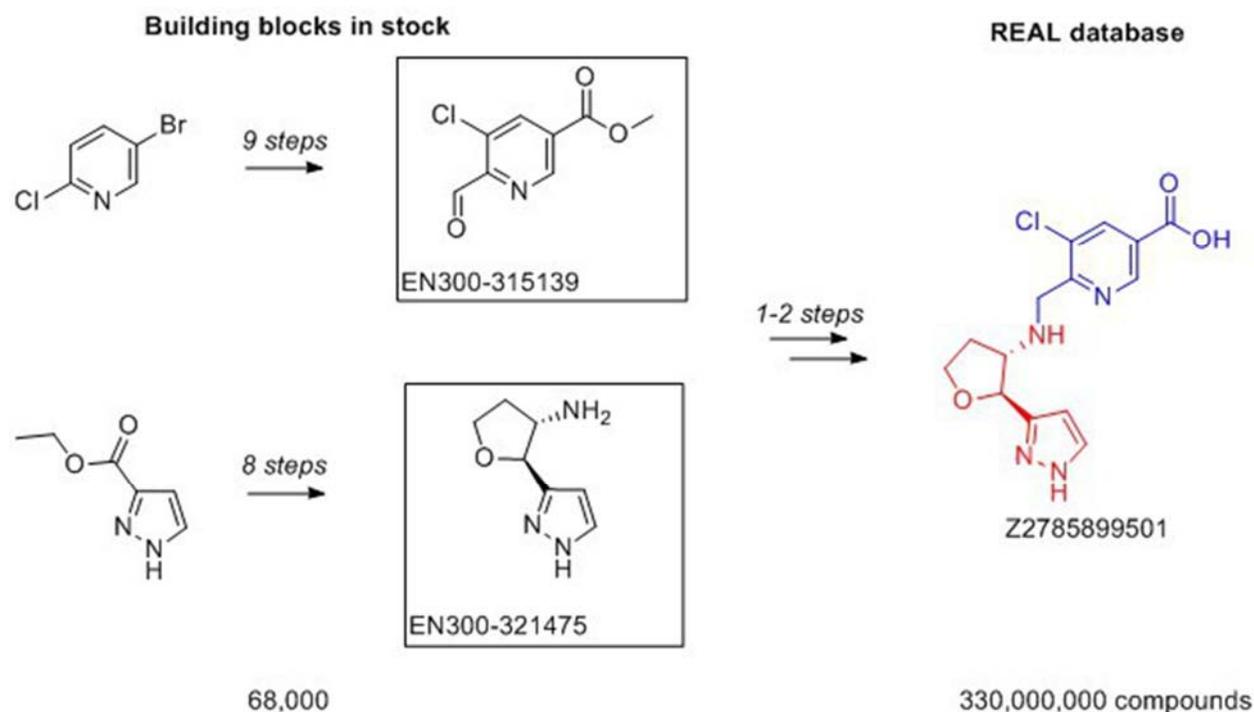
Yurii Moroz¹, *ysmoroz@gmail.com*, **Mykhailo Vybornyi**²,
vybornyi.mykhailo@gmail.com, *Pavel Mykhailiuk*². (1) ChemBioCenter, Taras
Shevchenko National University of Kyiv, Kyiv, Ukraine (2) Chemistry, Enamine Ltd,
Kiev, Ukraine

Docking screens are limitless in selecting ligands because both in-stock and virtual compounds are dockable. The main drawback of virtual compounds, however, is whether the selected molecules are actually synthetically accessible at a reasonable price. We have offered a solution by defining synthesizable regions in virtual chemical space – REAL database of enumerated chemical structures (REAL = reasily accessible).

The REAL database is:

- experience-driven: only well-developed chemistry and in-stock building blocks are utilized;
- highly feasible: transformations with a minimum number of steps, 85% success rate, 3-week synthesis;
- tested: 2,500,000 compounds have been synthesized.

The REAL database has been offered as a bulk or as a number of sets including REAL Fragments, REAL Drug-like, REAL Covalent modifiers, REAL PPI inhibitors, REAL natural product-like, - to name a few. Common features of the REAL compounds enable easy transition from fragments to lead-like or drug-like molecules simplifying optimization and generation of hit follow-up libraries. Applicability of REAL arrays has been demonstrated in a number projects.



MEDI 377

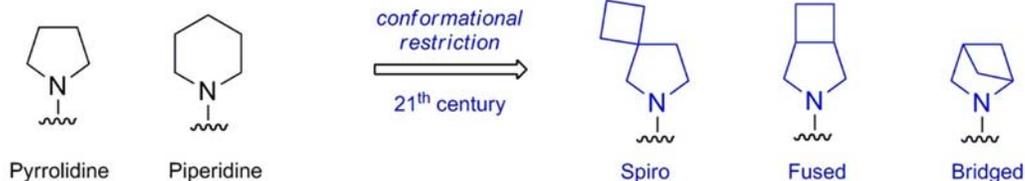
Synthesis of novel bicyclic amines and their application for drug design

Pavel Mykhailiuk, Pavel.Mykhailiuk@gmail.com. Chemistry, Enamine Ltd, Kiev, Ukraine

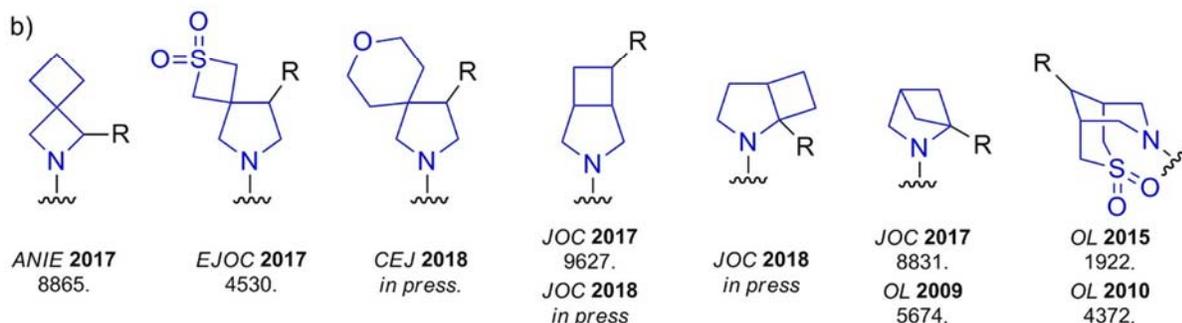
Trends in drug discovery are changing rapidly. During the past decade, terms “*Scaffold hopping*,” “*Escape the Flatland*” and “*Conformational restriction*” have been introduced, and have already found huge practical application. In this context, in recent years medicinal chemists often use bicyclic F_{sp^3} -rich building blocks in drug discovery projects.

In this work, we have designed, synthesized and applied novel multifunctional bicyclic cores for drug discovery. Details of the synthesis and application of the obtained compounds will be discussed.

a) >100 FDA-approved drugs



b)



MEDI 378

Design, synthesis, and evaluation of improved aminoglycosides

Michael G. Pirrone¹, mpirrone@chem.wayne.edu, **Takahiko Matsushita**¹, **Girish C. Sati**¹, **Takayuki Kato**¹, **Sven N. Hobbie**², **Thomas Schrepfer**⁴, **Jochen Schacht**⁴, **Andrea Vasella**³, **Erik C. Bottger**², **David Crich**¹. (1) Department of Chemistry, Wayne State University, Detroit, Michigan, United States (2) Institute of Medical Microbiology, University of Zurich, Zurich, Switzerland (3) Department of Organic Chemistry, ETH, Zurich, Switzerland (4) Kresge Hearing Research Institute, University of Michigan, Ann Arbor, Michigan, United States

Research in our laboratories into the design and synthesis of a series of highly active paromomycin derivatives will be presented resulting in a lead compound that displays antibacterial activity equal to or greater than the parent paromomycin for several strains of Gram-negative and Gram-positive bacteria with significant improvement in activity against many strains of antibiotic resistant bacteria. Selected compounds, including the lead, also display enhanced selectivity for bacterial over several ESKAPE pathogens.

All aspects of synthesis, biological evaluation, and conformational analysis by NMR spectroscopy will be covered in the presentation.

MEDI 379

Fully automated radiosynthesis of carbon-11-labeled 5-HT₆R antagonists as new candidate PET radioligands for imaging of Alzheimer's disease

Min Wang, wang1@iupui.edu, Mingzhang Gao, Qi-Huang Zheng. Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, Indiana, United States

Alzheimer's disease (AD) is a complicated neurodegenerative disorder, and none effective strategy is approved for preventing, curing and slowing the progress of AD. The available medications such as AChEIs and a NMDA receptor antagonist can only be used to treat the cognitive problems of AD. Serotonin 6 receptor (5-HT₆R) has become a promising alternative target for symptomatic treatment of AD, and 5-HT₆R antagonists have been hypothesized to improve cognition, learning, and memory. Recently a new series of 5-HT₆R antagonists has been developed by Suven for potential treatment of AD, and the representative compounds, 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl)methyl]-1*H*-indole (**1a**), 5-methoxy-3-((4-methylpiperazin-1-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole (**1b**), 1-((4-isopropylphenyl)sulfonyl)-5-methoxy-3-((4-methylpiperazin-1-yl)methyl)-1*H*-indole (**1c**) and 1-((4-fluorophenyl)sulfonyl)-5-methoxy-3-((4-methylpiperazin-1-yl)methyl)-1*H*-indole (**1d**), exhibited high binding affinity to human 5-HT₆R with K_i value 2.0, 4.3, 1.6 and 5.0 nM, respectively, and high selectivity over 100 target sites. We are interested in the development of PET AD imaging agents. Here we present a fully automated radiosynthesis of carbon-11-labeled 5-HT₆R antagonists as new candidate PET radioligands for imaging of AD. 1-[(2-Bromophenyl)sulfonyl]-5-[¹¹C]methoxy-3-[(4-methyl-1-piperazinyl)methyl]-1*H*-indole (*O*-[¹¹C]**1a**) and 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-[¹¹C]methyl-1-piperazinyl)methyl]-1*H*-indole (*N*-[¹¹C]**1a**), 5-[¹¹C]methoxy-3-((4-methylpiperazin-1-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole (*O*-[¹¹C]**1b**) and 5-methoxy-3-((4-[¹¹C]methylpiperazin-1-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole (*N*-[¹¹C]**1b**), 1-((4-isopropylphenyl)sulfonyl)-5-[¹¹C]methoxy-3-((4-methylpiperazin-1-yl)methyl)-1*H*-indole (*O*-[¹¹C]**1c**) and 1-((4-isopropylphenyl)sulfonyl)-5-methoxy-3-((4-[¹¹C]methylpiperazin-1-yl)methyl)-1*H*-indole (*N*-[¹¹C]**1c**), 1-((4-fluorophenyl)sulfonyl)-5-[¹¹C]methoxy-3-((4-methylpiperazin-1-yl)methyl)-1*H*-indole (*O*-[¹¹C]**1d**) and 1-((4-fluorophenyl)sulfonyl)-5-methoxy-3-((4-[¹¹C]methylpiperazin-1-yl)methyl)-1*H*-indole (*N*-[¹¹C]**1d**), were prepared from their *O*- or *N*-desmethylated precursors with [¹¹C]CH₃OTf through *O*- or *N*-[¹¹C]methylation and isolated by HPLC-SPE method in 40-50% decay corrected radiochemical yield. The radiochemical purity was >99%, and the molar activity (MA) at EOB was 370-740 GBq/μmol with a total synthesis time of ~40-minutes from EOB.

MEDI 380

Interaction of novel immunogenic cell death-inducing azonafides with DNA: A biophysical study

Sergey G. Tarasov², tarasovs@mail.nih.gov, **Pedro Andrade Bonilla**², **Wei Zhang**², **Sourav Sinha**¹, **N Tarasova**². (1) *Oncolinx Pharmaceuticals, LLC, Buffalo, New York, United States* (2) *National Cancer Institute at Frederick, Frederick, Maryland, United States*

Immune checkpoint inhibitors are able to provide curative treatment in some, but not all, cancer patients. They could be much more effective when combined with agents that induce immunogenic cell death (ICD), a mechanism of cell death that induces antitumor immune response through activation of dendritic cells. However, ICD-inducing toxins are a few, and none of them are tumor-specific. We are developing azonafide derivatives for generation of antibody-drug conjugates (ADC) because azonafides showed to be very potent inducers of ICD, are highly toxic to tumor cells, and have structures amenable to conjugation. Azonafides have been suggested to exert their toxicity through DNA intercalation. However, structural mechanisms, affinity and sequence selectivity of azonafide - DNA interactions have not been explored. Using intrinsic fluorescence of the compounds we applied microscale thermophoresis (MST) and fluorescence polarization (FP) to characterize interactions of newly prepared Azonafide derivatives with DNA. Fluorescence polarization allowed for the most efficient and straightforward determination of KDs that was in nanomolar and subnanomolar range for most of the tested compounds. DNA binding quenches azonafides' fluorescence, and we used this property for yet another way of determining KDs that agreed well with FP data. MST provided for highly sensitive detection of binding that was accompanied not only by significant change in thermophoretic mobility, but also by a switch in its direction: DNA-bound compounds moved towards the heat, while free compounds move away from the heat. Obtained data is now used for further optimization of compounds for clinical use.

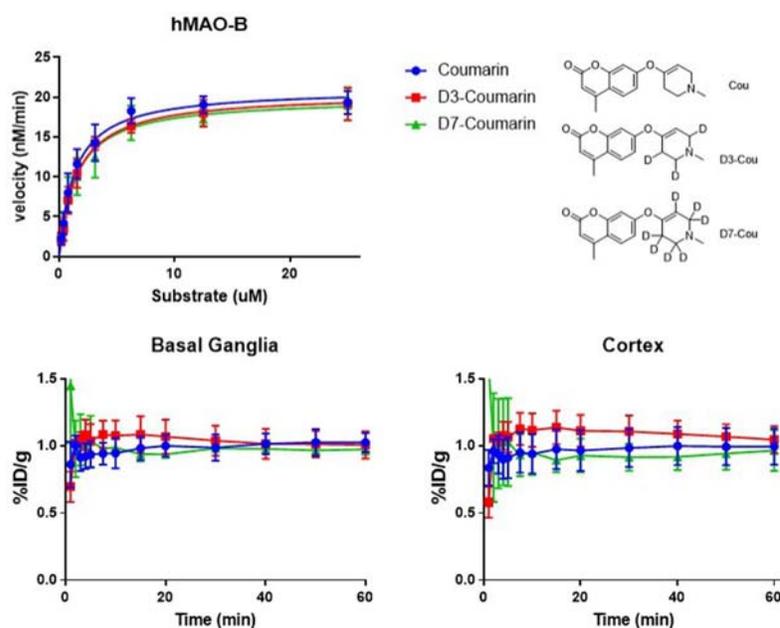
MEDI 381

Kinetic isotope effects of a 1,2,3,6-tetrahydropyridine-derived MAO-B substrate

Lindsey Drake¹, lrdrake@umich.edu, **Anthony Mufarreh**², **Jonathan Pham**², **Allen F. Brooks**², **Michael Kilbourn**², **Peter Scott**^{1,2}. (1) *Medicinal Chemistry, University of Michigan, Ann Arbor, Michigan, United States* (2) *Radiology, University of Michigan, Ann Arbor, Michigan, United States*

Monoamine oxidases are flavoproteins responsible for the metabolism of the monoamine neurotransmitters serotonin, dopamine, and epinephrine. The isozyme MAO-B is more abundant in the brain and has been found overexpressed on astrocytes in human brains of dementia patients. Visualizing the *in vivo* activity of MAO-B is a valuable tool in the ongoing investigation into astrocyte activation in neurodegeneration.

MAO-B has been studied using PET imaging with radiolabeled inhibitors, most notably the irreversible ligand [^{11}C]deprenyl. We desired to develop a trapped metabolite PET agent and previously reported the synthesis and evaluation of three substrates based on the known MAO substrate MPTP. These 4-aryloxy-MPTP derivatives include an ether linkage to other substituents which removes the toxicity potential. The rate of uptake and trapping in nonhuman primate of the MAO-B specific substrate, [^{11}C]Cou, was rapid and we tested if deuterium substitution in the tetrahydropyridine ring could slow the *in vivo* kinetic parameters. There is a long history of deuterium substitution effectively slowing the turnover of MAO-B substrates, such as MPTP, as well as the radiotracer [^{11}C]deprenyl. Two versions were synthesized, D3 and D7, and *in vitro* kinetic evaluation was performed in hMAO-B Supersomes. Carbon-11 radiolabeling was done by N-methylation with [^{11}C]CH $_3$ OTf in EtOH-d $_6$ followed by reduction by NaBD $_4$. The *in vivo* uptake and trapping of [^{11}C]Cou, [^{11}C]D3-Cou, and [^{11}C]D7-Cou were evaluated in healthy nonhuman primate. Deuterium substitutions on the tetrahydropyridine ring of Cou did not produce changes in the *in vitro* kinetic properties (turnover rate (k_{cat}) or K_M in the hMAO-B assay), and did not alter the *in vivo* rates of uptake and trapping in the primate brain. These results represent a divergence from the MPTP precedent and we propose that the oxidation step is not rate-limiting for the Cou substrate. We hypothesize that, due to the bent structure of the ether linkage in the Cou compound as compared to MPTP, the rate of association of substrate to enzyme or the release of imine product may be more rate limiting than the oxidation step.

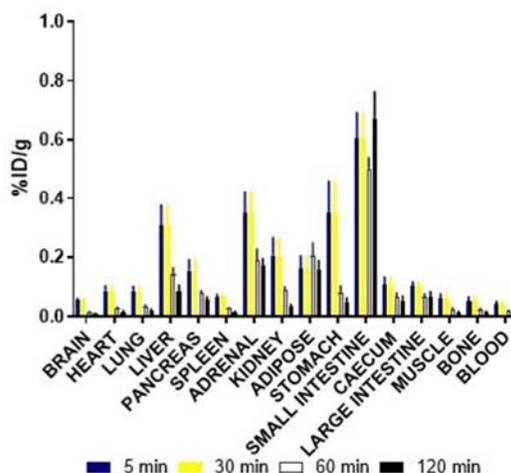
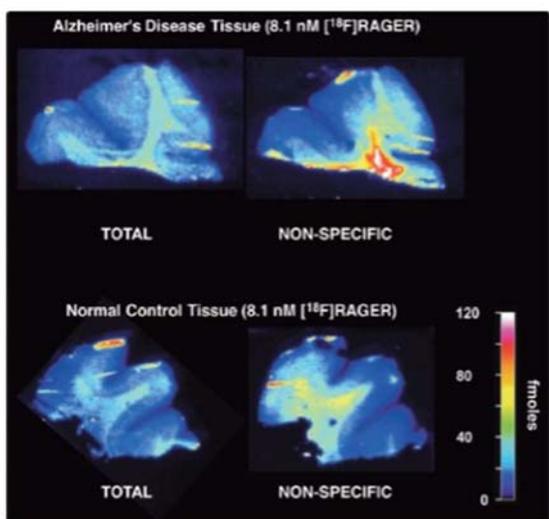
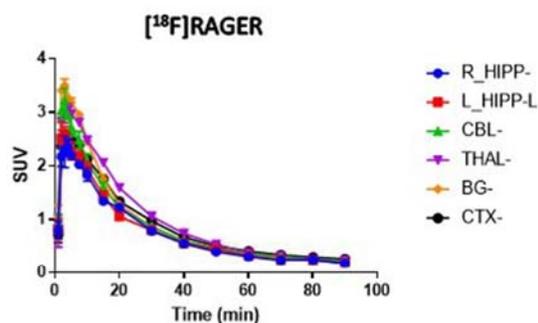
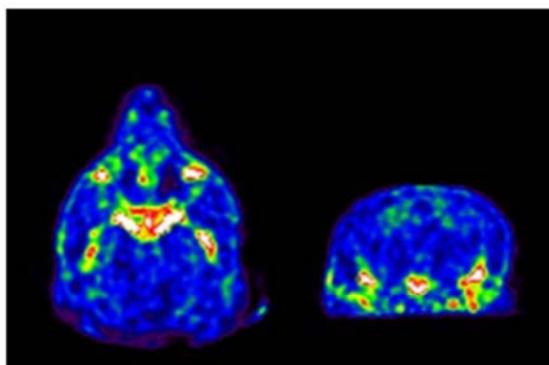


MEDI 382

Two strategies for imaging the receptor for advanced glycation end products

Lindsey Drake¹, lrdrake@umich.edu, Allen F. Brooks², Peter Scott^{2,1}. (1) Medicinal Chemistry, University of Michigan, Ann Arbor, Michigan, United States (2) Radiology, University of Michigan, Ann Arbor, Michigan, United States

The receptor for advanced glycation endproducts (RAGE) is a membrane-bound receptor implicated in diseases of inflammation. Increased levels of RAGE have also been identified in post-mortem brain sections of patients with neurodegenerative disorders. With the goal of understanding RAGE's, and inflammation's, role in neurodegenerative disease, we aimed to develop PET tracers for the extra- and intracellular membranes of RAGE. There are multiple isoforms of RAGE, including a circulating soluble form with a possible role as a scavenger receptor and its distinct role in disease progression is unknown. We developed the first small molecule radioligand for the extracellular domain, [¹⁸F]RAGER. It has high affinity for RAGE ($K_d = 15$ nM), shows specific binding in Alzheimer's disease brain sections and colocalizes with RAGE immunohistochemistry, has good CNS penetration in rat and monkey, and increased uptake in areas of the brain known to express RAGE. Biodistribution studies were performed in Sprague Dawley rat and confirmed rapid brain uptake. Screening for possible CNS off target binding returned >90% inhibition at 10 μ M (melatonin MT₁; $K_i = 93$ nM); however, blocking studies in nonhuman primate demonstrated *in vivo* no significant binding to MT₁. In addition to this extracellular radioligand, we developed [¹⁸F]InRAGER, which binds to the intracellular face of RAGE and is only present in the full length form. [¹⁸F]InRAGER ($K_d = 1$ nM) was synthesized in relatively low yield from halogen exchange, radiochemical yield being 1%. Small animal PET imaging revealed that it is blood-brain barrier permeable in rodents. Further evaluation of this radioligand including an optimized radiosynthesis to increase specific molar activity and radiochemical yield, specific binding evaluation on post-mortem human brain tissue, and small animal PET imaging in nonhuman primate will be reported. The combined use of extra and intracellular radioligands will assist in the ongoing investigation into the roles of soluble RAGE and the full length receptor in neuroinflammation.



MEDI 383

Aromatic sulfonamide library of human carbonic anhydrase IX inhibitors – towards anticancer drug design through chemical and crystallographic structure correlations with the thermodynamics of binding

Vaida Linkuviene, Asta Zubriene, Vaida Paketuryte, Alexey Smirnov, Vytautas Petrauskas, **Daumantas Matulis**, matulis@ibt.lt. Biothermodynamics and Drug Design, Institute of Biotechnology, Vilnius University, Vilnius, Lithuania

A series of over 700 aromatic primary sulfonamides bearing various substituents were synthesized with the goal to determine the chemical structure correlations with the thermodynamics of binding to the family of human carbonic anhydrase (CA) isoforms. The primary goal was to understand the structural features determining the affinity and selectivity towards an anticancer target, isoform CA IX. The proteins, all twelve human CA isoform catalytic domains, were cloned and expressed in bacterial and human cell cultures and affinity-purified in large quantities, sufficient for titration calorimetry (ITC) and crystallography. The binding affinities were determined by the thermal shift assay (FTSA or differential scanning fluorimetry), ITC, inhibition of enzymatic activity, and SPR. The enthalpy and entropy changes upon binding were determined by ITC for a

selection of compounds and CA isoforms. A correlation map between the compound chemical structure and the binding Gibbs energies and enthalpies was drawn. The map showed which structural features of the compounds yielded the highest increments in affinity and exothermicity of compound binding. Furthermore, only some structural features were useful in generating compounds that selectively bind to cancer-expressing CA isoforms, but would not bind to essential-for-life human CA isoforms. Over 60 X-ray crystal structures showed the position of compounds bound in the enzyme active center.

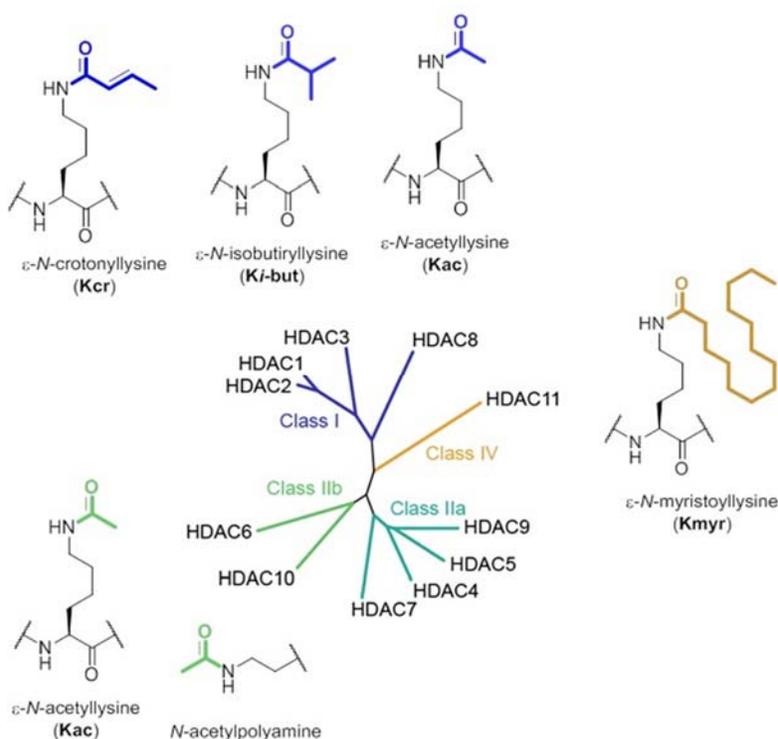
Target-based drug design is based on the discovery and selection of a most-strongly binding compound to a target protein. However, the binding affinity and the binding mechanism is a result of an interplay of highly compensating enthalpic and entropic contributions. Even homologous compounds having similar affinities often exhibited significantly different enthalpies and entropies of binding. It was essential to dissect the contributions from binding-linked reactions such as buffer, ligand or protein protonation. After the subtraction of pH-dependent buffer contribution to the enthalpy of binding, the *intrinsic* Gibbs energies and enthalpies of binding were obtained. It was important to calculate the intrinsic parameters and use only them in the structure-thermodynamics correlation maps when designing compounds of higher affinity as drug candidates.

MEDI 384

Elucidating the enzymatic activity of HDAC11

Carlos Moreno Yruela, *carlos.myruela@sund.ku.dk*, **Iacopo Galleano**, **Andreas S. Madsen**, **Christian A. Olsen**. *Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark*

HDAC11 is the most recently discovered member of the family of enzymes called the histone deacetylases (HDACs). These are involved in the epigenetic regulation of gene expression and are therefore targets for the treatment of various human diseases including cancer. The canonical enzymatic activity assigned to HDACs is the hydrolysis of acetyl modifications of lysine side chains at the tail of histone proteins, which leads to euchromatin formation and gene silencing. Intriguingly, HDAC11 only exhibits minor *in vitro* deacetylase activity, which is also a drawback for the study of its biological function. Here, we describe the ability of HDAC11 to hydrolyze long chain acyl modifications of lysine much more efficiently than acetyl groups. This novel enzymatic activity is highly selective in terms of substrate sequence and length of the acyl chain, opposed to the more promiscuous *in vitro* activity described for other fatty acid hydrolases such as SIRT2 and SIRT6. Previously reported HDAC inhibitors were tested for their ability to inhibit HDAC11-mediated demyristoylation. Interestingly, compounds marketed for cancer treatment such as vorinostat and romidepsin did not inhibit HDAC11, whereas the peptide macrocycle trapoxin A, and hydroxamic acid-containing analogues of apicidin A and trapoxin B showed potencies in the nanomolar range. In addition, modified apicidin A presented a slow, tight-binding inhibition profile. These results facilitate the future development of probes to study HDAC11 and, ultimately, unveil its role in human biology and diseases such as cancer.



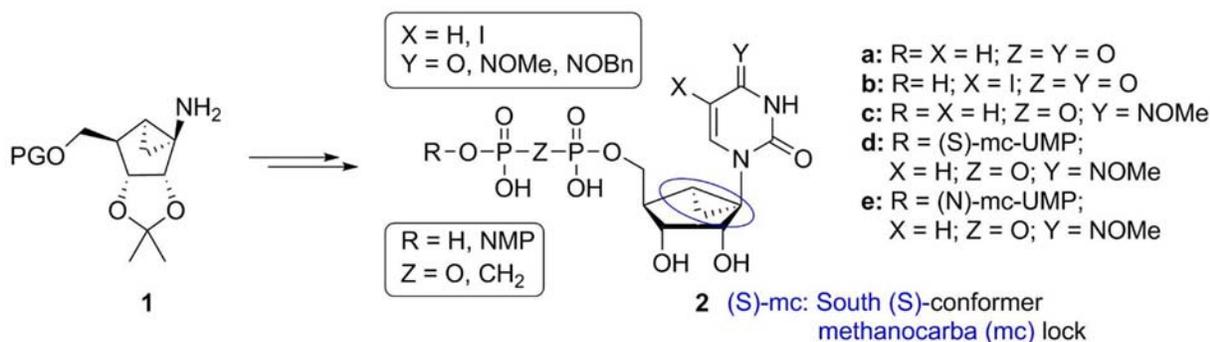
MEDI 385

Conformationally locked UDP and U_{P3}U analogues as P2Y₆ receptor agonists

Kiran S. Toti¹, kiran.toti@nih.gov, **Shanu Jain¹**, **Antonella Ciancetta¹**, **Ramachandran Balasubramanian¹**, **Saibal Chakraborty¹**, **Ryan Surujdin¹**, **Zhen-Dan Shi²**, **Kenneth A. Jacobson¹**. (1) Molecular Recognition Section, LBC, NIDDK, National Institutes of Health, Bethesda, Maryland, United States (2) Imaging Probe Development Center, NHLBI, National Institutes of Health, Rockville, Maryland, United States

P2Y₆ is a G_{q/11}-protein coupled receptor (GPCR) and is one of the least studied in the P2YR family, but gaining attention in drug discovery for cancer, diabetes, inflammation, and neurodegenerative diseases. UDP is an endogenous P2Y₆R agonist and is also activated by the dinucleotides such as U_{P3}U. All the reported agonists are nucleotide mimics, and only two antagonist classes reported: a diisothiocyanate MRS2578 (IC₅₀ = 37 nM; irreversible) and a 3-nitro-2H-chromene TIM-38 (IC₅₀ = 4.3 μM). The active conformation of nucleosides and nucleotides in nature bound to macromolecules, such as enzymes, receptors and transporters, typically has a North (N) or South (S) sugar pucker. Using conformationally-locked bicyclic methanocarba (mc) analogues, we identified (S)-mc-UDP (**2a**) as a potent and selective P2Y₆R agonist. No other P2YR prefers nucleotides bearing (S)-mc-locked ribose moiety over (N)-mc-locked or the flexible ribosides. We determined the preference at the binding site of the distal nucleoside in dinucleoside triphosphates, i.e. U_{P3}U analogues. P2Y₆R structures are

unknown, and the sequentially close P2Y₁R structure was not a suitable template due to differences in the second extracellular loop that contacts ligands. However, a hybrid-homology model based on rhodopsin-CXCR4 structures allowed molecular dynamics simulations of bound nucleotides consistent with observed SAR. To further probe the conformational preference of P2Y₆ agonists, both (S) and (N)-locked methanocarba analogues were synthesized (**2b-d** and **2e**, respectively). **2b,c** are the most potent mononucleotides at P2Y₆R, and **2e** among dinucleotides, suggesting a preference for the (N)-conformer at the distal binding site. A summary of the existing SAR, synthetic protocols to novel molecules, biological activities and rationalization of the results based on molecular modeling will be presented.



MEDI 386

Synthesis, structural characterization and butyrylcholinesterase inhibition studies of ferrocene based anilides

Ataf Ali Altaf¹, atafali_ataf@yahoo.com, **Amin Badshah**², aminbadshah@yahoo.com, **Debbie C. Crans**³. (1) Department of Chemistry, University of Gujrat, Gujrat, Punjab, Pakistan (2) QAU, Islamabad, Pakistan (3) Colorado State University, Fort Collins, Colorado, United States

Series of ferrocene based anilides, with general formula C₅H₅-Fe-C₅H₄-C₆H₄-NH-CO-C₆H₄-R (where R = H, F, Cl, CH₃ and OCH₃), have been successfully synthesized. The compounds were characterized by elemental analysis, FTIR, ¹H NMR and ¹³C NMR spectroscopies and X-ray crystallography. Solid state studies indicate the presence of secondary bonding forces and suggested the biological potential. Crystal engineering analysis suggest the potential use to inhibit butyrylcholinesterase activity. All compounds were found to inhibit butyrylcholinesterase. The most active compound show 50% inhibition at a concentration of 9 ± 0.2 μM similar to the know drug Galantamine (with IC₅₀ 8 μM). Although compounds with ferrocene at *meta* to amide linkage were found to be slightly more active than the other structural isomers they and H-bonding derivatives were not significantly stronger inhibitors. However all the isomers were found to have similar affinities for the enzyme suggesting that the major driving factor is hydrophobic interactions with the protein and supported by the PadDock Score in docking calculations.

MEDI 387

Design, synthesis, insecticidal activity and structure–activity relationship (SAR) of (1R)-(+)-verbenone derivatives

Minkyoung Kim¹, *kyoung2k@naver.com*, **Kyeong Lee**¹, **Yongseok Choi**². (1) Dongguk university, Goyang, Korea (the Republic of) (2) Korea University, Seoul, Korea (the Republic of)

In recent years, crop damage from harmful pests has become more common and the continued application of traditional pesticides can often lead to the development of more resistant pests, thus bringing about enormous losses in crop production. *Plutella xylostella* (*P. xylostella*) is a highly migratory, cosmopolitan species and one of the most important pest of cruciferous crops worldwide. Pyridalyl as a novel class of insecticides has good efficacy against *P. xylostella*.

The steroidal insect molting hormone, 20-hydroxyecdysone (20E), binds to the EcR which becomes active and transactivates the expression of a group of molt-related genes. As a result, the molting hormone agonists are exhibiting insecticidal activity associated with a precocious incomplete molt that is ultimately lethal. The non-steroidal commercialized ecdysone receptor insecticides have advantages such as high selectivity, and greater metabolic stability, and low toxicity for human. However, the resistance to them has increased rapidly.

We will discuss the structure-activity relationships study of the (1R)-(+)-verbenone analogues and their biological activity.

MEDI 388

Potential lead compounds for the treatment of Alzheimer's disease: A peptide that blocks amyloid β induced neurotoxicity

Kiyoshi Fukuhara¹, *fukuhara@pharm.showa-u.ac.jp*, **Takuya Arai**¹, **Akiko Ohno**², **Kazunori Mori**¹, **Motoko Shibamura**¹, **Naoki Miyata**³, **Hidehiko Nakagawa**³. (1) School of Pharmacy, Showa University, Tokyo, Japan (2) NIHS, Kawasaki, Japan (3) Nagoya City University, Nagoya, Japan

In the pathogenesis of Alzheimer's diseases (AD), the aggregation pathway of β -amyloid ($A\beta$) is a key target to prevent or delay the onset of AD. The aggregation and fibrillation of the 40-mer and 42-mer peptides ($A\beta_{40}$, $A\beta_{42}$) has been suggested to contribute to the oxidative stress that is responsible for neurotoxicity. Especially, the aggregative ability and neurotoxicity of $A\beta_{42}$ are considerably greater than those of $A\beta_{40}$, probably due to its high lipophilic C-terminal domain. In this work, we conjugated the antioxidant trolox (Tx) or caffeic acid (CA) to $A\beta_{42}$ C-terminal motifs ($A\beta_{x-42}$) to synthesize Tx- $A\beta_{x-42}$ and CA- $A\beta_{x-42}$, respectively. Most of these compounds were found to exhibit anti-aggregation activities toward $A\beta_{42}$. Among them, Tx- $A\beta_{36-42}$ and CA- $A\beta_{38-42}$ exhibited potent inhibitory activities against $A\beta_{42}$ aggregation, indicating that the inhibitory activity increased with the length of the C-terminal motif. Possible

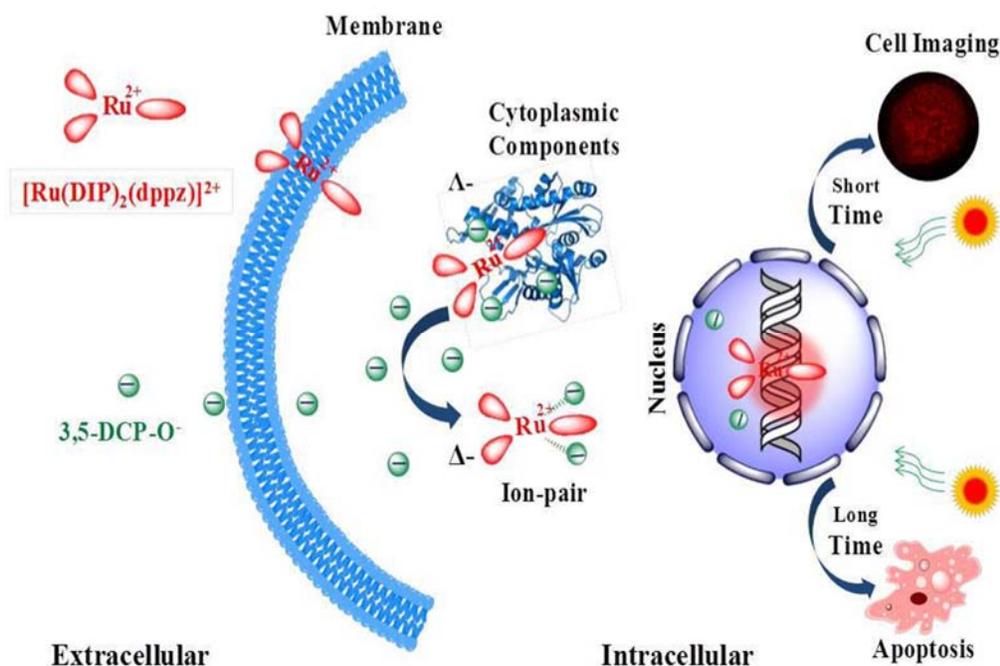
protective effects of the Tx-A β 36-42 and CA-A β 38-42 against A β 42 induced neurotoxicity was investigated with SH-SY5Y neuroblastoma cells. The Tx-A β 36-42 significantly reduced the neuronal death evoked by A β 42, whereas only weak neuroprotective effects were observed by Trolox and caffeic acid. During the progression of AD, A β 42 plays a critical role in promoting oxidative stress leading to cytotoxicity. In fact, Tx-A β 36-42 and CA-A β 38-42 demonstrated potent antioxidative activities toward A β 42-induced intracellular ROS generation. These results prove that conjugating C-terminal motif to Trolox and caffeic acid is crucial for the protective effects on A β -induced neurotoxicity. Tx-A β 36-42 and CA-A β 38-42 may be a starting point for the future development of drugs that prevent neurotoxicity and deposition of A β in the brain of AD.

MEDI 389

Unprecedented enantiomeric discrimination of the two chiral-forms of DNA “light-switching” Ru(II) cationic complex by living-cells via ion-pairing with achiral counter-anions

Ben-Zhan Zhu, bzhu@rcees.ac.cn. State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco-Environmental Sciences, The Chinese Academy of Sciences, Beijing, China

Targeted delivery of diagnostic-probes and therapeutics into specific compartments inside a cell is of utmost importance in the improvement of disease detection and treatment. The molecular DNA “light-switch” ruthenium(II)-polypyridyl complex, [Ru(DIP)₂(dppz)]²⁺ (where DIP = 4,7-diphenyl-1,10-phenanthroline and dppz = dipyridophenazine) has been shown to be accumulated only in the cytoplasm and membrane, but excluded from its intended nuclear DNA target. Here we show that *rac*-[Ru(DIP)₂(dppz)]²⁺ can be redirected into live-cell nucleus by chlorinated phenols by ion-pairing mechanism, while maintaining its original DNA recognition characteristics. To our surprise, further studies with the pure enantiomers (Δ - and Λ -) of [Ru(DIP)₂(dppz)]²⁺ showed that only the Δ -enantiomer was selectively delivered to the nucleus, while the Λ -enantiomer remain in cytoplasm, in the presence of 3,5-dichlorophenol. More interestingly, enantioselective apoptotic cell death was induced for cells pretreated with [Ru(DIP)₂(dppz)]²⁺/3,5-dichlorophenol upon prolonged visible-light irradiation. Analogous results were observed when 3,5-dichlorophenol was substituted by flufenamic acid, a currently clinically used non-steroid anti-inflammatory drug. This represent the first report of enantiomeric discrimination of the two chiral-forms of DNA “light-switch” Ru(II) cationic complex by living-cells via ion-pairing with achiral counter-anions. We suggest that this novel ion-pairing method and concept can be employed to deliver other similar cationic and bioactive metal complexes with promising therapeutic and diagnostic potentials to their preferred intracellular targets.



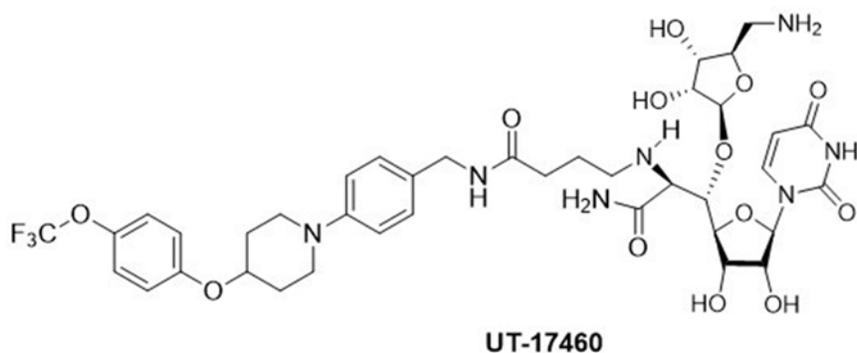
Proposed molecular mechanism for redirecting the positively-charged $[\text{Ru}(\text{DIP})_2(\text{dppz})]^{2+}$ cation into nucleus as a unique enantioselective live-cell nuclear DNA-imaging and photosensitizing agent via forming neutral and relatively stable Yin-Yang ion-pair with the negatively-charged chlorophenolate counter-anion.

MEDI 390

N-glycosylation inhibitors towards novel anti-cancer chemotherapeutics

Katsuhiko Mitachi, Shakiba Eslamimehr, Sara M. Kurosu, **Michio Kurosu**, mkurosu@uthsc.edu. Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, Tennessee, United States

Abnormal glycosylation of cell surface proteins takes place during which normal cells progress to a malignant neoplastic state. Our preliminary studies have demonstrated that selective dolichyl-phosphate *N*-acetylglucosaminophosphotransferase (DPAGT1) inhibitors have the promising therapeutic potential for certain solid cancers that require increased branching of *N*-linked glycans in their growth progressions. Selective DPAGT1 inhibitors are effective in killing a series of solid cancers *in vitro*, and displayed strong synergistic effects with FDA-approved anticancer drugs. We report scalable synthetic scheme for novel DPAGT1 inhibitors and detailed *in vitro* analyses of a selective DPAGT1 inhibitor, UT-17460 against pancreatic cancers.



MEDI 391

Design, synthesis and biological evaluation of novel discodermolide analogues leading to suppression of senescence and an increase cancer cell death

Boying Guo¹, guoboy@sas.upenn.edu, **Amos B. Smith**², **Hayley M. Mcdaid**³, **Susan B. Horwitz**³. (1) Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania, United States (2) Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania, United States (3) department of medicine, Albert Einstein College of Medicine, New York, New York, United States

(+)-Discodermolide, a polyketide natural product is a potent microtubule stabilizing agent. Unfortunately, discodermolide failed in an early Phase I clinical trial due to pneumotoxicity, that we reason likely due to senescence-associated toxicity in lung tissue. To explore this possibility, we initiated a synthesis program to evaluate novel discodermolide analogues, focusing on the suppression of senescence possessing an increase in cancer cell kill. Towards this end, we report here the design, synthesis and biological evaluation of a series of novel discodermolide analogues. Chemical modifications of the diene and the lactone fragments of discodermolide proved to increase suppression of senescence. Equally important, these analogues also displayed superior cancer cell killing ability compared to discodermolide and Taxol.

MEDI 392

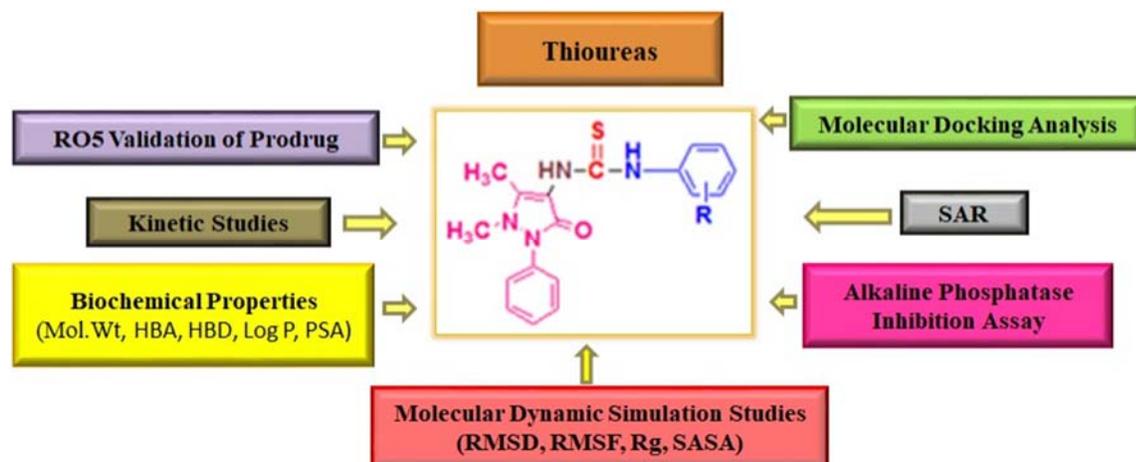
Insight into the drug likeness of 4-aminoantipyrine based thioureas: Synthesis, biological evaluation, molecular docking and molecular dynamic simulation studies

Asma Khurshid^{2,1}, asmakhurshid2000@hotmail.com, **Aamer Saeed**². (1) Department of Metallurgy and Materials Engineering (DMME), Pakistan Institute of Engineering and Applied Sciences, Islamabad, Punjab, Pakistan (2) Department of Chemistry, Organic Chemistry Sub-Division, Quaid-i-Azam University, Islamabad, Islamabad, Punjab, Pakistan

4-Aminophenazone (antipyrine) belongs to a group of pyrazolone ring containing non-steroidal anti-inflammatory drugs (NSAIDs). Based on the medicinal importance of this

drug, and our interest in pyrazole as a biological active pharmacophore, we converted antipyrine to its aryl thiourea derivatives which manifested potential bioactivities besides showing their drug candidacy as anticancer drug.

The newly synthesized aryl thiourea derivatives of 4-aminophenazone were screened against calf intestinal alkaline phosphatase in order to evaluate their anticancer properties besides studying their cytotoxic effect using Brine Shrimp Assay. Kinetic studies aided to understand the mode of enzyme inhibition by the most active member of the series. Biochemical properties like molar refractivity, molecular lipophilicity and PSA value (for drug absorption prediction) etc., of all the synthesized pro-drugs indicated that they show very good drug likeness score. While, RO5 analysis also justified the therapeutic potential of synthesized thioureas. The chemo-informatics analyses showed that all compounds possess <10 HBA and <5 HBD which may confirm their good penetration within the body. Structure activity relationship (SAR) was established on the basis of molecular docking studies which indicated that π - π stacking interaction is also important besides hydrogen bonding for exhibiting high binding energy values shown by 3-methyl and 4-chloro substituted derivatives. Besides these studies molecular dynamic simulation was also carried out to study root mean square deviation and fluctuation, radius of gyration and solvent accessible surface area of targeted protein in support of drug likeness of the synthesized compounds. The computational results are in congruence with the results obtained from biological assays.



MEDI 393

Colorectal cancer inhibition and cellular activities of (Z)-2-cinnamamido-3-phenyl-N-propylpropenamide (MOS-1512A)

Kasim Alireza, kasimalireza@gmail.com. Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia

The third leading cause of cancer in both men and women worldwide is Colorectal cancer (CRC). There are several available drugs for treatment of colorectal cancer. However, the biggest issue for these drugs is the emerging resistance, leading to

decrease in the therapeutic efficacies, relapse and tumor recurrence. Our supervisors developed a small molecule agent coded MOS-1512A as an inhibitor of some cancer cell lines. We wanted to test the compound against CRC cell lines and to investigate its selectivity against normal cell lines. We also intended to investigate its cellular activities and mechanisms of anticancer effects. Methods. The anticancer potency was determined by sulforhodamine B (SRB method) on HCT116 colon cancer cell line as well as C-166 mouse skin normal cell line. The IC₅₀ was calculated using Graphpad Prism and was found to be 32 $\mu\text{M}/\text{mL}$ for HCT-116 and $>100 \mu\text{M}/\text{mL}$ for C-166 cell lines. Morphological changes of cancer cell nuclei after treatment of MOS-1512A were performed by staining cancer cells with DAPI. Subcellular mechanisms were tested by immunofluorescence assays of cleaved caspase-3, cyclin B, cyclin D and P-histone3. Conclusion. MOS-1512A is a moderately active anticancer agent that demonstrated high selectivity and low resistance of CRC cell lines over normal cells. CRC cell lines underwent apoptosis, DNA fragmentation and nuclear condensation after treatment by MOS-1512A. The compound represents an excellent molecular framework to develop potent and safe anti-cancer drugs.

MEDI 394

In vitro* and *in vivo* activity of peptidomimetic compounds that target the periodontal pathogen *Porphyromonas gingivalis

Pravin Patil¹, Jinlian Tan², Donald R. Demuth², **Frederick A. Luzzio¹**,
faluzz01@louisville.edu. (1) Department of Chemistry, University of Louisville,
Louisville, Kentucky, United States (2) Department of Oral Immunology and Infectious
Diseases, University of Louisville, Louisville, Kentucky, United States

The interaction of the periodontal pathogen *Porphyromonas gingivalis* with oral streptococci is important for initial colonization of the oral cavity by *P. gingivalis* and is mediated by a discrete motif of the streptococcal antigen I/II protein. A synthetic peptide encompassing this motif functions as a potent inhibitor of *P. gingivalis* adherence but the use of peptides as topically applied therapeutic agents in the oral cavity has limitations arising from the relatively high cost of peptide synthesis and their susceptibility to degradation by proteases expressed by oral organisms. In this study, we demonstrate the *in vitro* and *in vivo* activity of five small molecule mimetics of the streptococcal peptide. Using a three species biofilm model, all five compounds were shown to effectively inhibit the incorporation of *P. gingivalis* into *in vitro* biofilms and exhibited IC₅₀ values of 10 to 20 μM . Four of the five compounds also significantly reduced maxillary alveolar bone resorption induced by *P. gingivalis* infection in a mouse model of periodontitis. All of the compounds were non-toxic towards a human telomerase immortalized gingival keratinocyte cell line. Three compounds exhibited slight toxicity against the murine macrophage J774A.1 cell line at the highest concentration tested. Compound PCP-III-201 was non-toxic to both cell lines and the most potent inhibitor of *P. gingivalis* virulence and thus may represent a novel potential therapeutic agent that targets *P. gingivalis* by preventing its colonization of the oral cavity. The syntheses of the compounds and the bioassay data will be presented.

MEDI 395

Synthesis of fluorescent goldnanocluster used in metal pollution sensing

Kasturi Sanyal, *kasturibhattacharya@yahoo.co.in*. *Department of Chemistry, Khalishani Mahavidyalaya, Kolkata, West Bengal, India*

Fluorescent Gold nanoclusters (Au NCs) with sizes smaller than 3 nm are a specific type of gold nanomaterials as unlike the most popular and well-known spherical, large gold nanoparticles, Au NCs do not exhibit surface plasmon resonance (SPR) absorption in the visible region but have fluorescence in the visible to near-infrared (NIR) region. With advantages of long lifetime, large Stokes shift, and biocompatibility, Au NCs have become interesting sensing and imaging materials⁽¹⁻⁴⁾ in last decade.

Au NCs prepared from Au³⁺ in the presence of small thiol compounds have been reported over the past decade,⁽⁵⁾ their use for biological applications have not been well recognized, mainly because of their low quantum yield (usually less than 1%), poor watersolubility, photo and chemical instability, and difficulty for conjugation. In the past decade, many strategies for the preparation of stable, water dispersible, fluorescent, and biocompatible Au NCs have been reported⁽⁶⁻⁸⁾. The optical properties of biocompatible Au NCs are dependent on their size, surface ligand or template, and the surrounding medium, and thus they can be studied to develop sensitive and selective sensing and imaging systems for the detection of various analytes. Introduction of alkanethiol ligands onto the surface of AuNPs can be used in the synthesis of gold nanoparticles with QYs = 0.03⁹. These nanoparticles have shown applications in immunoassay¹⁰ and intracellular imaging¹¹. However, exploration of AuNPs-based sensors remains at a very early stage.

Heavy-metal ions, such as mercury, lead, arsenic, cadmium, can cause serious and permanent damage to human organs due to their accumulative characters in the environment and biological system. Therefore, detection of these heavy-metal ions are extremely important. Specially, soluble inorganic arsenic is acutely toxic. Intake of inorganic arsenic over a long period can lead to chronic arsenic poisoning (arsenicosis). Effects, which can take years to develop depending on the exposure level, include skin lesions, peripheral neuropathy, diabetes, cardiovascular diseases, and cancer.

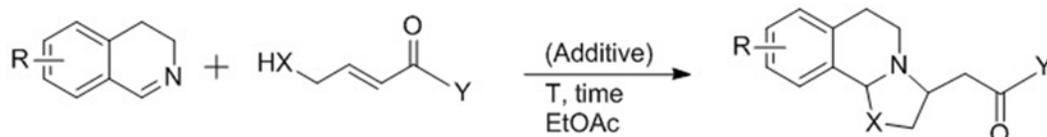
In this paper, we have reported a synthesis of a sensor for the essential biological metal ion As⁺³ based on the aggregation-induced quenching of gold nano clusters. We have demonstrated that the prepared Au NCs could be applied to AS³⁺ detection, and it exhibit high sensitivity and excellent selectivity to As³⁺ over other metal ion present.

MEDI 396

Synthesis of the analogs of oxazolidine moiety contained in antitumor agents

Te-Fang Yang, *tfyang@ncnu.edu.tw*, *Sheng-Han Huang*, *Yu-Wei Shih*. *Applied Chemistry, National Chi Nan University, Puli, Nantou, Taiwan*

Quinocarcin and tetrazomine are well known antitumor agents and attracted much attention from medicinal chemists. One of the moieties contained in these two natural products is the oxazolotetrahydroisoquinoline skeleton. Thus, we carried out the synthesis oxazolo[2,3-a]tetrahydroisoquinolines and related compounds, using a new and green procedure. As shown in the following scheme, an individual tandem reaction of dihydroisoquiniline with γ -hydroxy- α,β -unsaturated ketone and (*E*)-4-mercapto-2-butenic ester gave the target products, respectively. It is noteworthy that the reaction finished in 15 minutes without any catalyst or additive when atom X is oxygen.



X = O, No Additive, t = 15 min, T = r. t., Y = aryl or alkyl group
 X = S, Additive = AcOH, t = 1 h, T = reflux, Y = OMe, OEt, OBn, or N(Me)OMe

Scheme 1

MEDI 397

Synthesis and identification of prodrug: Using diclofenac sodium as the main drug

Indra Gunawan, ig1204807@qu.edu.qa, Hani D. Tabba. Department of Chemistry and Earth Sciences, Qatar University, Doha, Qatar

Prodrugs are used for facilitating drug delivery in order to decrease the toxicity of drugs. A prodrug is a compound that gets chemically transformed in order to result in the release of the desired pharmacological effect needed. Diclofenac sodium is the main drug used which has been reacted with two different compounds such as salicylic acid and paracetamol. The purpose of reacting Diclofenac sodium with the two mentioned compounds is to improve the bioavailability and the enhancement on the transdermal delivery of the main drug resulting in a new compound called prodrug. The main proofs that a new compound has been developed was by using two main methods, firstly, the new compound showed a relatively lower melting point than the actual drug. Secondly, the disappearance of the functional groups mainly the amine group by the utilization of Fourier-transform infrared spectroscopy. The NMR analysis has been done to define the structures of the new compound. Methods used to indicate the new compound showed that it was synthesized successfully.

MEDI 398

Novel biochemical insights in cerebrospinal fluid of patients with Neurosyphilis based on metabonomics study

Suwen Qi, *qisuwen@szu.edu.cn*, Ruitian Luo, Qiwen Chen, Depeng Xu. Shenzhen University, Shenzhen, China

Aim: Neurosyphilis is a chronic central nervous system infectious disease caused by *Treponema pallidum*. Our aim was to study the metabolic profiling in cerebrospinal fluid of Neurosyphilis patients and identify some specific biomarkers.

Methods: 20 cerebrospinal fluid samples from Neurosyphilis patients and 18 non-Neurosyphilis samples were analyzed by liquid chromatograph–mass spectrometer (LC-MS). The LC-MS data were preprocessed by supervised pattern recognition to obtain diagnostic models. Both Orthogonal projections to latent structures discriminant analysis (OPLS-DA) and t-test were adopted to obtain specific metabolites for Neurosyphilis.

Several significant biomarkers were further validated by classical biochemical assays.

Results: LC-MS data showed the metabolites in CSF from Neurosyphilis are different from non-Neurosyphilis group. PLS-DA model parameters R²_Y and Q²_Y both were more than 0.7 and indicated satisfactory diagnostic performance. Thromboxane (TX) B₂, Docosanamide, Lactic acid were identified as novel biomarkers for Neurosyphilis.

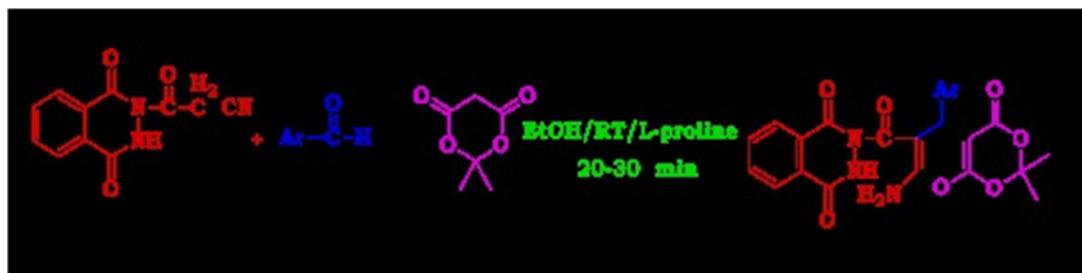
Conclusions: The metabolic study of CSF from Neurosyphilis may provide new way to explore the pathogenesis of Neurosyphilis.

MEDI 399

Synthesis and anti-microbial evaluation of novel dihydrophthalazine-1, 4-diones congeners via green synthetic methodology

Venkataramana Chittireddy, *vrr9@yahoo.com*. Department of Chemistry, J N T University Hyderabad, Hyderabad, Telangana, India

Nitrogen-containing heterocyclic compounds are ubiquitous in nature, and are part of biologically active pharmaceuticals and agrochemicals. Among a large variety of nitrogen-containing compounds, heterocycles containing hydrazine moiety has received considerable attention due of their pharmacological properties and clinical applications. Here in, we report green and eco-friendly synthesis of novel dihydrophthalazine-1, 4-diones congeners as potential anti-microbial agents. The targeted chemical entities (4) have been developed by condensation of 3-(1,4-dioxo-3,4-dihydrophthalazin-(1H)-yl)-3-oxopropanenitrile (1), benzaldehydes (2) and Meldrum's acid (3) using L-proline as recyclable green catalyst in eco-friendly ethanol at RT for 15-30 min.



MEDI 400

Chemical synthesis and biological evaluation of unnatural analogs of Amorfrutin

Leonard Barasa, *leonard.barasa15@stjohns.edu. Pharmaceutical Sciences, St. John's University, Jamaica, New York, United States*

Amorfrutins are natural products characterized by isoprenoid-substituted benzoic acid derivatives. They are reported to be originally isolated from fruits of *Amorpha fruticosa* L. (bastard indigo) and from the roots of *Glycyrrhiza foetida* Desf. (licorice). Peroxisome proliferator-activated receptor gamma has emerged as a highly sought target for cancer and inflammatory diseases. Due to their promise in being partial agonist, and low μM activity, research efforts have been focused on developing structural derivatives with improved pharmacological properties, and low toxicity. We have devised a modular synthetic approach to generate a structurally diverse library of amorfrutin analogs. Since there have been no extensive studies done to evaluate the structure activity relationship (SAR), the first-generation analogs we have synthesized will shed light on the SAR of this class of natural products. We plan to evaluate the anti-cancer and anti-inflammatory principles in pertinent *in vitro* and *in vivo* models. The bioactivity data will guide us in designing the subsequent generations of analogs.

MEDI 401

Drug-drug interactions severity prediction using PASS approach

Alexander Dmitriev¹, Dmitry Filimonov¹, Alexey Lagunin^{1,2}, Anastasiya Rudik¹, Dmitry Karasev^{1,2}, Khalimat Murtazalieva^{1,2}, Vladimir Poroikov¹, vladimir.poroikov@ibmc.msk.ru. (1) Department for Bioinformatics, Institute of Biomedical Chemistry, Moscow, Russian Federation (2) Department for Bioinformatics, Pirogov Russian National Research Medical University, Moscow, Russian Federation

When several drugs are co-administrated, a drug-drug interaction (DDI) phenomenon may appear. Many DDIs are due to changes in the metabolism of drugs. In this case, DDI is manifested by the effect of one drug on the biotransformation of other drugs, its slowdown (in case of inhibition of drug-metabolizing enzymes) or acceleration (in case of induction of drug-metabolizing enzymes), which leads to change in the pharmacological action of co-administrated drugs.

The severity of DDIs can be classified by applying different classification systems. One of the most advanced is OpeRational ClassificAtion (ORCA) system for the classification of DDI, created for physicians to assess the risk of co-administration of two drugs. ORCA divides DDI into five classes: contraindicated (class 1), provisionally contraindicated (class 2), conditional (class 3), minimal risk (class 4), no interaction (class 5). For computer prediction of the severity of DDI, we collected a training set consisting of approximately 4000 pairs from 500 drugs that belong to the ORCA classes 1-3 of DDI in case of co-administration. The prediction of DDI classes is based on a combination of substructural MNA descriptors (Multilevel Neighbourhoods of Atoms),

and naïve Bayesian classification algorithm implemented in the PASS (Prediction of Activity Spectra for Substances) software.

The average invariant accuracy of prediction, calculated in the leave-one-out and 20-fold cross-validation procedures, were approximately 0.9.

The drug-drug interactions severity prediction based on xenobiotic structural formulas and the PASS prediction algorithm provides accuracy sufficient for practical application in the fields of the biomedical and pharmaceutical chemistry. Such prediction prior to clinical use can increase the safety of new drugs being developed and their application in medical practice.

MEDI 402

Discovery of pharmacological potential of 9,10-anthaquinone dithiocarbamates: Virtual screening and experimental study

Maryna Stasevych¹, Viktor Zvarych¹, Volodymyr Novikov¹, Svetlana Zagorodnya², Olga Povnitsa², Maryna Chaika², Maria Nesterkina³, Iryna Kravchenko³, Tatyana Glorizova⁴, Vladimir Poroikov⁴, vladimir.poroikov@ibmc.msk.ru. (1) Lviv Polytechnic National University, Lviv, Ukraine (2) Institute of Microbiology and Virology of the NAS of Ukraine, Kyiv, Ukraine (3) Odessa National Polytechnic University, Odessa, Ukraine (4) Department for Bioinformatics, Institute of Biomedical Chemistry, Moscow, Russian Federation

Computational approaches are widely used in drug design, in the finding and optimization of lead compounds. The *Way2Drug* platform [<http://www.way2drug.com/dr>] provides access to information about drugs launched in U.S. and Russian Federation, and the opportunities of computer-aided prediction of biological activity for drug-like compounds.

Using the computational tools of the platform such as *PASS*, *Cell Line Cytotoxicity Predictor*, *Acute Rat Toxicity* for prediction, we selected the most promising "hits" for the synthesis and testing of biological activity for the search of potential low toxic drug-like compounds with antitumor, antioxidant, antibacterial, antifungal, antiviral, anticonvulsant activities, etc. among 9,10-anthaquinone dithiocarbamates.

Experimental tests *in vitro* showed 10 perspective dithiocarbamates of 9,10-anthaquinone with cytotoxicity to the human lines of lung carcinoma (*A549*), *larynx carcinoma (Hep-2)*, cervix carcinoma (*HeLa*), Burkitt's lymphoma (*Raji*), primary culture from B-cell lymphoma (*BL*) and hamster chinese ovary (*CHO*) cells. Six compounds showed high antimicrobial activity against test-cultures of *Escherichia coli B-906*, *Staphylococcus aureus 209-P*, *Mycobacterium luteum B-917*, *Candida tenuis VKM Y-70* and *Aspergillus niger VKM F-1119*. Three dithiocarbamates revealed antiviral action against *Herpes simplex virus type 2* and two compounds – against *Epstein-Barr virus*. The experimental study of anticonvulsant activity indicated the presence of a moderate effect on short intervals of time (6 hours) for five synthesized compounds. The study of acute oral toxicity shows LD₅₀ >1000 mg/kg for five potential drug-like compounds. Therefore, predicted cytotoxic, antimicrobial, antifungal, antiviral, anticonvulsant

activities and acute oral toxicity using tools of the *Way2Drug* platform were confirmed in *in vitro* studies.

MEDI 403

Structure activity relationship (SAR) studies of NNRTI (non-nucleoside reverse transcriptase inhibitors) and nucleotide reverse transcriptase (NRTI) used to combat HIV, using Gaussian computational techniques

Saraswathi Narayan, *snarayan@stevenson.edu*, **Destinie Z. Burgan**, **Karleigh Y. Baldwin**. *Chemistry, Stevenson University, Owings Mills, Maryland, United States*

Nevirapine (NVP) a non-nucleotide reverse transcriptase inhibitor (NNRTI) and AZT (an anti-viral nucleoside-analog reverse transcriptase inhibitor (NRTI) that treats Human Immunodeficiency Virus 1 (HIV-1) do not completely suppress HIV-1 and lead to drug resistance in addition to other side effects. In this investigation Structure Activity Relationship (SAR) studies were made by modifying the structures of the lead compounds Nevirapine a Nucleoside Reverse Transcriptase (NRTI) and Azidothymidine (AZT) a Non-Nucleoside Reverse Transcriptase (NNRT) using Gaussian computational method. Several molecular properties like total energy, dipole moment and solvation energy in water and n-octanol of Nevirapine and AZT analogs using Density Functional Theory (DFT) and Hartree Fock (HF) with various Basis sets were calculated. The results are interpreted in terms of narrowing the search for the drugs that could possibly be used for treating this deadly virus that have fewer side effects.

MEDI 404

Discovery and characterization of small molecules of long noncoding MALAT1 triple helix with anti-cancer therapeutic potential

Fardokht Abulwerdi¹, *fardabul@umich.edu*, **Wenbo Xu**², **Abeer Ageeli**³, **Michael Yonkunas**³, **Gayatri Arun**², **John Schneekloth**⁴, **Nathan J. Baird**³, **David Spector**², **Stuart Le Grice**¹. (1) *Basic Research Laboratory, National Cancer Institute, Frederick, Maryland, United States* (2) *Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, United States* (3) *Department of Chemistry and Biochemistry, University of the Sciences, Philadelphia, Pennsylvania, United States* (4) *National Cancer Institute, Frederick, Maryland, United States*

Long noncoding RNAs (lncRNAs) have diverse biological functions and are associated with various disease states, including cancer. Human metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) features a highly conserved triple helix at its 3'-sequence which contributes to its stability and is highly associated with its increased oncogenic activity. MALAT1 plays a crucial role in breast cancer tumor progression and metastasis, making it an attractive target for cancer therapy. Small molecules offer an opportunity to target highly structured RNA motifs such as a triple helix. Therefore, as a first step in developing a therapeutic strategy, we elected to perform a high throughput

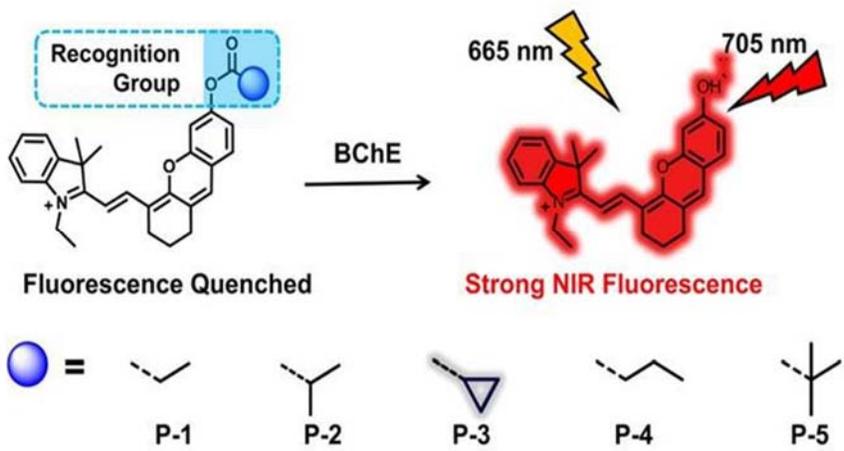
small molecule microarray screening of ~26,000 small molecules to identify compounds binding to a 5'-fluorescently-labeled MALAT1 triple helix motif. After statistical analysis and visual inspection, 188 hit molecules were identified. From the hit list, 28 compounds representing the most selective binders were re-purchased. We next elected to evaluate the compounds in a mouse mammary cancer organoids derived from MMTV (*mouse mammary tumor virus*)-PyMT luminal B tumors and grown in 3D matrigel. MMTV-PyMT tumors are undifferentiated, aggressive mammary carcinomas that are prone to metastasizing to the lungs. All 28 compounds were evaluated in this model and our results showed that when treated with 1 μ M of hit candidates **5** and **16**, MALAT1 expression in organoids reduced by 54% and 41% respectively. We also observed a 38% and 27% decrease in organoid branching, a property of organoids which correlates with metastasis, with **5** and **16** respectively. A recently developed four-dimensional fluorescence resonance energy transfer (4D FRET) assay provided a detailed conformational landscape of MALAT1 triple helix interactions with **5** and **16** and determined their dissociation constants (K_{ds}) to be in the low micromolar range. Computational modeling predicted their basis of binding to MALAT1 triple helix. The superior compound **5** further modulated downstream MALAT1 target genes in a dose-dependent manner while sparing multiple endocrine neoplasia beta (MENbeta) lncRNA which shares a similar triple helix to MALAT1. These results demonstrate the feasibility of targeting of an RNA triple helix with small molecules and contribute to the development of new classes of anti-cancer therapeutics and molecular probes for treatment and understanding of MALAT1-driven breast cancer.

MEDI 405

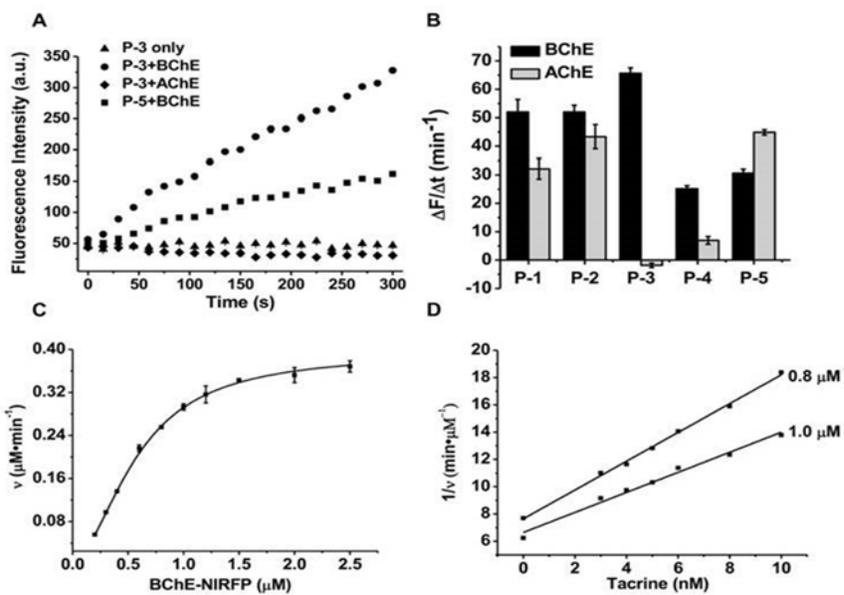
Detection of butyrylcholinesterase in living systems using a highly specific near-infrared fluorogenic substrate

Guang-Fu Yang, gfyang@mail.ccnu.edu.cn, Shi-Yu Liu, Wen-Chao Yang. Central China Normal University, Wuhan, China

Precision small-molecule probes have attracted extensive interest for imaging specific protein biomarkers in living cells. However, it still remains a great challenge to design extremely selective probes to be taken as the substrate solely by an enzyme while other analogous enzymes coexist in cells. Here we report a rationally designed small-molecule substrate that can detect butyrylcholinesterase (BChE) in living cells but does not react at all with its cousin acetylcholinesterase (AChE). This probe, named **BChE-NIRFP**, is a bulky fluorogenic ester capable of emitting strong near-infrared fluorescence upon hydrolysis by BChE. We demonstrate that **BChE-NIRFP** not only functions as an exquisite substrate for BChE via *in vitro* assays but also represents a superb “signal-on” imaging tool to track the activity of BChE in human cells, zebrafish, and a mouse model of Alzheimer's disease (AD). Given the importance of BChE to AD and other human diseases, **BChE-NIRFP** is expected to facilitate future biomedical investigations to define the relationship between BChE and diverse human diseases.



Probe design. Five NIR fluorogenic esters were synthesized and investigated as the substrate for BChE



Characterization of fluorogenic substrates for BChE. (A) Signaling profiles of **P-3** and **P-5** (10 μM) upon treatment of BChE or AChE (20 $\mu\text{g}/\text{mL}$). (B) BChE/AChE selectivity calculated from the signaling profiles of candidate substrates (10 μM) toward BChE and AChE (20 $\mu\text{g}/\text{mL}$). (C) Michaelis-Menten curve of **BChE-NIRFP** catalyzed by BChE (8 $\mu\text{g}/\text{mL}$). (D) Dixon plots of inhibitory kinetics of Tacrine with **BChE-NIRFP** (0.8 μM and 1 μM) as the substrate.

MEDI 406

Biological activity of photoactivated iron metallocene anti-cancer compounds

Pauline Olsen, *pmolsen@ucsd.edu*, **Joseph M. O Connor**. *Univ of California, La Jolla, California, United States*

Ferrocene is a promising scaffold for new medicinal therapies due to advantages that include cost, biological stability, membrane permeability and electrochemistry. We have synthesized benzoyl-ferrocene derivatives that photochemically release free iron(II) in cells. By creating a library of derivatives, we have optimized for a highly specific photodynamic therapy (PDT) effect. We hypothesize that the observed cytotoxicity is due to the release of iron(II), which catalyzes the Fenton reaction, leading to the formation of toxic reactive oxygen species (ROS) in the cell. More specifically, we believe these agents function by triggering a ferroptosis cell death mechanism. Through a series of *in vitro* experiments we have determined that photolysis leads to a dose-dependent increase in lipid peroxidation. Additionally, we found that cytosolic ROS concentrations are the same in the dark and after photolysis, thereby supporting a hypothesis that ferrocene derivatives will function as highly specific PDT anti-cancer agents.

MEDI 407

Asymmetric total synthesis of novel resolvin conjugates in tissue regeneration (RCTR)

Ting F. Lam, *tingfunl@usc.edu*, **Robert Nshimiyimana**, **Nicos A. Petasis**. *Dept of Chemistry and Loker Hydrocarbon Institute, University of Southern California, Los Angeles, California, United States*

The discovery, structural characterization, and biological investigation of several new series of enzymatically hydroxylated derivatives of docosahexaenoic acid (DHA), including the resolvins, protectins, and maresins, led to the recognition of a new class of lipid mediators that promote the resolution of inflammation, known as specialized pro-resolving mediators (SPM). More recently, several new types of DHA-derived sulfidoconjugate derivatives were discovered from the same biosynthetic precursors and shown to accelerate tissue regeneration. These include the maresin conjugates in tissue regeneration (MCTR), and similar sulfidoconjugates derived from protectin precursors (PCTR), or resolvin precursors (RCTR). We have previously completed the stereocontrolled total synthesis of MCTRs and PCTRs, which helped to confirm their postulated biosynthesis, and to investigate their novel biological actions. Our biomimetic synthetic approach involved the stereocontrolled total synthesis of the epoxide precursors of MCTRs and PCTRs, followed by opening the epoxide by the corresponding cysteine components. Herein, we detailed our related efforts involving the asymmetric total synthesis of resolvin-derived sulfidoconjugates (RCTRs).

MEDI 408

Stereocontrolled total synthesis of novel resolvin-related sulfidoconjugates

Robert Nshimiyimana, nshimiyi@usc.edu, **Ting F. Lam**, **Nicos A. Petasis**. Dept of Chemistry and Loker Hydrocarbon Institute, University of Southern California, Los Angeles, California, United States

Investigations on the enzymatic oxygenation of DHA led to the discovery and study of several types of resolvins, protectins, and maresins, which promote the resolution of inflammation, and are known as specialized pro-resolving mediators (SPM). More recently, these efforts led to the identification of several new types of DHA-derived sulfidoconjugate derivatives, including the protectin conjugates in tissue regeneration (PCTR), and similar sulfidoconjugates derived from maresin precursors (MCTR), or resolvins precursors (RCTR). We have previously completed the stereocontrolled total synthesis of MCTRs and PCTRs, that confirmed their structure and stereochemistry, and their postulated biosynthesis, and also enabled the study on their novel biological actions. Our synthetic strategy was based on the stereocontrolled total synthesis of the epoxide precursors of MCTRs and PCTRs, followed by opening the epoxide by glutathione and related cysteine components. Herein, we detailed our recent efforts aimed at the stereocontrolled total synthesis of novel resolvins-related sulfidoconjugates.

MEDI 409

Improved synthesis of *cis*-1, 4-cyclohexanediol

Wenbo Liu, wenbo_liu@pharmablock.com, **Hui Li**, **Minmin Yang**. Department of Research, Pharmablock Sciences (Nanjing), Nanjing Jiangsu, China

We have developed an improved route to *cis*-1,4-cyclohexanediol (**1**) from inexpensive material 1,4-dioxaspiro[4.5]decan-8-one (**2**). Hundreds of grams of **1** could be obtained from a single batch in 5 steps with an overall yield of 25-30%. During the process, *cis* and *trans*-isomers of **6** were separated and converted to *cis*-1, 4-cyclohexanediol (**1**) respectively [**Figure1**].

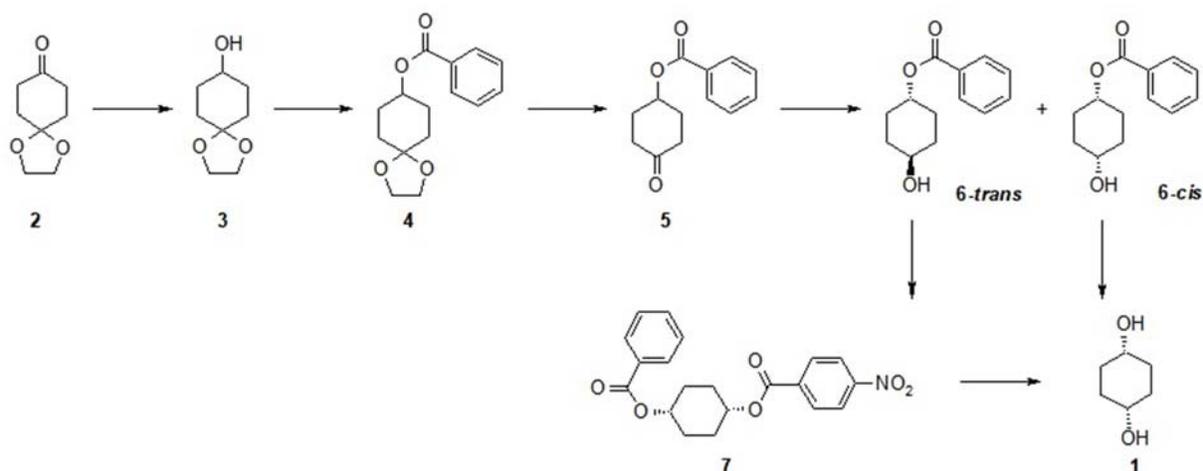


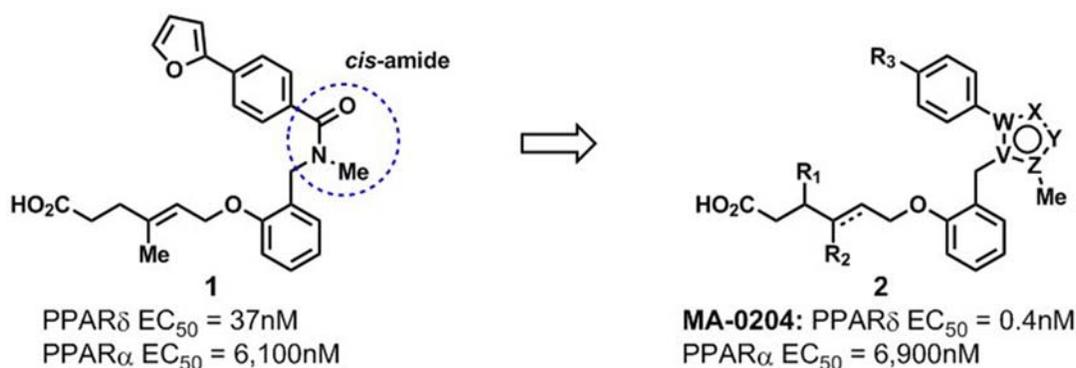
Figure 1: Synthetic route to *cis*-1, 4-cyclohexanediol

MEDI 410

PPAR δ modulators improve mitochondrial function: Potential treatment for Duchenne muscular dystrophy (DMD)

Bharat Lagu¹, blagu@mitobridge.com, Arthur F. Kluge¹, Effie Tozzo¹, Matthew Goddeeris¹, Peter Dwyer¹, Andrew Basinsky¹, Ross Fredenburg¹, Ramesh Senaiar², Mahaboobi Jaleel², Narasimha R. Krishnamurthy², Anirudha Lakshminarasimhan², Nirbhay K Tiwari², Taisuke Takahashi³, Michael A. Patane¹. (1) Mitobridge, Inc., Cambridge, Massachusetts, United States (2) Aurigene Discovery, Bangalore, Karnataka, India (3) Astellas Pharma, Tsukuba, Japan

X-ray structure of a selective PPAR δ modulator **1** bound to the ligand binding domain (LBD) of PPAR δ , revealed that the amide moiety exists in thermodynamically unfavorable *cis*-amide conformation. Among several heterocyclic analogs (**2**) that were tried as bioisosteric replacements of the *cis*-amide, imidazoles emerged as highly potent and selective modulators of PPAR δ . Further exploration of SAR helped optimize the pharmacokinetic parameters. The lead compound, **MA-0204** increased PPAR δ target gene expression and improved mitochondrial functions in DMD patient cells suggesting a role for the selective PPAR δ modulator as a treatment of DMD.



MEDI 411

Novel synthetic method for 5-aminooxan-3-ol hydrochloride

Jilong Li, li_jilong@PharmaBlock.com, Lei Qi, Qinlong Fei, Hui Li, Minmin Yang. Pharmablock Sciences (Nanjing), Nanjing Jiangsu, China

5-Aminooxan-3-ols are useful building blocks in designing kinase inhibitors. We developed a novel route to synthesize 5-aminooxan-3-ol hydrochloride, from commercial available oxane-3,5-dione. Our method has a number of attractive features, including mild reaction conditions, good yield and easy purification [Figure1]. The ketone group of key intermediate **4** can be readily converted into other functional groups, such as nitrile, ester and fluoride, allowing more opportunities.

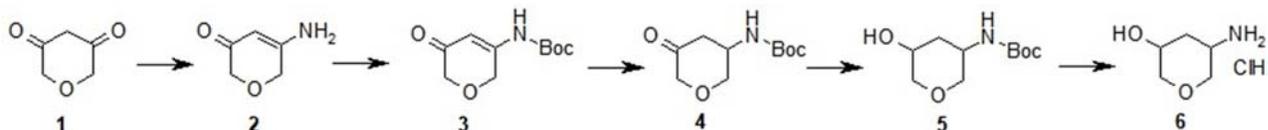


Figure 1: Synthetic route to 5-aminooxan-3-ol hydrochloride

MEDI 412

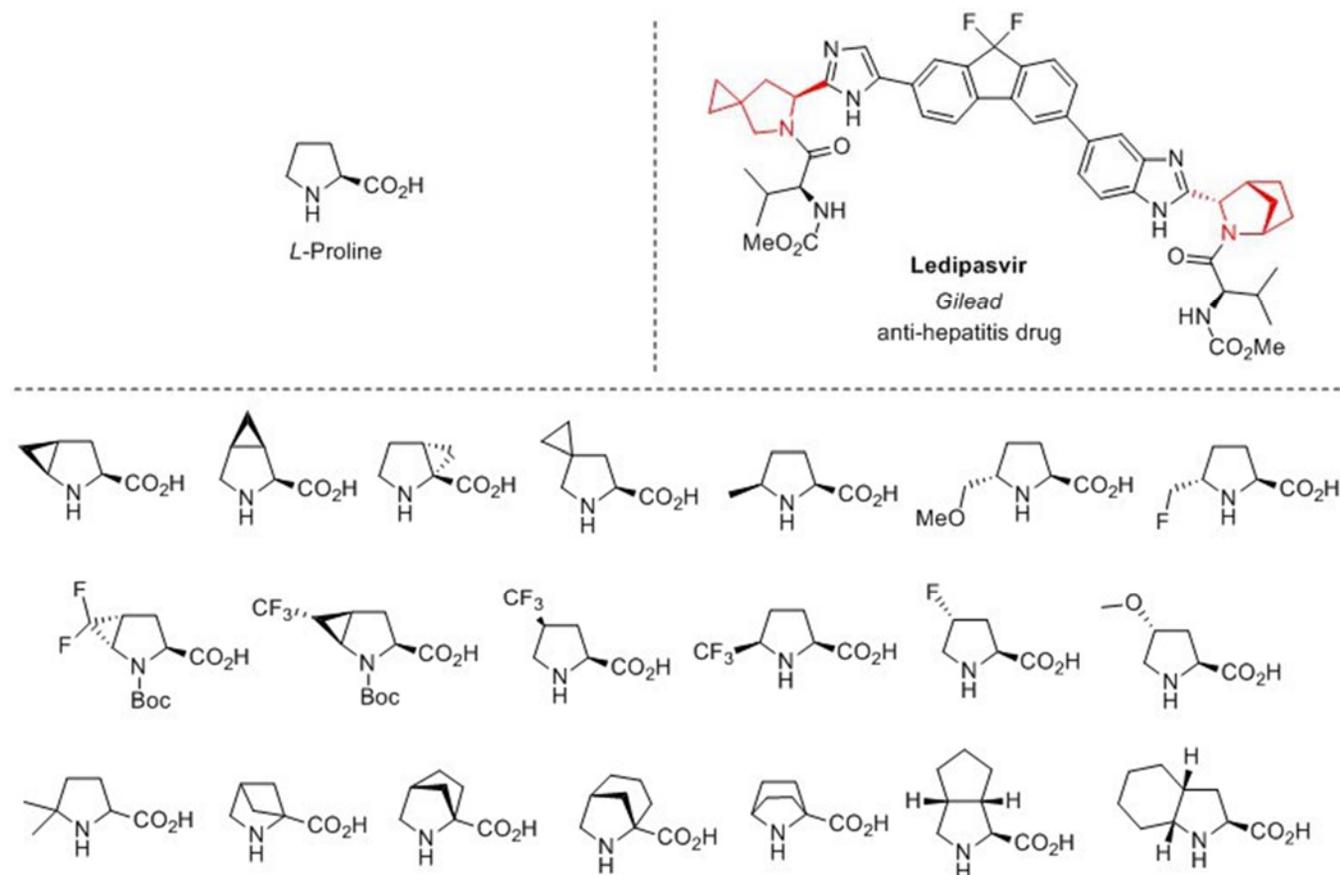
Synthesis and application of unnatural proline analogues: Advanced building blocks for medicinal chemistry

Pavel Mykhailiuk², Yurii Moroz¹, ysmoroz@gmail.com, Oleg Michurin². (1) ChemBioCenter, Taras Shevchenko National University of Kyiv, Kyiv, Ukraine (2) Chemistry, Enamine Ltd, Kiev, Ukraine

L-Proline is a natural amino acid playing an important role in drug discovery as a cheap chiral bifunctional building block. In this context, over the past decade unnatural analogues of Proline also became extremely popular. For example, in 2010 Gilead launched *Ledipasvir* – a drug bearing the residues of two unnatural analogues of L-

Proline.

In this work, we have rationally designed, synthesized and applied a library of novel/previously scarcely available analogues of Proline in medicinal chemistry. Details of the synthesis and application of the obtained compounds will be discussed.



MEDI 413

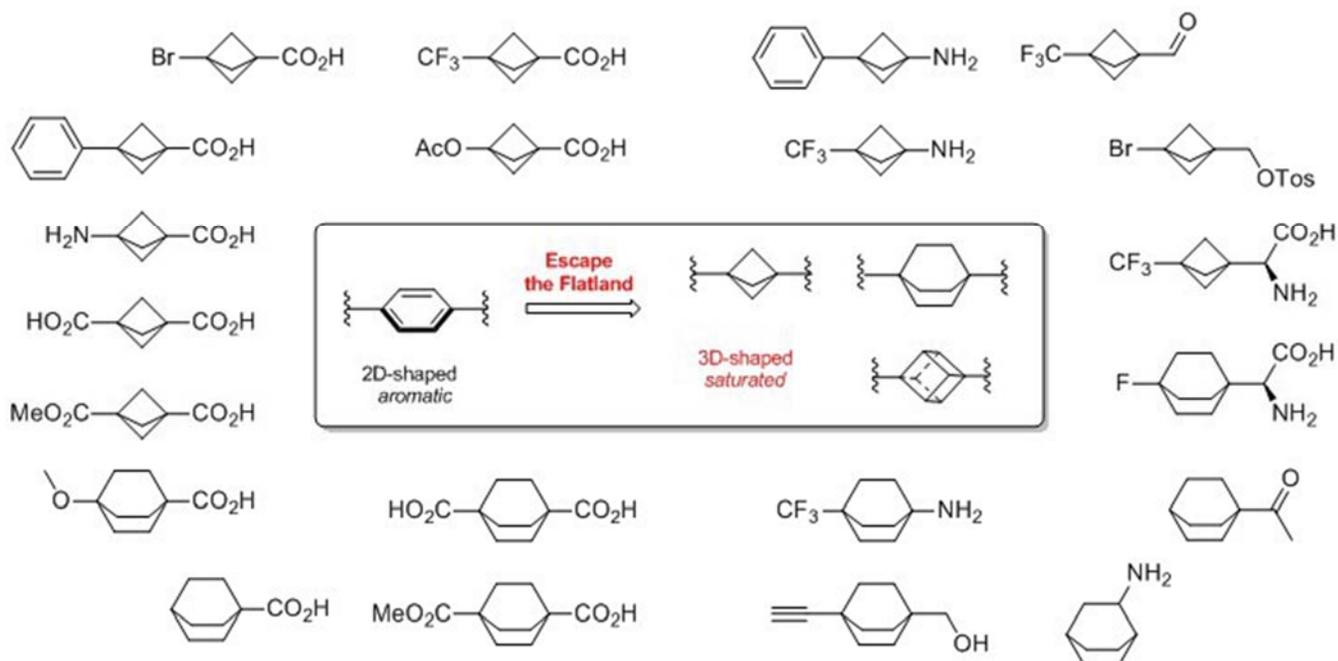
Design, synthesis and application of novel building blocks to “Escape the Flatland” in medicinal chemistry

Yurii Moroz¹, ysmoroz@gmail.com, **Pavel Mykhailiuk**², pavel.mykhailiuk@gmail.com, **Andrey Tolmachev**^{2,1}. (1) ChemBioCenter, Taras Shevchenko National University of Kyiv, Kyiv, Ukraine (2) Chemistry, Enamine Ltd, Kiev, Ukraine

Given the modern trend in medicinal chemistry – “Escape the Flatland” – saturated 3D-shaped building blocks do play an important role. Compared to their aromatic 2D-shaped counterparts, the saturated analogues usually possess higher water solubility, higher activity and lower toxicity.

In this work, therefore, we have rationally designed and synthesized a library of novel

saturated bioisosters of benzene. Details of the synthesis and application of the obtained compounds will be discussed.

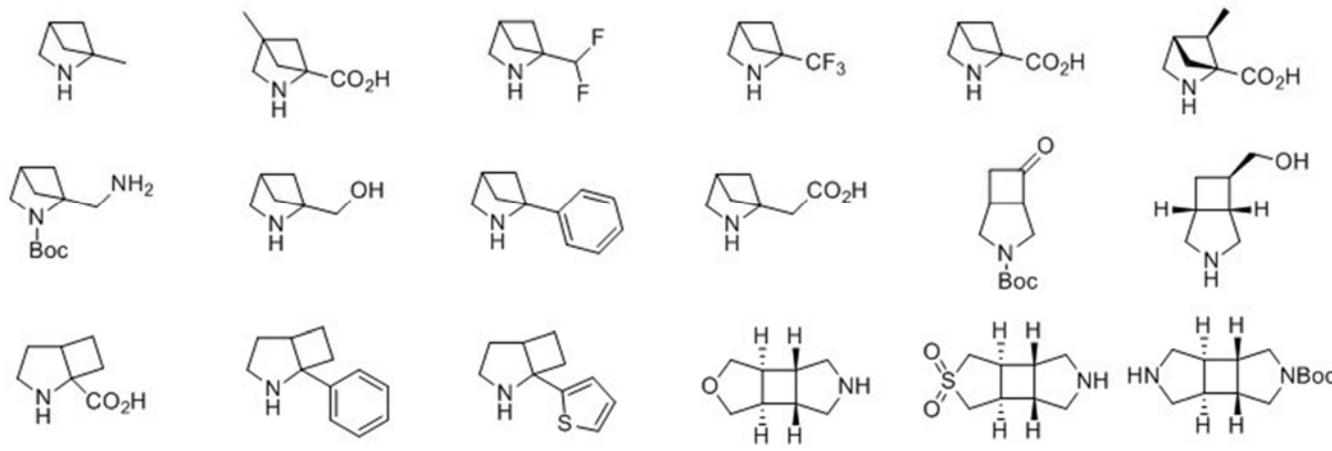
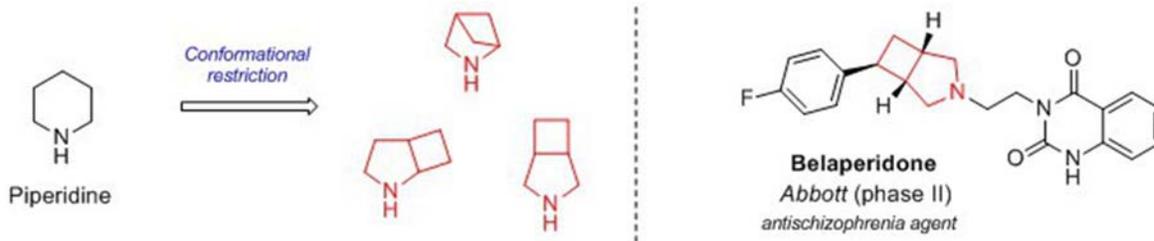


MEDI 414

[2+2]-Photochemical synthesis and application of bicyclic amines: Advanced building blocks for medicinal chemistry

Yurii Moroz¹, ysmoroz@gmail.com, **Pavel Mykhailiuk**², Pavel.Mykhailiuk@gmail.com, **Vadim Levterov**². (1) ChemBioCenter, Taras Shevchenko National University of Kyiv, Kyiv, Ukraine (2) Chemistry, Enamine Ltd, Kiev, Ukraine

“Conformational restriction” concept has already gained a considerable attention in medicinal chemistry. Scientists are looking more and more now on 3D-shaped saturated building blocks. In this context, intrinsically conformationally rigid bicyclic amines seem to be promising for drug discovery. For example, *Belaperidone* - a drug candidate of *Abbott* - bearing a residue of a bicyclic amine, reached phase II of clinical trials. In this work, we have rationally designed, synthesized and applied a library of novel/previously scarcely available diverse bicyclic amines in medicinal chemistry. The key synthesis step was photochemical [2+2]-cycloaddition. Details of the synthesis and application of the obtained compounds will be discussed.



MEDI 415

Polyfunctional building blocks for drug discovery

Oleksii Gavrylenko¹, oleksii.gavr@gmail.com, **Yurii Moroz**², **Boris Rogovoy**¹. (1) *Chemspace, Kiev, Ukraine* (2) *ChemBioCenter, Taras Shevchenko National University of Kyiv, Kyiv, Ukraine*

Polyfunctional building blocks have gained an attention to produce sized screening compound libraries and DNA-encoded libraries (DELs). Despite high interest, a small offer has been found among the purchasable molecules. We propose bifunctional and trifunctional building block sets containing 72,000 and 7,500 compounds respectively. The sets contain molecules with orthogonal functionalities compatible with DEL chemistry. The compounds have favorable physicochemical profiles and can be accessed via robust synthetic chemistry procedures that have already been able to deliver over 40,000 compounds.

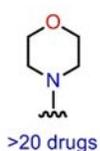
MEDI 416

Design, synthesis and application of novel morpholine surrogates

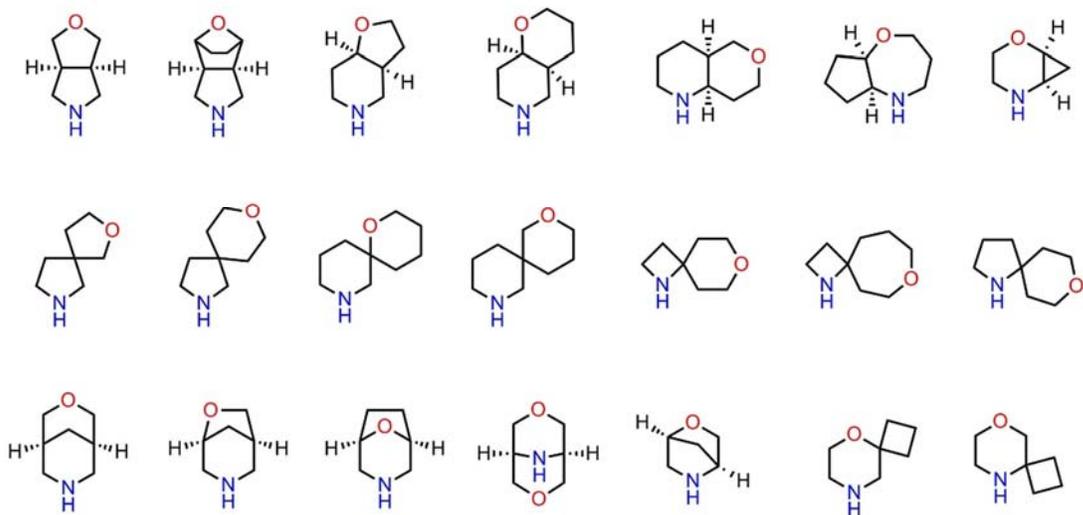
Pavel Mykhailiuk, pavel.mykhailiuk@gmail.com. *Chemistry, Enamine Ltd, Kiev, Ukraine*

Morpholine is an established building block in drug discovery – more than 20 FDA-approved drugs contain its residue. In this work, therefore, we have rationally designed and synthesized a library of novel/previously scarcely available bicyclic morpholine surrogates. Details of the synthesis and application of this library will be discussed.

Known motif



Novel motifs

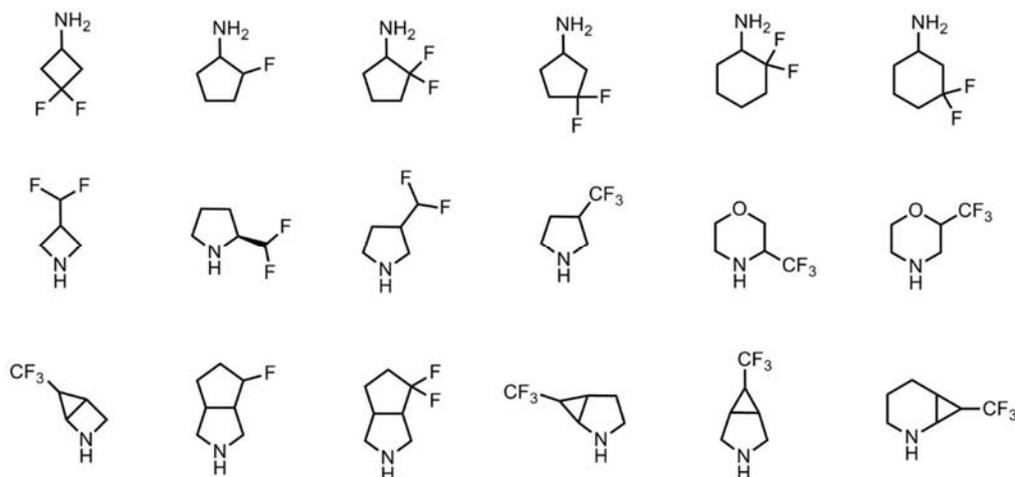


MEDI 417

Design and synthesis of novel fluorinated amines

Pavel Mykhailiuk, pavel.mykhailiuk@gmail.com. Chemistry, Enamine Ltd, Kiev, Ukraine

Modern drug discovery is hard to imagine without fluorine: ca. 20% of all pharmaceuticals contain this element. To date, however, only a tiny part of the theoretically possible building block structures are synthesized. Many simple combinations of fluorine with carbon and nitrogen atoms are still unknown. Commercially accessible fluorinated alicyclic amines are mostly limited to pyrrolidines and piperidines. The latter are quite popular in medicinal chemistry (Figure). In this work, we synthesized a library of novel aliphatic saturated amines. Details of their design and synthesis will be reported.



MEDI 418

Total synthesis of nosokophic acid

Deisy Pena¹, deisympr@gmail.com, **Timothy Tetrault**¹, **Marc A. Boudreau**². (1) *Chemistry, University of New Hampshire, Kittery, Maine, United States* (2) *Department of Chemistry, University of New Hampshire, Durham, New Hampshire, United States*

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major nosocomial Gram-positive pathogen that has developed multi-resistance to β -lactam antibiotics. Moreover, MRSA resistance to the last-resort antibiotic, vancomycin, has been reported. This suggests that MRSA will likely acquire further resistance to vancomycin in the future. It is therefore increasingly necessary to find new antibiotics and to devise novel measures that are effective against MRSA infections.

Recently, nosokophic acid, a predicted intermediate in the biosynthesis of phosphoglycolipid natural products, was isolated from the culture broth of *Streptomyces* sp. K04-0144. Interestingly, nosokophic acid shows no anti-MRSA activity, but markedly potentiates imipenem activity against MRSA. This important outcome has attracted our attention to develop the total synthesis of this natural product. Thus, this poster will summarize our efforts on the total synthesis of nosokophic acid.

MEDI 419

Distorted phthalocyanines via click-chemistry: Synthesis, photoacoustic, photothermal and cell studies

Waqar Rizvi¹, waqar.rizvi86@gmail.com, **Emaad Khwaja**², **Naga Venkata Satya Dinesh K. Bhupathiraju**², **Alei Rizvi**², **Charles M. Drain**². (1) *Chemistry & Biochemistry, Hunter College and The Graduate Center CUNY, Valley Stream, New York, United States* (2) *Chemistry Dept, Hunter College CUNY, New York, New York, United States*

Nucleophilic aromatic substitution chemistry on perfluorophthalocyanines was used to develop facile synthetic methods for generating Pc derivatives with near IR absorption. The photophysics of these molecules can be fine-tuned via simple click-type substitution chemistry resulting in a decrease in the HOMO-LUMO gap for each substitution. This leads to a red-shifted absorbance that should be ideal for various biomedical and materials applications. A commercially available, cost effective surfactant, isodecyloxypropyl-1,3-diaminopropane (tomamine®), is appended onto zinc 1,2,3,4,8,9,10,11,15,16,17,18,22,23,24,25-hexadecafluorophthalocyanine (ZnF₁₆Pc). This substitution red-shifts the UV-vis absorbance and helps in solubility. Varying the equivalents of tomamine, we were able to isolate mono, di, tri and tetra-substituted products with UV-visible absorbance, lowest energy Q bands, at ca. 748, 765, 786 and 805 nm respectively. An unexpected discovery showed that addition of a 7-membered ring on the outside of ZnF₁₆Pc induces steric interactions that cause the otherwise planar Pc macrocycle to twist and distort. This distortion results in an unexpectedly large shift in the UV-visible spectral peaks. The resulting peak is also much broader because of flexibility in the macrocycle. These compounds are highly soluble in organic and aqueous solvents and showed high photoacoustic and photothermal conversions for photoacoustic imaging and photothermal therapy of cancers.

MEDI 420

Click chemistry on chlorins

NVS Dinesh K Bhupathiraju¹, nb216@hunter.cuny.edu, **Waqar Rizvi**², **Charles M. Drain**³. (1) Chemistry, Hunter College, New York, New York, United States (2) Chemistry, Hunter College, Valley Stream, New York, United States (3) Chemistry Dept, Hunter College Cuny, New York, New York, United States

Chlorophyll is a naturally occurring chlorin and was studied because of its unique photophysical properties. Since then several chlorins have been synthesized for application in medicine, analytics, and materials. Chlorin synthesis is challenging and requires multi steps which generally results in low yields. We have synthesized chlorins with a fused N-methyl pyrrolidine (N-methyl chlorin) or a fused N-H pyrrolidine (N-H chlorin) on to 5, 10, 15, 20-tetrakis-(2, 3, 4, 5, 6-pentafluorophenyl)-porphyrin (TPPF₂₀) using sarcosine or glycine-based azomethine ylide via 1,3-dipolar cyclo addition reaction in good yields. Here in we are presenting the substitution of biomotifs such as glucose, lysine and DNA on to N-methyl chlorin and N-H chlorin using click reactions. These chlorin bioconjugates were then tested *in-vitro* and *in-vivo*.

MEDI 421

Using adducts and fragments to identify compounds in mass-directed flash column chromatography

John R. Bickler, bob.bickler@biotage.com. Biotage, LLC, Hampstead, North Carolina, United States

With the growing popularity and use of mass-directed flash chromatography to purify specific compounds it is important to understand that the expected mass or masses may not be detected as the expected M+H or M-H ions but also to consider their possible adducts and fragments.

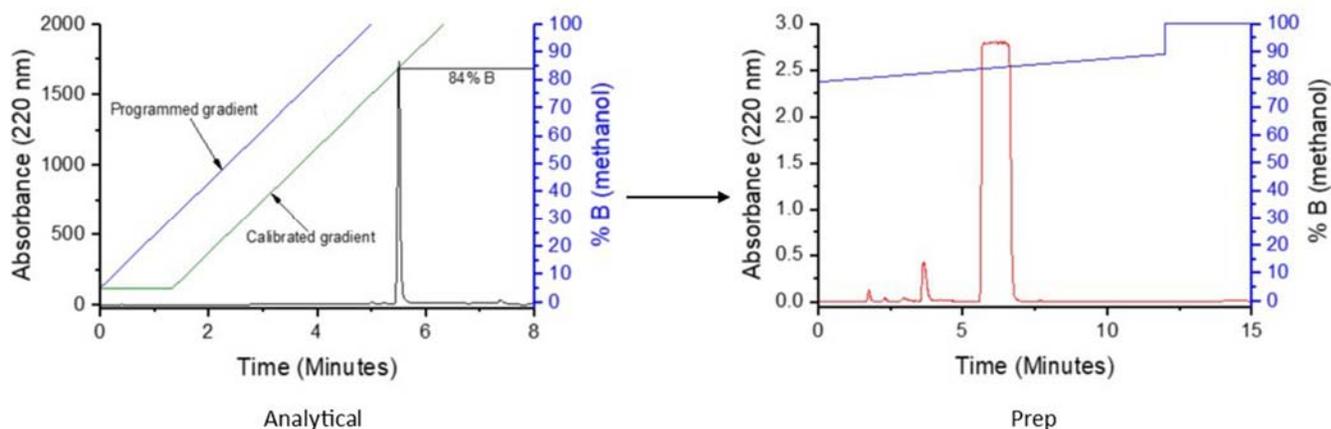
In this poster we show how using adducts and fragments can help isolate the targeted sample compounds.

MEDI 422

Calibration of analytical HPLC to generate preparative LC gradients

Jack E. Silver, jacksilver86@gmail.com, Roberto Sorgo, Aaron Darter. Teledyne ISCO, Lincoln, Nebraska, United States

Preparative LC (liquid chromatography) is widely used to purify reaction mixtures. One bottleneck in the purification process is method development. Significant time can be required to produce an efficient preparative purification method that resolves the desired compound from impurities and minimizes both time and solvent usage. This work describes a simple method of calibrating analytical HPLC systems to match the preparative LC system using the existing scouting gradients typically employed by a research group. After the calibration is complete, a determined delay volume is applied to the scouting gradient. This delay volume encompasses any dwell volumes, column volumes, mixing volumes, solvent misproportioning, and other corrections that are needed to match the analytical system to the preparative system. After the calibration is complete, the user only needs to enter the retention time of the desired compound from the analytical HPLC scouting run to calculate a preparative method. Although the calculated gradient is designed to run over 12 minutes with targeted compounds eluting at ~6 minutes, other gradient lengths may be run.



Preparative gradient generated from an analytical scouting gradient

MEDI 423

Methanol as an alternative mobile phase solvent for reversed-phase peptide purification

*Elizabeth Denton*¹, elizabeth.denton@yale.edu, *John R. Bickler*², *John J. Urh*¹. (1) *Biotage, Charlotte, North Carolina, United States* (2) *Biotage, LLC, Hampstead, North Carolina, United States*

Interest in peptides as therapeutic agents continues to expand as more peptide-based drugs enter clinical trials and move on as approved medications. With this increased interest though, comes a significant demand for better workflow strategies enabling efficient progress from amino acid building block to final purified peptide product. With regard to peptide purification, many new stationary phase sorbents have come to the market as well as several new approaches to gradient design. Very little consideration has been given to the identity of the mobile phase solvents though.

Methanol is often exchanged for acetonitrile in reversed phase small molecule purification, but is rarely considered for peptide purification. One potential limitation for this strategy is the increased backpressure caused by methanol's higher viscosity. When using flash chromatography for reversed phase peptide purification though, the elevated backpressure is not a problem. Herein we demonstrate that methanol can indeed serve as an alternative, greener solvent for reversed phase purification of peptides using flash chromatography.

MEDI 424

Development of HPLC methods for analysis of cholesteryl esters with alkyl chains of odd number length

*Kayla Lilly*¹, klilly@mail.niagara.edu, *Mary Q. Irving*², *Julie Hughes*¹, *Jerome Schentag*², *Lawrence Mielnicki*¹, Imm@niagara.edu, *Mary McCourt*¹. (1) *Chemistry Dept, Niagara Univ, Niagara Univ, New York, United States* (2) *CPL Associates, Buffalo, New York, United States*

Previous work in this laboratory using Cholesteryl ester vesicles to encapsulate and deliver a wide variety of substances (e.g. chromophores, antibiotics, peptides, IgG antibodies and plasmid DNA) has shown cholesteryl ester vesicle-mediated delivery of FITC-labelled peptides into various mouse tissues (including brain) after oral administration. Vital to the analysis of these vesicles is the determination and quantitation of ester composition using High Performance Liquid Chromatography (HPLC). Ongoing work has resulted in development of methods for a limited number of cholesteryl esters, both short (C6-C10) and moderate (C12-C16) alkyl chain lengths. These methods were for chains of even number length. The present research project expands the development of HPLC analyses to include esters with alkyl chains of odd number length, from C9 to C19. The current lipid analysis method was the start point for

quantitative analysis of the odd chain length esters. Initial work has included modification of the mobile phase solvents to determine ideal solubility of the esters that will optimize quantitative results using the HPLC. Current methods for the short and even chains appears sufficient for chain lengths C9 to C13 as determined by standard curve determination of known concentrations. However, the longer chain esters have differential solubility characteristics as well as weaker detection at 205nm. Determination of the optimum solubility for the longer chain esters is critical for quantitative HPLC results. These methods showed linear standard curves, which will allow for determination of lipid content of cholesteryl ester vesicles with the longer odd number alkyl chain esters.

MEDI 425

***pro*-Pyrrolobenzodiazepine (*pro*-PBD) bioconjugates, part 3: Design and synthesis of *pro*-PBD conjugates containing a self-immolative substituted disulfide linkers**

Iontcho R. Vlahov, Longwu Qi, Hari K. Santhapuram, hkrishna@endocyte.com, Garth L. Parham, Kevin Y. Wang, Jeremy F. Vaughn, Spencer J. Hahn, Marilynn Vetzal, Melissa Nelson, Joseph Reddy, Christopher P. Leamon. Endocyte Inc, West Lafayette, Indiana, United States

Naturally occurring pyrrolo[2,1-c][1,4]benzodiazepines (PBDs) are a group of highly potent antitumor antibiotics, isolated from various streptomycin species. PBDs covalently bond and cross-link with discrete sequences of base pairs in the minor groove of DNA. A wide range of synthetic PBDs and PBD dimers have been shown to be highly potent cytotoxic agents, and have been used as payloads in antibody drug conjugates (ADCs). However, all PBDs as stand-alone agents or as delivered *via* small molecule drug conjugates (SMDCs), cause undesired off-target toxicity. Recently, we designed folate conjugated *pro*-PBDs, masking the imine moiety with its synthetic precursors: namely, 1,3-oxazolidine carbamate and an aromatic amine. The 1,3-oxazolidine carbamate provided a conjugation site for attachment of *pro*-PBD to a targeting ligand. After delivery to the targeted cell and internalization, reductive cleavage of the linker system results in the generation of a 1,3-oxazolidine. The oxazolidine reacts with water to form an aldehyde which subsequently reacts intramolecularly to ultimately form the PBD diazepine ring. Herein, we report the design and synthesis of folate conjugates of *pro*-PBDs and self-immolative sterically hindered disulfide linker systems, which pave the way toward novel, highly-specific therapeutics which have the potential to minimize off-target toxicities.

MEDI 426

***pro*-Pyrrolobenzodiazepine (*pro*-PBD) bioconjugates, part 4: Design of novel oxime-based *pro*-PBD conjugates that release active drug via intramolecular diazepine-ring-closure**

Iontcho R. Vlahov, Albert Felten, afelten@endocyte.com, Ning Zou, Kevin Y. Wang, Spencer J. Hahn, Jeremy F. Vaughn, Marilyn Vetzal, Michael Frieden, Melissa Nelson, Joseph Reddy, Christopher P. Leamon. Endocyte, Inc., West Lafayette, Indiana, United States

Pyrrrolo[2,1-c][1,4]benzodiazepines (PBDs) are a group of antitumor antibiotics produced by various *actinomyces* bacteria which have emerged as some of the most potent chemotherapeutic compounds. PBD dimers (bis-PBDs) arrest DNA replication by selectively alkylating and crosslinking DNA at sequence specific sites found in the DNA minor groove. Due to their potent cytotoxicity and antitumor activity, PBDs have been widely utilized as payloads in antibody drug conjugates (ADC). However, when used as stand-alone therapeutics or as the warhead for small molecule drug conjugates (SMDCs), the reactive imine functionality has the potential to cause off-target toxicities. As an elegant solution to this undesired effect, a diazepine-ring-opened conjugated prodrug was developed. Our *pro*-PBD employs an aromatic amine and oxime ether in lieu of the reactive imine found in the active drug. The *pre-N-10* aromatic amine is used as an attachment point for both an enzymatic responsive and reduction sensitive self-immolative linker. By regioselectively attaching folic acid (FA) via a water-soluble spacer to the cleavable linker, we can direct our novel prodrug towards folate-receptor(FR)-over-expressing cancer cells. Once the prodrug (*pro*-PBD) conjugate enters a targeted cell, cleavage of the linker system triggers the generation of an aromatic amine which undergoes condensation with the oxime ether and forms a PBD molecule.

MEDI 427

Drug delivery of xanthohumol to adipocytes using ultrasmall superparamagnetic iron oxide nanoparticles (USPIO)

Irاندokht Khaki Najafabadi¹, irاندokhtkh@pcom.edu, Vicky V. Mody¹, Janaiya Samuels¹, Royce Dansby-Sparks², Srujana Raylam¹, Ajay Singh³, Rahul Deshmukh⁴. (1) Pharmaceutical Sciences, PCOM School of Pharmacy, Suwanee, Georgia, United States (2) Chemistry, University of North Georgia, Dahlonega, Georgia, United States (3) Pharmaceutical Sciences, South University, Savannah, Georgia, United States (4) Pharmaceutical Sciences, Rosalind Franklin University School of Pharmacy, Chicago, Illinois, United States

According to the CDC's National Center for Health Statistics, more than one-third (36.5%) of U.S. adults are obese. Obesity is the main risk factor for cardiovascular disease and type-2-diabetes. Nutraceuticals such as xanthohumol (XN) have shown potential to inhibit adipogenesis, however, their bioavailability has remained controversial. Hence there is a need to develop targeted therapy, which will increase the concentration of xanthohumol in the adipose tissue. Currently, nanoparticles are used for drug delivery where conventional therapies have proven to be less effective. Among various types of nanoparticles, USPIO have found considerable attention in drug delivery as they are easy to synthesize, inert, and are biocompatible. However, to use them for drug delivery system, the USPIO need to be surface functionalized by ligands

such as 3-aminotripropyl ethoxysilane. The use of 3APTES provides an amine ($-NH_2$) functional group on the surface of USPIO. Once amine functionalized, the USPIO- NH_2 was then conjugated to a XN viadicalcarboxylic PEG linker (HOOC-PEG-COOH) to yield USPIO-PEG-XN. However, to increase the specificity of the nanoparticles to the white adipose tissue (WAT), a WAT specific peptide, P3 (CKGGRAKDC) will be conjugated onto USPIO-PEG-XN to yield a final product USPIO-PEG-XN-P3. The p3 peptide has been reported to bind specifically to WAT vasculature through the membrane protein prohibitin, hence the presence of P3 onto the nanoparticle will increase the specificity and selectivity of the nanoparticle to the adipose tissue. The presence of amine functional groups on the surface of nanoparticles was confirmed *via* FTIR and quantified using ninhydrin Assay. The ninhydrin assay revealed the presence of 25microM of amine groups per mg of the USPIO. The amount of XN onto the surface of nanoparticles was quantified using HPLC-UV. The HPLC analysis confirmed the presence of 6.1microg of XN per mg of the USPIO. TEM analysis showed that the USPIO, USPIO- NH_2 , and USPIO-PEG-XN were all spherical in shape with the average particle size of 20, 25, and 50nm, respectively. The cell viability studies using 3T3 L1 murine adipocyte cell line confirmed that the synthesized USPIO-PEG-XN particles did not induce cytotoxicity. In addition, USPIO-PEG-XN at 3.25microM significantly decreased adipogenesis compared to the XN as measured by decrease in the lipid content using AdipoRed™ lipid quantification assay.

MEDI 428

Hygromycin A, an antimicrobial with selective activity against *Borrelia burgdorferi* for treatment of Lyme disease

Yu Imai, Xiaoqian Wu, Mariaelena Caboni, Quentin Favre-Godal, Samantha Niles, Krumpoch Megan, Akira Iinishi, a.iinishi@northeastern.edu, Kim Lewis. Biology, Antimicrobial Discovery Center, Northeastern University, Boston, Massachusetts, United States

Lyme disease is a tickborne illness caused by the bacterium *Borrelia burgdorferi* which is transmissible to humans through the bite of infected blacklegged ticks. In the United States, more than 300,000 cases of Lyme Disease are diagnosed yearly, and this number has been steadily increasing over the past 25 years. The majority of cases are successfully treated with oral antibiotics; however, some patients experience symptoms after treatment, referred to as post-treatment Lyme disease syndrome (PTLDS). Better therapeutic options could decrease the incidence of PTLDS. We developed a screen for compounds acting selectively against *B. burgdorferi*. Screening of extracts from soil bacteria led us to rediscover hygromycin A. This antibiotic was originally discovered in 1953 *Streptomyces hygroscopicus* by Selman Waksman and his colleagues. The compound had low activity against typical pathogens and was not pursued. Hygromycin A *S. aureus* MIC is 32 $\mu g/mL$ *E. coli* MIC is 1,000 $\mu g/mL$. By contrast, *B. burgdorferi* MIC is 0.12 $\mu g/mL$ – it is 250-fold more active against this pathogen as compared to *S. aureus*. Hygromycin A delivered subcutaneously cleared *B. burgdorferi* in a mouse model of Lyme disease. Importantly, orally administered

hygromycin A was similarly effective in treating the infection. Currently used antibiotics to treat Lyme disease have been borrowed from other applications. Hygromycin A holds the promise of providing superior, and selective, treatment of Lyme disease.

MEDI 429

Evaluation of antibacterial activity of *Vangueria volkensii* extracts

Alfred K. Addo-Mensah, *alfred.addo-mensah@tamiu.edu*, Douglas Holland. LBVSC 319, TAMIU Dept Biology Chemistry, Laredo, Texas, United States

Medicinal plants have been used for thousands of years and continues to play a critical role in the healthcare system worldwide, with an estimate of 80% of all pharmaceutical drugs are of plant based in origin. Additionally, antibiotic resistant bacteria are becoming increasingly more prevalent, whereas the development of novel antibiotics is lagging. Due to these trends, the investigation of plants to determine if they possess any medicinal properties is essential. In the present study, medicinal compounds in the stem, bark, and leaves of *Vangueria volkensii* were extracted sequentially via Soxhlet extraction using petroleum ether (PE), acetone (ACE), and 9:1 ethanol/water (E/W) respectively. Utilizing the disc diffusion method, the antimicrobial activities indicated by the size of the Zone of Inhibition (ZOI) of each extract at concentrations 5, 15, 25, and 50 mg mL⁻¹ were evaluated against six bacteria. Gram-positive [*E. faecalis* (EF), *S. aureus* (SA), Methicillin-Resistant *S. aureus* (MRSA)] and Gram-negative [*E. coli* B (EC), *S. enteritidis* (SE), *S. flexneri*(SF)] were selected based on availability. Preliminary results show that the antimicrobial activity was low to moderately active against all bacteria. Whereas the E/W and ACE extracts and the leaves extracts showed higher activity compared to their respective counterparts. This paper will report the antibacterial activity of *V. volkensii* against the selected bacteria and how it compares with known antibacterials.

MEDI 430

Synthesis and biological evaluation of benzimidazoles as FKBP inhibitors

Surya K. De, *suryakd@hotmail.com*. Chemistry, Plex Pharmaceuticals, San Diego, California, United States

Neurodegenerative disorders are CNS diseases characterized by synaptic loss, neuronal atrophy, and death as common pathological hallmarks. Parkinson's disease (PD) is one of the most common neurological disorders, affecting over 6.3 million people globally, and 1.5 million people in North America. Parkinson's disease (PD) belongs to a group of conditions called motor system disorders, which are the result of the loss of dopamine-producing neurons in the substantia nigra. A hallmark of PD neuronal degeneration is aberrant aggregation of alpha-synuclein (α -SYN). In PD, the protein is present in a fibrillar, aggregated form inside cytoplasmic inclusions called Lewy bodies. Enzymes of the FK506 binding protein (FKBP) family accelerate the

aggregation of recombinant α -SYN *in vitro* and FK506, a specific FKBP inhibitor, abrogates this effect.

FKBPs are members of the immunophilin family of proteins. These proteins are enzymes with peptidyl-prolyl cis-trans isomerase (PPIase) activity and bind to immunosuppressants such as FK506. PPIase enzymes catalyze cis-trans isomerization of X-Pro peptide bonds, an essential and rate-limiting step in the process of protein folding. The human FKBP family contains 15 principal members with many different functions. Among these, four members, namely, FKBP12, FKBP38, FKBP52, and FKBP65, are enriched in the human brain. Importantly, numerous clinical and pre-clinical studies have demonstrated that two FKPBs, FKBP12 and FKBP52, are involved in PD pathology. The results of this new series of FKBP 12 and FKBP-52 inhibitors will be presented.

MEDI 431

Disabling the resistance of methicillin-resistant *Staphylococcus epidermidis* (MRSE)

*Anh K. Lam*¹, *anhlam@ou.edu*, *Melissa Foxley*³, *Charles V. Rice*². (1) *Chemistry & Biochemistry, University of Oklahoma, Moore, Oklahoma, United States* (2) *Chemistry and Biochemistry, University of Oklahoma, Norman, Oklahoma, United States* (3) *University of Oklahoma, Norman, Oklahoma, United States*

Staphylococcus epidermidis is the most copious species on human skin and mucosal membranes that constitutes the commensal flora. However, since the practice of modern medicine adapted the use of indwelling prosthetic medical devices, *S. epidermidis* has become one of the most common causes of primary bacteremia. *S. epidermidis* patients might be hard to diagnose, because it has natural niches on human skin and its ability to adhere to inanimate surfaces to form biofilm. *S. epidermidis* has also acquired resistance to many antibiotics. Most clinical isolates of *S. epidermidis* in North America are resistant to multiple antimicrobial agents (73-88% resistant to oxacillin) due to the presence of *mecA* – the gene bestowing β -lactam antibiotic resistance by encoding PBP2a – just like in MRSA. In our study, the resistance factor of MRSE was disabled by a new approach using 600-Da branched polyethyleneimine (BPEI). Cationic BPEI targets anionic wall teichoic acid which then hinders the proper functions of PBP2a. Our data show that BPEI lowers the MIC of several β -lactam antibiotics and synergizes their activity against MRSE. Growth curve data show the potentiation between BPEI and oxacillin to kill the bacteria. TEM and SEM images show abnormalities in the cellular septum and cell wall of the treated samples.

MEDI 432

Regioselectivity of N-substituted 3-nitropyrazole alkylations

Si Tong Bao¹, sbao@wellesley.edu, Jeniffer Perea², Natalie Norman¹, Adrian Huang¹. (1) Chemistry, Wellesley College, Wellesley, Massachusetts, United States (2) Chemistry, Wellesley College, Wellesley, Massachusetts, United States

Pyrazoles, 5-membered heterocyclic compounds with two adjacent nitrogen atoms, are a major motif in agrochemical and pharmaceutical chemistry. N-substituted pyrazoles such as celecoxib, a N1 substituted pyrazole derivative marketed as a non-steroidal anti-inflammatory drug (NSAID), have received attention in medicinal chemistry. The common method of preparing N-substituted pyrazoles involves condensation reactions of monosubstituted hydrazines and 1,3-dielectrophiles. However, such an approach has major disadvantages because this method often leads to an unpredictable distribution of N1 and N2 regioisomers. These regioisomers then have to be separated in costly and time-consuming processes as they generally have different bioavailabilities. Given these shortcomings, we believe that regioselective N-substitution reaction of 1H-pyrazoles would be a more efficient approach to synthesizing our target N1 pyrazole. Using the commercially available 3-nitropyrazole, a highly versatile intermediate for further substitution on the pyrazole ring as our nucleophile, we have conducted a series of N-alkylation experiments using alkyl electrophiles of different electronic and stereochemical properties. ¹HNMR, ¹³CNMR and X-ray crystallography were used to confirm the structure of the final products and DFT calculations were carried out to justify the regioselectivity. Our results show that more reactive and less sterically hindered electrophiles provide higher yield and regioselectivity. The resulting N1-substituted 3-nitropyrazoles are valuable precursors to various 3-substituted pyrazoles through established reactions, which can then be employed to prepare analogues of drugs such as celecoxib and emicerfont, a CRF1 receptor antagonist.

MEDI 433

Targeting trimethylamine oxide biosynthesis pathway discovery of new inhibitors against TMA lysate protects against atherosclerosis lesion, MI and stroke

Ashraf Duzan, a.duzan@vikes.csuohio.edu. Clinical Bioanalytical Chemistry & Molecular medicine, Cleveland State University, Westlake, Ohio, United States

Recent clinical research points to trimethylamine oxide (TMAO) as a biomarker molecule associated with several homeostasis disruptions, such as cardiovascular disease. Our goal in this project is to alter the biosynthetic pathway of TMAO through the inhibition of the gut microbial trimethylamine (TMA) lyase: the choline utilization cluster enzyme (CutC/D). We are using structure activity relationships (SAR) to predict new classes of chemical structures as potential efficient inhibitors. Thus, we are exploring the synthesis of new chemical compounds, non-lethal to gut microbial community, with high enzymatic efficacy both *in vitro* and *in vivo*. We are preparing and assessing inhibitors that can work either through irreversible non-competitive or competitive mechanisms, have minimal side effects, possess appropriate physico-chemical pharmaceutical properties as needed for a drug. Our leading candidates have

excellent enzyme blocking efficiency and display good pharmacokinetic/ pharmacodynamics properties.

MEDI 434

Targeting the trimethylamine oxide biosynthesis pathway: Discovery new novel inhibitors against gut microbial TMA lysate protects against atherosclerosis lesion, MI and stroke

Ashraf Duzan^{1,2}, a.duzan@vikes.csuohio.edu, **Adam Roberts**^{1,3}, **Jennifer Buffa**^{1,3}, **Stanley Hazen**^{1,3}, **Valentin Gogonea**^{1,2}. (1) Department of Cellular & Molecular Medicine, Cleveland Clinic, Cleveland, Ohio, United States (2) Department of Chemistry, Cleveland State University, Cleveland, Ohio, United States (3) Center for Microbiome and Human Health, Cleveland Clinic, Cleveland, Ohio, United States

Recent clinical research evidence has marked TMAO as a biomarker molecule associated with several homeostasis disruptions, such as myocardial infarction, atherosclerosis, secondary hypertension, irritable bowel syndrome, chronic kidney disease, strokes, and heart failure. The priority is to stop the biosynthesis pathway of TMAO through inhibition gut microbial TMA lysate CutC/D. In fact, structure activity relationships (QSAR) provide the ability to predict potent inhibitors. Moreover, develop suicide substrate inhibitors analogues of the microbial TMA lysate CutC. Time-dependent and irreversible inhibition with no toxicity on gut microbial communities are potential therapeutic approach to suppress platelet hyperactivity and prevent any thrombotic stroke associated with cardiovascular disease. Our targets of this study are (1). Synthesis of potent inhibitors that has highly efficacy in vitro and in vivo study with specificity ; (2) Non-lethal effect on gut microbial community; (3) The leading inhibitor works as irreversible non-competitive inhibitor to get high potency and fewer side effects. (4). Our inhibitor possess physic-chemical pharmaceutical properties as necessary for drug effect. (5). The leading compounds do show acceptable pharmacokinetic/ pharmacodynamics properties.

MEDI 435

DCBCO1303-a promising inhibitor of smo-mediators of hedgehog pathway signalling

Mann Yan Kuo, mykuo@mail.dcb.org.tw. Institute of Pharmaceutics, Development center for biotechnology, New Taipei City, Taiwan

The hedgehog (Hh) pathway is a critical embryonic signaling cascade regulating cell growth, proliferation and differentiation. Hh signaling is significantly less active in adult tissues, where its primary role appears to be the maintenance of stem cell populations in skin and the central nervous system. Smoothed (Smo), a 7-pass transmembrane receptor with a GPCR-like structure, is a key component of the Hh signaling pathway, the activity of which is suppressed by the 12-pass transmembrane protein Patched

(Ptch). Therefore, components of the Hh pathway (such as Shh, SMO, and GLI1/2) are viable therapeutic targets for anti-tumor strategy. We report here the development of a potent Smo antagonist designated DCBCO1303 with Hh signaling pathway inhibition activity. DCBCO1303 demonstrated Hh signaling pathway antagonist activity in a 293 cell-based Gli-luciferase inhibition assay upon agonist treatment (IC₅₀ = 3.5 nM), and retains inhibition activity against the Smo wild-type and D473H mutant responsible for resistance to GDC-0449 in medulloblastoma patients with IC₅₀ of 5.1 and 43.7nM, respectively. Treatment of a medulloblastoma allograft model with DCBCO1303 (10-40 mg/kg once a day) showed an effective dose-related antitumor activity mediated by inhibition of the Hh pathway (Gli 1 mRNA inhibition correlated with tumor growth inhibition). Thus, our efforts for a potent Smo antagonist were directed toward the identification of DCBCO1303 as a very interesting new investigational drug suitable for clinical development.

MEDI 436

Studies into the enzymatic action and immunomodulatory activity of isopentenyl-diphosphate isomerase

Megan A. Schladetsch, megan.schladetsch@uconn.edu, Andrew J. Wiemer. Medicinal Chemistry, University of Connecticut, Storrs, Connecticut, United States

The isoprenoid biosynthesis pathway in humans, known as the mevalonate pathway, is a key metabolic pathway in the synthesis of a variety of both sterol and non-sterol isoprenoid compounds. Intermediates of the pathway affect several human pathologies, making the pathway rich in potential therapeutic targets. Modification of certain pathway enzymes via small molecule inhibitors could be of great therapeutic value for cancer treatments. The human isopentenyl-diphosphate isomerase is of particular interest in this pathway because it catalyzes the interconversion of isopentenyl diphosphate to dimethylallyl diphosphate, generating the necessary substrates for the synthesis of larger biologically relevant isoprenoids. Isopentenyl diphosphate is also an immunostimulatory molecule, whose binding to specific butyrophilin proteins activates the anti-infective and anti-cancer immune response in V γ 9V δ 2 T cells. Identifying small molecule analogs of isopentenyl diphosphate that can initiate the anti-cancer response of V γ 9V δ 2 T cells and understanding the specificity of small molecule interactions with isopentenyl-diphosphate isomerase versus butyrophilin 3A1 are primary goals of this research work.

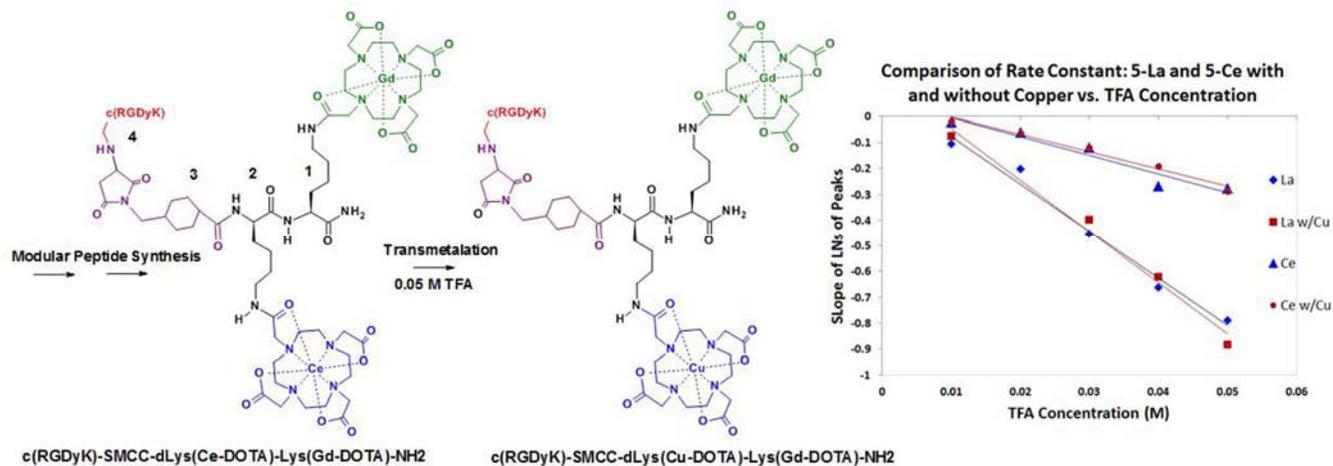
MEDI 437

Practical modular synthesis of targeted imaging agents for MRI, PET and PET-MRI

Kelsea Jones¹, kgj5109@rit.edu, Anne Marie Sweeny-Jones^{2,4}, Jessica Perez⁵, Stephanie Beach^{6,7}, Chelsea Weidman⁶, Michael Regan^{8,9}, Scott Williams⁶, Hans F. Schmitthenner^{2,3}. (1) Chemistry, Rochester Institute of Technology, Avon, New York,

United States (2) School of Chemistry and Materials Science, Rochester Institute of Technology, Rochester, New York, United States (3) Center for Imaging Science, Rochester Institute of Technology, Rochester, New York, United States (4) Chemistry, Georgia Institute of Technology, Atlanta, Georgia, United States (5) School of Chemistry, Rochester, New York, United States (7) Chemistry, Boston University, Boston, Massachusetts, United States (8) Chemistry, Rochester Institute of Technology, Rochester, New York, United States (9) Chemistry, Clarkson University, Potsdam, New York, United States

A modular synthesis of multi- or dual-metal targeted imaging agents for PET, SPECT and MRI has been developed. In the peptide-based approach, metals chelated to DOTA are placed on the side chains of amino acids early in the synthesis followed by coupling to modules, then to linkers and targeting agents in the last step, enabling the use of a variety of targeting systems for a given imaging system. The method can be applied to the synthesis of multi-gadolinium MRI agents for higher relaxivity, or to combine two different metals offering dual-modal PET/SPECT-MRI agents. It was first found that a metal introduced early can double as a protecting group for DOTA, averting the need for the common but troublesome tri-*t*-butyl protection. It was further discovered that two labile metals, La⁺³ or Ce⁺³, can be used as placeholders, then transmetalated rapidly in mild acid by Cu⁺², Ga⁺³, In⁺³ and Y⁺³. These masked PET agents can be shipped without encumbrance to clinical labs where radioactive metals for PET can be inserted rapidly in the final transmetalation in mild acid. Conditions for metal exchange were optimized in a kinetic study in dilute TFA. Gd⁺³ was found to be inert to exchange enabling synthesis of PET-MRI agents. The modular method was applied to the synthesis of single modal (MRI and PET) and dual modal (PET-MRI) targeted agents utilizing c(RGDyK) for lung cancer and urea DCL for prostate cancer.



A. Modular synthesis of targeted PET-MRI imaging agent showing transmetalation step; B. Transmetalation of La and Ce by Cu, optimized by kinetic studies in dilute TFA

MEDI 438

Activity prediction by target fingerprinting

Petra Schneider, petra@insili.com. Chemistry and Applied Biosciences, Swiss Federal Institute of Technology (ETH), Zurich, Switzerland

Predicting the macromolecular targets of bioactive molecules can be useful for understanding a bioactive compound's mode of action and potential off-target liabilities and for guiding the design of new ligands with the desired activity spectra. It has been realized that even designated selective drugs may have more macromolecular targets than is commonly thought. Consequently, it will be mandatory to consider multi-target activities for the design of future medicines. Computational models assist medicinal chemists in this effort by helping to eliminate unsuitable lead structures and spot undesired drug effects early in the discovery process. We present the application of a straightforward computational method (TIGER, target-inference generator) to find previously unknown targets of pharmacologically active compounds based on their predicted target activity fingerprints. The obtained results advocate this machine-learning approach for polypharmacology-based molecular design, drug re-purposing, and the "de-orphaning" of phenotypic drug effects.

MEDI 439

Prenylated isoflavones: Comparison of distribution coefficients, hydrogen bonding acidity values and positions within detergent micelles

Sara Tuck¹, sara.tuck@go.tarleton.edu, William L. Whaley¹, Michael Abraham². (1) Chemistry, Geosciences & Physics, Tarleton State University, Stephenville, Texas, United States (2) Chemistry, University College of London, London, United Kingdom

The isoflavones are a subclass of flavonoids that have anti-cancer, anti-atherosclerosis and neuroprotective activities. The absorption, distribution, metabolism and excretion (ADME) properties of these compounds are not well-characterized. The logarithm of the octanol-water partition coefficient (LogP_{oct}) is used as an index of hydrophobicity for most drug molecules. Compounds with LogP_{oct} values between 2.0 and 4.0 tend to partition across lipid bilayers by passive adsorption and diffusion. Partition coefficients determined using a buffered aqueous phase and an equilibrated octanol phase are called distribution coefficients and are reported as LogD_{oct} values. The diprenylated isoflavones, osajin and pomiferin, exhibited LogD_{oct} (pH=7.4) values of 3.26 (+/- 0.13) and 3.16 (+/-0.09), respectively. The incorporation of these compounds into SDS micelles (in D2O) was also monitored using proton NMR spectroscopy. Both osajin and pomiferin were found to be present in the hydrophobic core of the SDS micelles and not at the aqueous interface. Osajin contains a single hydroxyl group on the aromatic A-ring while pomiferin contains a catechol (dihydroxy) group. These phenolic hydroxyl groups contribute to the Abraham hydrogen bonding acidity values (A) which were determined to be greater than 0.7 for both compounds using a method based on proton NMR

spectroscopy. LogD_{oct} and A are key parameters used in the general solvation equation which is useful for predicting some ADME properties of potential drugs. Osajin and pomiferin should partition into lipid membranes and pomiferin is a potent free-radical scavenger which should protect lipid structures from damage by reactive oxygen species (ROS).

MEDI 440

Theranostic antibody-drug conjugates for potential dual application in targeted therapy and fluorescence imaging of colorectal cancer

Siyuan Ren¹, *sren6@hawk.iit.edu*, **Xiang Sun**¹, **Hua Xu**¹, **Trung Hai Nguyen**¹, **Chi Soo Kang**¹, **Negar Sadeghipour**², **Xiaochun Xu**², **Ningjie Wu**¹, **Yu Chen**¹, **Kenneth Tichauer**², **David D. Minh**¹, **Hyun S. Chong**¹. (1) Chemistry, Illinois Institute of Technology, Chicago, Illinois, United States (2) Biomedical Engineering, Illinois Institute of Technology, Chicago, Illinois, United States

We report development of theranostic conjugates for dual application in targeted anti-cancer therapy and near infrared fluorescent imaging. A new polyaminocarboxylate-based cytotoxic chelating agent (CAB-NE3TA) was synthesized and evaluated for inhibitory activity against melanoma (A375), cervical (HeLa), colon cancer (HT29 and LS174T), breast cancer (MDA-MB231), ovary cancer (SKOV-3), liver cancer (HepG2) cells. The new anti-tumor agent was significantly potent in destroying the cancer cells when compared to the clinically available iron chelating anti-tumor agent (DFO). Encouraged by the in vitro cytotoxicity data, we then designed a theranostic platform (CAB-NE3TA-PAN-IR800) constructed on an internalizing EGFR-targeted antibody (panitumumab, PAN) labeled with a near IR fluorescent dye. We also built the first atomistic model of the EGFR-PAN complex and loaded it with the cytotoxic CAB-NE3TA and the near IR dye. The theranostic conjugate was evaluated for in vivo biodistribution and anti-tumor activity using a mouse model of colorectal cancer and displayed highly selective tumor uptake and rapid blood and organ clearance. The in vitro and in vivo data suggest potential theranostic applications of CAB-NE3TA-based protein conjugates for simultaneous therapy and imaging of cancers.

MEDI 441

New bifunctional ligands of Zr-89 for potential applications in antibody-targeted positron emission tomography (PET) imaging and precision medicine

Yanda Chen, *ychen214@hawk.iit.edu*, **Siyuan Ren**, **Chi Soo Kang**, **Yujie Liu**, **Shuyuan Zhang**, **Hyun S. Chong**. Chemistry, Illinois Institute of Technology, Chicago, Illinois, United States

Positron emission tomography (PET) is a sensitive diagnostic modality and has been demonstrated to give highly sensitive detection and staging of various diseases. Among the positron emitting radionuclides utilized for PET imaging, Zr-89 has the advantage of

a relatively long physical half-life ($t_{1/2} = 78.4$ h) and is suitable for use in immuno-PET imaging where a sensitive antibody with a long biological half-life is employed. In antibody-targeted PET imaging, an effective bifunctional chelator is expected to complex Zr-89 rapidly and tightly to minimize radiolytic damage resulting from extended exposure of the antibody during radiolabeling and in vivo toxicity from dissociation of Zr-89 from the complex.

Although the Zr-89-immuno-PET holds great promise for imaging of many diseases as evidenced by numerous preclinical trials, the absence of an optimal bifunctional ligand for complexation of Zr-89 with high in vivo stability limited broad and successful clinical applications of Zr-89 based PET imaging.

In an effort to develop superior bifunctional ligands of Zr-89, we have assessed various donor systems for complexation with Zr-89. In this presentation, we report synthesis and evaluation of new bifunctional ligands with structural variations. The new chelators were evaluated for radiolabeling kinetics with Zr-89 at room temperature. In vitro stability of the corresponding complexes in human serum and when challenged by excess EDTA were assessed in comparison to desferoxamine (DFO). DFO is one of the most frequently explored chelators for PET imaging applications. The new lead chelators were extremely rapid in binding Zr-89 (> 99% radiolabeling efficiency, room temperature) and present a favourable serum stability profile. The new bifunctional ligands were successfully conjugated to a HER2-specific antibody (Herceptin) for comparative in vivo evaluation using mice. The result of the radiolabeling kinetics and serum stability data indicate that the new bifunctional chelators of Zr-89 are promising candidates for immuno-PET imaging applications.

MEDI 442

Targeted nanoparticles for pathogen-specific drug delivery

Logan Schnorbus¹, schnorbul6@students.rowan.edu, Lark J. Perez². (1) Chemistry & Biochemistry, Rowan University, Hopewell, New Jersey, United States (2) Chemistry and Biochemistry, Rowan University, Trenton, New Jersey, United States

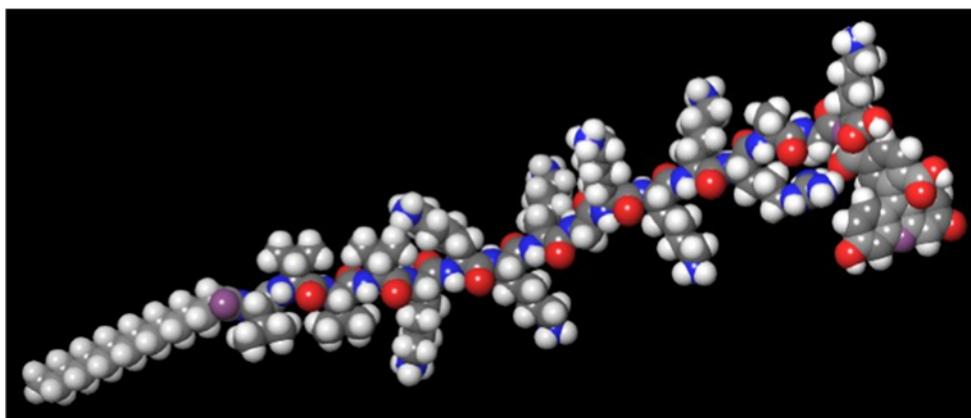
We propose to encapsulate broad-spectrum antibiotics into pathogen-targeted polymeric nanoparticles to facilitate targeted drug delivery. Pathogen specific targeting is achieved by application of sugar-functionalized nanoparticles as drug carriers targeted for species-specific lectin binding. The *Pseudomonas aeruginosa* lectins, LecA and LecB, are two sugar-binding proteins distinct in structure, binding preference and involvement of biofilm formation in this pathogen. We will describe the presentation of LecA and LecB binding motifs on a series of polymeric nanoparticle cores and preliminary investigations of biological activity.

MEDI 443

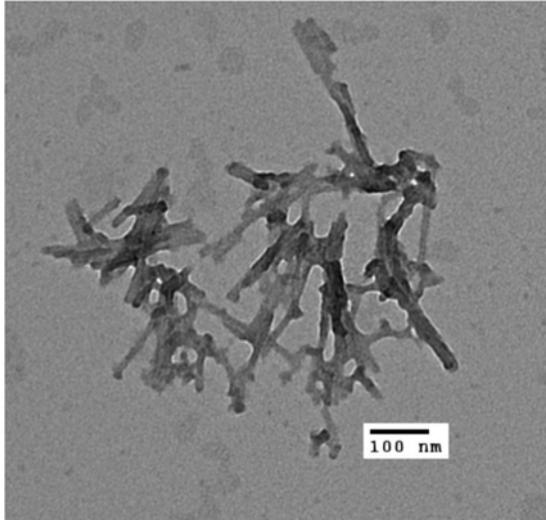
Fructose-enhanced antimicrobial activity of self-assembled nano peptide amphiphiles for treating antibiotic resistant infections

Ming Gao², gao.min@husky.neu.edu, **Kanny Chang**², **danquan Wang**³, **Yuan Li**², **Linlin Sun**², **Steven Lustig**², **Thomas Webster**¹. (1) 313 Snell Engineering Center, Northeastern University, Boston, Massachusetts, United States (2) Chemical Engineering, Northeastern University, Boston, Massachusetts, United States (3) Pharmaceutical Sciences, Northeastern University, Boston, Massachusetts, United States

In recent years, numerous bacteria have become resistant to conventional antibiotics. Moreover, an increasing body of research has indicated that by addition of specific metabolites, the antibacterial activity of certain drugs can be enhanced. To treat antibiotic resistant bacterial infections and to reduce the use of antibiotics, a type of self-assembled nano peptide amphiphiles (SANPA) has been designed in this study. Here, SANPAs are self-assembled into nanorod structures with approximately a diameter of 10.5 nm after reached the critical micelle concentration (CMC) at 47.86 μM . Both Gram-positive bacteria and Gram-negative bacteria have been tested using SANPAs with fructose supplementation. Impressively, with an 30 minutes fructose preincubation, SANPA eliminated the bacteria growth outperformed the none-fructose treatment at all concentrations. Cytotoxicity assays indicated that the presence of fructose seemed to slightly ameliorate the cytotoxic effect of the treatment on human fetal osteoblast and human dermal fibroblast. Real-time polymerase chain reaction (RT-PCR) were used to track six *E.coli* genes to further investigate the underlying mechanism. In conclusion, we demonstrated that SANPAs-like nanomaterials have promising potential to treat antibiotic resistant infections, and the variability inherent to developing novel antibacterial treatments.



SANPA single molecule



TEM image

MEDI 444

Solid lipid nanoparticles (SLN) from ketogenic diet lipids: Anxiolytic and anticonvulsant effect

Erendira V. Toledo, evts0709@gmail.com. Laboratory of Pharmaceutical Technology, UNAM, Mexico State, Mexico State, Mexico

The blood-brain barrier is an active tissue that protects the brain from the outside and, at the same time, prevents the passage of substances to the central nervous system, so the treatment of central nervous system disorders is a challenge. Solid lipid nanoparticles are among the mechanisms that have been proposed to cross the blood-brain barrier. In order to carry out the election of the lipids to be used to produce the SLN, those that belonged to the ketogenic diet were chosen, which could have an anticonvulsant effect. The main objective of this study was to produce solid lipid nanoparticles from ketogenic diet lipids for being administered in mice, to prove if these lipids have an anxiolytic and anticonvulsant effect.

MEDI 445

Aminolipid structure-activity relationships in lipid nanoparticle *in vivo* performance

Mark A. Cornebise¹, mark.cornebise@modernatx.com, Kerry Benenato¹, Luis Brito¹, William Butcher¹, Kevin Davis¹, jessica deterling¹, kimberly hassett¹, Natalie Jordan¹, Laureen Knowles¹, E. S. Kumarasinghe¹, Dawn Mampreian¹, Jaclyn Milton¹, Karen Olsen¹, Staci Sabnis¹, Timothy Salerno¹, Jose Sanabria¹, Arnold Sengooba¹, Pooja Shah¹, Matthew Stanton², Angela Woods¹. (1) Moderna Therapeutics, Cambridge,

Massachusetts, United States (2) Generation Bio, Cambridge, Massachusetts, United States

Lipid nanoparticles (LNPs) are a versatile modality for the delivery of mRNA therapeutics. Depending on the indication, different routes of administration (ROAs) may be utilized to elicit optimal performance and pharmacological response. Intravenous (IV) administration provides rapid systemic exposure, while intramuscular (IM) injections are absorbed more slowly and may access different circulatory systems (e.g. lymphatic) and local tissues. Additionally, some ROAs are preferred for certain therapies (e.g. IM for vaccines). As part of our ongoing investigation into the effect of modifying different aspects of LNP formulations we prepared several series of aminolipids to explore the effect of structural variations on the characteristics and performance of the corresponding assembled LNPs. These were tested *via* IV and IM administration in vivo and the results compared to MC3 LNPs to generate Structure-Activity Relationship (SAR) data. We identified trends in expression data that suggest aminolipid structural differences produce divergent SAR between IV and IM ROAs.

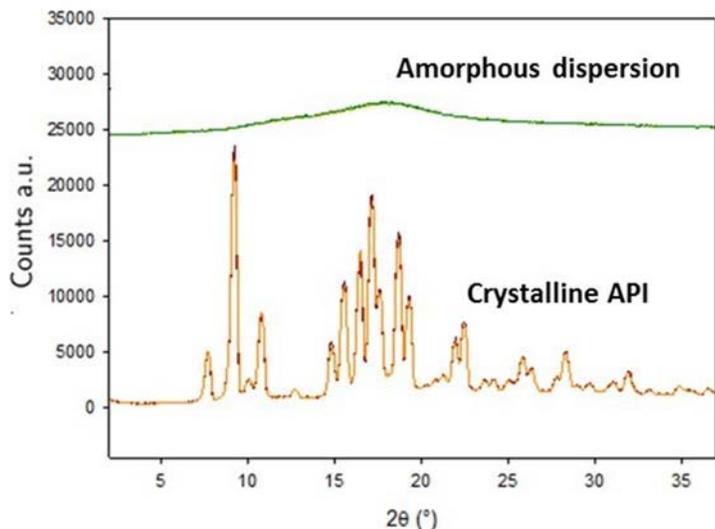
MEDI 446

Preparation and characterization of new solid micro and nanodispersions of amorphous drugs

Jorge Cruz, jorgemky@gmail.com, Paula Eugenia Morales, Cecilia Martínez, Marcelo Videia, Luz M. Martínez. Tecnológico de Monterrey, Monterrey, Mexico

Because of the use of combinatorial chemistry there are new pharmaceutical active ingredients (APIs) that cannot be used in commercial pharmaceutical products due to their low solubility in aqueous medium. Two of the most promising strategies to solve these problems are: 1) conversion of the APIs from crystalline to amorphous state and 2) the preparation of formulations in solid dispersions. In the first strategy, the enhanced solubility of the amorphous state is due that no additional energy is required to break the crystalline network during the dissolution process. In the case of dispersions, a decreased in the particle size of the API and an increment of porosity of the final product favors the solubility process. By synergizing these two strategies and forming a solid dispersion where both the excipient and the API are in amorphous state, the solubility process of poorly soluble drugs can be maximized. In our research group, we have developed a new method to prepare formulations in the form of solid vitreous dispersions, called two-phase amorphous-amorphous solid drug dispersion (AASD). The AASD consists of a sugar-based excipient that is an amorphous matrix for the API, which is dispersed in the form of micro and nano-clusters in an amorphous state. In the present work this methodology was applied to produce a new amorphous drug formulation in the form of solid nano-dispersion that has the potential to be used for the treatment of hypercholesterolemia. X-ray powder diffraction technique was used to carry out structural characterization to demonstrate the amorphous state of the dispersions, where the AASD-formulation showed stability in the amorphous state. The particle size of the API in the AASD was characterized through DLS, having an average size of

particle of the API of 375nm. We are currently working in the evaluation of the solubility enhancement of the new formulation, which has already presented an increase compared to the crystalline commercial API.



PXRD pattern of AASD and crystalline API

MEDI 447

Design and development of small molecule RelA/RSH inhibitors

Donald C. Hall^{1,2}, dchj265@gmail.com, **Haifeng Ji**³, **Garth D. Ehrlich**², **Jaroslav Krol**². (1) Chemistry, Drexel University, Delta, Pennsylvania, United States (2) Microbiology & Immunology, Drexel University College of Medicine, Philadelphia, Pennsylvania, United States (3) Dept of Chemistry, Drexel University, Philadelphia, Pennsylvania, United States

The resistance of clinical infections is one of the fastest growing issues in the medical field today. A large number of these resistant infections can be attributed to biofilms. It is estimated that 80% of infections have some biofilm related aspect to them. These biofilms can be defined as a surface adhered aggregate of cells surrounded by a protective matrix. Biofilms are capable of collective antibiotic resistance. Because of the large role that biofilms play in clinical infections it is imperative to find a way to inhibit biofilm formation and induce biofilm degradation; this would subsequently re-potentiate antibiotics. This research focuses on the design and testing of small molecule inhibitors for the enzymes RelA and RSH (RelA/SpoT homologs). RelA and RSH are ATP:GTP(GDP) pyrophosphate transferases that control the synthesis of the stringent response triggering “magic spot” alarmones. “Magic spot” alarmones are hyperphosphorylated nucleotides (guanosine pentaphosphate and guanosine tetraphosphate). These alarmones induce a major change in cellular metabolism whereby the bacteria are converted into persister cells. These persister cells have

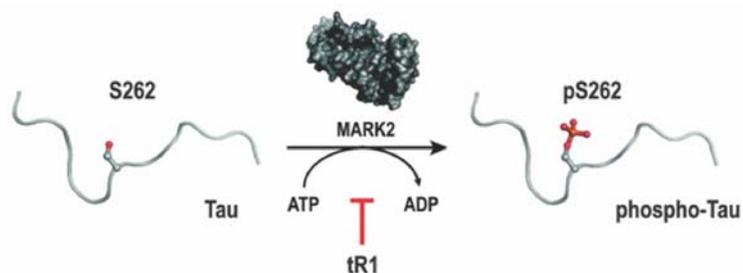
upregulated some genes (such as chaperones, toxin/antitoxin systems and oxidative stress protection) and downregulated genes involved in cell wall synthesis, translation and DNA replication. All these factors make them up to a 1000x more resistant to antibiotics than their planktonic counterparts. The use of computational models, organic synthesis, and *in vivo* and *in vitro* assays have been employed to produce and evaluate lead compound inhibitors. These compounds have been successfully tested for their ability to interrupt the stringent response as well as re-potentiate antibiotics for the treatment of infectious bacteria.

MEDI 448

Reducing tau phosphorylation using synthetic peptides: Developing peptide-based inhibitors of microtubule affinity regulating kinase 2 (MARK2)

Justin M. Holub¹, holub@ohio.edu, Najah Alqaeisoom¹, Cheng Qian², Danushka Arachchige¹, Robert Colvin². (1) Chemistry and Biochemistry, Ohio University, Athens, Ohio, United States (2) Ohio University, Athens, Ohio, United States

The microtubule-affinity regulating kinase (MARK) proteins are a family of Ser/Thr kinases involved in controlling cytoskeletal dynamics and maintaining cell polarity. A primary function of MARK2 is to phosphorylate microtubule-associated proteins such as MAP2, MAP4 and tau within their microtubule-binding repeat (R) domains. In neurons, tau preserves the structural integrity of the cytoskeleton by binding and stabilizing microtubules. The phosphorylated state of tau plays an important role in regulating its interaction with tubulin; tau that is phosphorylated dissociates from tubulin, leaving microtubules in highly dynamic states. Under pathological conditions, tau proteins can become abnormally phosphorylated, leading to loss of microtubule stability and neuronal cell death. Indeed, hyper-phosphorylated tau isoforms have been implicated in the pathogenesis of neurodegenerative disorders such as Alzheimer's disease and frontotemporal dementia. In this study, our objective was to develop a peptide-based kinase inhibitor of MARK2 function. This peptide (designated tR1) was designed as a direct sequence mimic of the tau R1 domain to selectively inhibit the MARK2-mediated phosphorylation of tau proteins *in vitro* and in cultured primary neurons. *In vitro* experiments showed that tR1 inhibits the MARK2-mediated phosphorylation of Ser262 within the tau R1 microtubule-binding domain. It was further demonstrated that tR1 is internalized by rat primary cortical neurons and can be delivered to the cytoplasm when co-treated with small-molecule endosome disruptors such as bafilomycin A1 or chloroquine. More critically, the tR1 peptide was found to inhibit the phosphorylation of endogenous tau at Ser262 in rat primary cortical neurons displaying hyper-active MARK2. Finally, the effects of tR1 were found to be selective for inhibiting tau phosphorylation at MARK2-dependent sites, as tR1 did not interfere with the activity of other kinases, such as GSK-3 β , that phosphorylate tau at Thr231. Importantly, these results have established tR1 as a novel peptide-based kinase inhibitor of MARK2 function that has significant therapeutic potential and the promising capacity to be developed as a tool to dissect the complex nature of MARK:tau biology.



MEDI 449

Synthesis of water soluble anthraquinoneaminoacrylamides and their glioblastoma cell viability

Nichole Pianovich¹, npianovi@uno.edu, **Branko S. Jursic**^{1,2}. (1) Chemistry, University of New Orleans, Chalmette, Louisiana, United States (2) STEPHARM, LLC., New Orleans, Louisiana, United States

Water soluble amines with acryl linker and anthraquinone moieties were synthesized to investigate the importance of their structural variations as potential anti-glioblastoma agents. Structural variations incorporated on to the amine moiety included derivatives of polyalcohols, morpholine, piperidine, and carboxylic acids. The size and shape of the amide moiety was varied, with the final variation introducing various amino saccharides. Several parameters were calculated whilst engineering these compounds, including: Clog P, molecular polarizability, polar surface area, minimal molecular projected area, and pKa. In addition, a simple and efficient procedure was developed to synthesize these compounds. It was demonstrated that acrylamides with 1-aminoanthraquinone and tri(hydroxymethyl)methyl moieties are the most promising drug candidates causing almost 90% of LN229 tumor cell death at 0.1 mg/ml. In addition, its molecular polarizability, polar surface area and minimal molecular projected area indicate there is potential for this molecule to cross the BBB.

MEDI 450

Synthesis and characterization of aspirin and indomethacin prodrugs

Abdelrahman Mahmoud, am1306019@qu.edu.qa, **Hani D. Tabb**a, **Yousef M. Hijji**. Department of Chemistry and Earth Sciences, Qatar University, Doha, Qatar

Prodrug synthesis is an approach that proved to be a good approach among strategies for improving drugs towards solving problems associated with their Solubility, Bioavailability, Stability, taste, or drug formulation prodrug is a compound that gets chemically transformed to result in the release of the desired pharmacological effect needed. In this paper we developed a method to synthesize prodrugs for sustained release of drugs. In this work, we used the parent drug (**Aspirin** or **Indomethacin**) carboxylic group is changed to the acid halide, followed by reaction with selected

alcohol or amine. We have characterized the produced respective esters or amides are fully identified using various spectroscopic techniques that we report here in this poster.

MEDI 451

Homology models of G protein-coupled receptors: quantitative studies to assess feasibility and applicability to drug discovery

Stefano Costanzi, *stefano.costanzi@gmail.com*. Chemistry, American University, Washington, District of Columbia, United States

G protein-coupled receptors (GPCRs) are a large superfamily of membrane-bound signaling protein endowed with a vast array of physiological functions and implicated in a plethora of pathological conditions. They are targeted by a large share of the currently available drugs and as regarded as an excellent platform for further drug discovery efforts. In recent years, structural biology efforts led to the experimental solution of the structure of a number of members of the superfamily. However, for many other members, structures remain unavailable. Homology modeling offers the opportunity to bank on the available structural information to generate hypotheses on the three-dimensional structure of the receptors for which experimental structures are unavailable.

Through this talk, I will discuss the results of a set of controlled experiments that my research group conducted to quantitatively assess the feasibility of homology modeling to GPCRs, with particular attention to the accuracy of the models and their applicability to docking-based virtual screening. In particular, I will illustrate how the accuracy of homology models is affected by the sequence-identity between the modeled receptors and templates. Furthermore, I will illustrate to what extent the accuracy of the models affects their applicability to virtual screening. Lastly, I will illustrate whether or not the activated or inactive state of the templates affects the selectivity of the resulting homology models for agonist and blockers in virtual screening.

MEDI 452

Way2drug platform – ligand-based approach to drug repurposing

Dmitry Druzhilovskiy¹, *dmitry.druzhilovsky@ibmc.msk.ru*, **Anastasiya Rudik**¹, **Dmitry Filimonov**¹, **G. Narahari Sastry**², **Vladimir Poroikov**¹. (1) Department for Bioinformatics, Institute of Biomedical Chemistry, Moscow, Russian Federation (2) Centre for Molecular Modeling, Indian Institute of Chemical Technology, Hyderabad, India

The aim of this project is to develop the efficient computational methods for identifying the promising pharmacological targets, for searching and designing their ligands, and the integration of the established computational approaches into a unified platform Way2Drug [www.way2drug.com]. At present, database of medicines approved by the U.S. Food and Drug Administration; database pharmaceutical substances registered in

the Russian Federation; knowledge base on the drug targets are available for use by registered users, the impact of which used/discovered for the treatment of cancer, diabetes, tuberculosis, etc. Platform provide the prediction of interaction with molecular targets, influence on gene expression, pharmacotherapeutic and side effects, metabolism, acute toxicity in rats with four modes of administration, cytotoxicity, etc., by the structural formula users may find drug substances similar to the structural formula of the compound used as a query by application MNA and QNA. Implemented hypertext links provide associations between pharmacological targets, the impact of which is predicted by PASS Online program, with UniProt, KEGG and PDB databases. We have developed web services for predicting interactions with ~ 80% of the molecular targets that are being studied in the target pharmacotherapeutic area. Physicochemical and ADMET characteristics may be estimated for the compound under study using the computational tools of our Indian collaborators.

MEDI 453

Cholesteryl ester vesicle-mediated delivery of GFP plasmid into retinal epithelial cells *in vitro*

Riley Meechan¹, rmeechan@mail.niagara.edu, Mary Q. Irving², Julie Hughes¹, John Fraser-McArthur³, Jerome Schentag², Lawrence Mielnicki¹, Mary McCourt¹. (1) Chemistry Dept, Niagara Univ, Niagara Univ, New York, United States (2) CPL Associates, Buffalo, New York, United States (3) Pharmacy and Pharmaceutical Sciences, State University of New York at Buffalo, Buffalo, New York, United States

This laboratory has developed neutral lipid (cholesteryl ester) based vesicles, that use naturally occurring cholesteryl esters to encapsulate and deliver a wide variety of substances, including fluorescein isothiocyanate (FITC) and other small molecules, vancomycin and other antibiotics, insulin and other peptides, IgG antibodies and other proteins as well as plasmid DNA and other nucleic acids. Previous work has shown cholesteryl ester vesicle-mediated delivery of FITC-labelled peptides into various mouse tissues (including brain) after oral administration. Cholesteryl ester vesicles may also be delivered directly into tissues. One such potential application is the delivery of ocular therapeutics. Systemic and topical (e.g., via eye drops) administration of drugs for treatment of diseases of the posterior segment of the eye, such as macular degeneration, are often undesirable. The systemic methods of treatment typically require higher total doses of the drug because these routes are inefficient at delivering only the precise amount of the drug to effectively treat the posterior segment. Such high doses increase the cost and may also cause side effects such as local inflammation or adverse systemic reactions. For most topical treatments, the drug is quickly washed out of the eye, limiting the effective time of treatment and generally providing too little exposure time for the drug to diffuse into the posterior segment where the disease is found. The present study examined the use of contact lenses soaked with green fluorescent protein encoding plasmid DNA loaded-cholesteryl ester vesicles for delivery into ARPE-19 retinal cells.

MEDI 454

Fragment-based approaches to targeting the CoA pathway

Anthony G. Coyne, *agc40@cam.ac.uk*. Chemistry, University of Cambridge, Cambridge, Cambridgeshire, United Kingdom

CoA is a fundamental co-factor found in all living systems and is involved in regulating key metabolomic processes. With the biosynthesis of CoA being essential for the viability of cells, inhibitors of its biosynthesis could be regarded as a potential pathway to prevent the growth of an organism such as a mycobacteria.

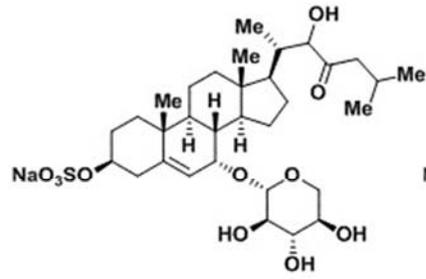
We have been interested in the CoA pathway of *Mycobacterium tuberculosis* for a number of years and we will present results where fragment-based approaches were used to develop inhibitors of enzymes on the CoA pathway. Fragment-based drug discovery has emerged as a powerful tool for the development of inhibitors and the results of our fragment screening and elaboration against two targets on the CoA pathway, CoaD and CoaBC will be discussed. We will show that a combination of synthetic and medicinal chemistry, structural biology and an array of biophysical techniques as part of the fragment based approach can be used to develop small molecule inhibitors of these two important targets. We will show that targeting CoaBC and CoaD present different challenges using fragment-based approaches and the strategies used for fragment elaboration.

MEDI 455

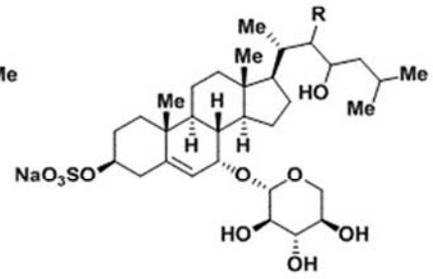
Three new cytotoxic steroidal glycosides isolated from *Conus pulicarius* collected in Kosrae, Micronesia

Yeon-Ju Lee, *yjlee@kiost.ac.kr*, **Su Hyun Kim**, **Hyi-Seung Lee**, **Jong Seok Lee**, **Jihoon Lee**. Marine Natural Product Chemistry Laboratory, Korea Institute of Ocean Science and Technology, Busan, Korea (the Republic of)

Three new sulfated steroidal glycosides, along with known cholesterol derivatives, were isolated from the visceral extract of the cone snail *Conus pulicarius*. The structure of each new compound was elucidated by nuclear magnetic resonance spectroscopy and high-resolution mass spectrometry. The characteristic structural features of the new compounds include the sulfate group at the C-3 position and the xylose linked to C-7, which is different from those of known steroidal glycosides. The three new compounds were named as Conusaponin A-C, as these are the first example of steroidal glycosides isolated from *Conus* species. These compounds exhibited significant in vitro cytotoxicity (GI_{50} values down to 0.5 μ M) against the K562 human leukemia cell line. This finding, combined with those regarding the previously reported steroidal glycosides with potent activities against various cancer cell lines, would provide new insights into the structure-activity relationships of cytotoxic sulfated steroidal glycosides.



Conusapnin A
 GI_{50} 1.5 μ M to K562 cells



R = H Conusaponin B GI_{50} 1.4 μ M to K562 cells
R = OH Conusaponin C GI_{50} 0.5 μ M to K562 cells