



Division of Medicinal Chemistry  
Scientific Abstracts  
for the  
257th National Meeting and Exposition

March 31-April 3, 2019  
Orlando, FL

# MEDI

## Division of Medicinal Chemistry

J. Schwarz, *Program Chair*

### SUNDAY MORNING

Section A

Orange County Convention Center  
Room W414AB

#### Small Molecule Immunomodulators in Cancer

E. F. DiMauro, S. A. Mitchell, *Organizers, Presiding*

**8:30** Introductory Remarks.

**8:35 MEDI 1.** Discovery of potent and structurally diverse IDO1 selective heme-displacing inhibitors from optimization of hits from a mass spectrometry based affinity (ALIS) screen. **Y. Han**, A. Achab, **C. Andrews**, J. Ballard, **I. Bharathan**, X. Chai, P. Chen, M. Cheng, D. Clausen, Y. Deng, A. Doty, H. Ferguson, X. Fradera, C. Gibeau, W. Glaab, L. Guo, S. He, B.A. Hopkins, X. Huang, W. Kang, J.A. Kozlowski, C. Lesburg, G. Li, J. Lim, K. Liu, M. Lu, T. Martinot, M.A. McGowan, J.R. Miller, E. Nickbarg, J. O'Neil, K. Otte, Q. Pu, S. Sanyal, N. Sciammetta, N. Smotrov, D. Sloman, N. Solban, X. Song, P. Spacciapoli, A. Bass, S. Vincent, C. White, D. Xiao, W. Yu, H. Zhou, H. Zhang, **D. Li**, A. Pasternak, D.J. Bennett

**9:05 MEDI 2.** Small molecule ectonucleotidase inhibitors for the immunotherapy of cancer.  
**C.E. Muller**

**9:35 MEDI 3.** Identification of BAY-218: A potent and selective small molecule AHR inhibitor, as a new modality to counteract tumor immunosuppression. **N. Schmees**, I. Gutcher, U. Roehn, H. Irlbacher, B. Bader, C. Kober, L. Roese, R. Carretero, I. Oezen, L. Zorn, M. Platten, I. Hartung, B. Kreft, D. Stoeckigt, H. Weinmann

**10:05 MEDI 4.** Discovery of novel cyclic dinucleotide STING agonists for cancer treatment. **W. Chang**, M.D. Altman, B.M. Andresen, S. Cemerski, M. Childers, A. Haidle, T.J. Henderson, J.P. Jewell, R. Liang, J. Lim, H. Liu, M. Lu, A. Northrup, R. Otte, S.A. Perera, J. Presland, T. Siu, Q. Truong, S. Walsh, K. Zhao, J. Cumming, W. Trotter

**10:35** Intermission.

**10:50 MEDI 5.** Discovery of JNJ-787: An Hpk1 inhibitor that enhances the anti-tumor immunity of anti-PD1 in mice. **L. Mevellec**, S. Descamps, C. Adelinet, B. Wroblowski, V. Vreys, A. Valckx, I. Boeckx, N. Van Slycken, C. Paulussen, L. Leclercq, T. Verhulst, B. Van der Leede, P. Angibaud, L. Meerpoel, J.P. Edwards, S. Laquerre, M. Lorenzi, J. Vialard

**11:20 MEDI 6.** Antiviral innate immunity through small molecules for protection against RNA viruses. **M. Gale**

**11:50 MEDI 7.** GS-4361: A novel IDO1 Inhibitor. **R.V. Kalla**, K. Elbel, M. Bartlett, J. Cosman, T.D. Perry, E. Elzein, X. Li, D.O. Koltun, E.Q. Parkhill, J.A. Zablocki, M. Clark, H. Maecker, S. Jawahar, D. Hendricks, A. Shornikov, D. Koditek, B. Stafford, D. Soohoo, J. Voigt, E. Lansdon, R. Mackman, B. Corkey

**12:20** Concluding Remarks.

Section B

Orange County Convention Center  
Room W331A

### General Orals

J. B. Schwarz, *Organizer*  
M. Lu, *Presiding*

**8:30 MEDI 8.** Discovery and optimization of inhibitors of the autophagy E1 enzyme, ATG7. **S. Huang**, S.J. Harrison, A.E. Gould

**8:50 MEDI 9.** Development of water soluble, brain permeable EP2 receptor antagonist: Lead-optimization and *in vitro* proof-of-concept studies. **R. Amaradhi**, A. Banik, S. Mohammed, V. Patro, A. Rojas, W. Wang, R. Dingledine, T. Ganesh

**9:10 MEDI 10.** SAR studies in the sulfonyl carboxamide class of core protein modulators of the hepatitis B virus. **S.D. Kuduk**

**9:30 MEDI 11.** Discovery and development of PI4KIII $\beta$  inhibitors as immunosuppressive agents for the prolongation of allogeneic organ engraftment. **J. Reuberson**

**9:50 MEDI 12.** Target identification studies of a utrophin modulator for treatment of Duchenne muscular dystrophy. **I. Wilkinson**, A. Vuorinen, J. Reynolds, K. Perkins, H. Dugdale, S. Squire, A. Casagrande, M. Geese, F. Wilson, G. Wynne, S. Mohammed, K. Huber, K. Davies, A. Russell

**10:10 MEDI 13.** Synthesis and biological evaluation of a new class of aryl isonitriles as antimicrobial agents. **K. Kyei-Baffour**, H. Mohammad, M.N. Seleem, M. Dai

**10:30 MEDI 14.** Hit-to-lead evolution of small-molecule PPAR $\alpha$  agonists: Working towards non-invasive options for retinal diseases. **A.S. Duerfeldt**

**10:50 MEDI 15.** Discovery of [ $^{11}\text{C}$ ]MK-6884: A positron emission tomography (PET) imaging agent for M4 PAM. **L. Tong**, W. Li, **X. Gao**, M. Lo, J.M. Wai, M.T. Rudd, D.M. Tellers, Z. Zeng, P. Miller, C. Salinas, K.A. Riffel, H. Haley, M. Purcell, M. Holahan, T. Bueters, J. Uslaner, J. Morrow, R. Mazzola

**11:10 MEDI 16.** Discovery and optimization of potent, selective, and bioavailable USP7 inhibitors to target tumor growth. **P. Leger**, D.X. Hu, B. Abraham, L. Adsusmilli, B. Biannic, D. Bradford, G. Cutler, X. Han, S. Jacobson, A. Jorapur, P. Kassner, D. Kaveri, J. Ketcham, A. Kim, J. Maung, J. McKinnell, Y. Ohol, A. Okano, L. Peiser, D. Pookot, P. Rana, N. Shah, G. Shibuya, M. Sun, S. Suthram, O. Talay, K. Young, J.B. Schwarz, D.J. Wustrow

**11:30 MEDI 17.** New ruthenium Formate catalyst MCAT-53<sup>TM</sup> for C-H activation useful for the synthesis of medicinally relevant molecules. **A. Mehta**, B. Saha, A. Koohang, M. Chorghade

**11:50 MEDI 18.** Discovery of a novel  $\alpha 7$  nAChR positive allosteric modulator for the treatment of cognitive disorders. **B.M. Crowley**, J. Balsells-Padros, J. Bao, B.T. Campbell, C.J. Daley, D. Guiadeen, B.C. Huff, J. Della Rocca, E.M. Joshi, K.J. Leavitt, D. Paul, J.M. Sanders, S. Tye, X. Wang, S.M. O'Connor, A.J. Harvey, J. Uslaner, J.L. Duffy, I.M. Bell

### **Drug Discovery: Informatics Approaches**

Sponsored by CINF, Cosponsored by MEDI

### **Wolfrom Award**

Sponsored by CARB, Cosponsored by CELL, MEDI, ORGN and PROF

### **Horton Award**

Sponsored by CARB, Cosponsored by CELL, MEDI, ORGN and PROF

### **SUNDAY AFTERNOON**

Section A

Orange County Convention Center  
Room W414AB

## General Orals

J. B. Schwarz, *Organizer, Presiding*

**1:30 MEDI 19.** Design of clinical candidate eFT226, a first-in-class inhibitor of the RNA helicase eIF4A. **C. Nilewski**, J.T. Ernst, P.A. Thompson, A.X. Xiang, C.V. Tran, G.K. Packard, T.D. Michels, P.A. Sprengeler, B. Eam, N.P. Young, S. Fish, J. Chen, M. Barrera, H. Howard, A. Parra, E. Sung, J. Staunton, I.N. Hung, G.S. Parker, G.G. Chiang, C.J. Wegerski, A. Nevarez, J. Clarine, S. Sperry, K.R. Webster, S.H. Reich

**1:55 MEDI 20.** Design and synthesis of a dual kinase-bromodomain inhibitor targeting ALK and BRD4. **E. Watts**, D. Heidenreich, E. Tucker, B. Bellenie, S. Knapp, L. Chesler, S. Hoelder

**2:20 MEDI 21.** Design, synthesis, and optimization of 2'2'-cyclic dinucleotides as STING agonists. **M. Lu**, M.D. Altman, A. Beard, F. Bennett, T. Cernak, W. Chang, M. Childers, S. Dreher, C. Lesburg, C. Li, R. Liang, J. Lim, H. Liu, L. Nogle, T. Siu, D. Steinhuebel, B. Taoka, Q. Truong, S. Walsh, J. Presland, S. Perera, S. Cemerski, J. Cumming, W. Trotter

**2:45 MEDI 22.** Geopharmaceuticals: New drug scaffolds from Baltic amber. **E.A. Ambrose**, C. McDermott

**3:10 MEDI 23.** Discovery of a novel series of small molecule modulators of TNF alpha binding and signalling through a novel mechanism of action. **T. Norman**, F. Lecomte, J. Kennedy, B. Carrington, J. Porter, J. O'Connell, A. Lawson, R. Davis, S. Rapecki, B. Kroeplien, A. Burgin, T. Arakaki

**3:35 MEDI 24.** Structure-based drug design towards small molecule interleukin-6 inhibitors. **D. Schultz**, L. Mao, G. Shi, W. Zhou, R. Huigens, C. Li

**4:00 MEDI 25.** Design and synthesis of novel central nervous system penetrant metabotropic glutamate receptor subtype 2 (mGlu<sub>2</sub>) negative allosteric modulators (NAMs) via scaffold hopping. **E.S. Childress**, J.M. Wieting, A.S. Felts, M.M. Breiner, M.F. Long, V.B. Luscombe, A.L. Rodriguez, H.P. Cho, A.L. Blobaum, C.M. Niswender, P.J. Conn, C.W. Lindsley

**4:25 MEDI 26.** Beyond the "Rule of 5" (bRo5): The evolution of efficient drug discovery. **C.A. Lipinski**

Section B

Orange County Convention Center  
Room W331A

**Targeted Protein Degradation: A Small Molecule Game-Changer for Medicine Discovery**

A. B. Benowitz, M. P. Bourbeau, *Organizers, Presiding*

**1:30 MEDI 27.** Use of heterobifunctional molecules that direct targeted protein degradation to explore signaling pathways. **C. Loh**, J. Kelleher, M. Weiss, V. Campbell, K. Yuan, C. Klaus, N. Mainolfi

**2:00 MEDI 28.** Design, characterization, and function of PROTACs targeting B-cell lymphoma 6 (BCL6). **W. McCoull**

**2:30 MEDI 29.** Co-opting and degrading IAPs. **S.T. Staben**

**3:00 MEDI 30.** Harnessing bioPROTACs to achieve rapid and robust protein knockdown. **S. Lim**, J. Chang, A. Partridge

**3:30 MEDI 31.** Targeting the undruggable: PROTAC approach to target transcriptional factors. **S. Wang**

**4:00 MEDI 32.** Lead optimisation of a series of RIPK2 PROTACs: Ripping up the rule book. **J.D. Harling**

### **Drug Discovery: Informatics Approaches**

Sponsored by CINF, Cosponsored by MEDI

### **Hudson Award**

Sponsored by CARB, Cosponsored by CELL, MEDI, ORGN and PROF

### **Isabell Award**

Sponsored by CARB, Cosponsored by CELL, MEDI, ORGN and PROF

### **Collaborations & Data Sharing in Rare & Orphan Disease Drug Discovery**

Sponsored by CINF, Cosponsored by MEDI

## Gin New Investigator Award

Sponsored by CARB, Cosponsored by CELL, MEDI, ORGN and PROF

## SUNDAY EVENING

Section A

Orange County Convention Center  
West Hall C

### General Posters

J. B. Schwarz, *Organizer*

#### 7:00 - 9:00

**MEDI 33.** Tip48/Tip49 inhibitors: Antipyrene derivatives with diamide linker as potential anticancer agents. **T. Hamada**, M. Ebisawa, T. Suzuki, T. Murata, T. Tsukada, R. Motoki, Y. Kagoshima, M. Hirasawa, K. Hagihara, Y. Fujii, R. Murakami, T. Takata, K. Iwanaga, N. Haginoya, K. Uoto

**MEDI 34.** Using small molecule adjuvants to combat antibiotic resistant bacteria in cystic fibrosis. **V.B. Hubble**, C. Melander

**MEDI 35.** Pt-Mal-LHRH attenuates breast cancer tumor growth and metastasis by targeting overexpression of the LHRH receptor. **M. Ndinguri**, C. Black, J. Rollins, L. Calderon

**MEDI 36.** Quinazoline derivatives as potential tubulin polymerization inhibitors. **F. Herrera-Vázquez**, R. Aguayo-Ortiz, L. Dominguez, F. Hernández-Luis

**MEDI 37.** Discovery of DS-6930: A potent selective PPAR $\gamma$  modulator. **K. Fujii**, T. Shinozuka, T. Tsukada, E. Tokumaru, K. Shimada, Y. Onishi, Y. Matsui, S. Wakimoto, M. Kuroha, T. Ogata, K. Araki, J. Ohsumi, R. Sawamura, N. Watanabe, H. Yamamoto, K. Fujimoto, Y. Tani, M. Mori, J. Tanaka

**MEDI 38.** Identification of novel PPAR  $\alpha/\gamma$  dual agonist by *in silico* screening and molecular dynamics simulations. **V. Nath**, V. Kumar

**MEDI 39.** Dual CDK4/ARK5 inhibition by ON 123300 for targeting metastatic colorectal cancer. **M. Reddy**, S. Cosenza, S. Divakar, B. Akula, M.R. Mallireddigari, P. Reddy

**MEDI 40.** Activity landscape modeling and molecular dynamics of dual inhibitors of DNMT1 and G9a. **E. Lopez**, F. Prieto-Martínez, J. Medina-Franco

- MEDI 41.** 4-Hydroxybenzthiazole inhibitors of catechol-*O*-methyltransferase. **P.J. De Leon, J. Barrow**
- MEDI 42.** MOEsaic: Application of matched molecular pairs to interactive SAR exploration. **A. Ajamian**
- MEDI 43.** Exploiting solvent effects in drug design and optimization. **A. Ajamian**
- MEDI 44.** Scaffold replacement and 3D ligand optimization applied to the discovery of tyrosine kinase inhibitors. **A. Ajamian**
- MEDI 45.** Protocol for validating small molecule structure assignment using calculated <sup>13</sup>C NMR chemical shifts with quantum mechanics and MOE. **A. Ajamian**
- MEDI 46.** First investigation of the antibacterial activity of the combination of 2-hexadecynoic acid and ciprofloxacin against multi-drug resistant *Staphylococcus aureus*. **S. Medina, T. Peres-De-Leon, C. Ocasio-Malave, D. Diaz, N.M. Carballeira, D.J. Sanabria Rios**
- MEDI 47.**  $\alpha$ -Glucosidase inhibition natural products from *Chromolaena odorata*. **C.T. Onyema, V.I. Ajiwe, A. Ata**
- MEDI 48.** Polyhydroxyalkanoate-celecoxib nanoparticles for systemic lupus erythematosus therapy with enhanced efficacy and reduced side effects. **J. Hu**
- MEDI 49.** Facial sebum levels and its relationship with the severity of acne vulgaris in African adolescents. **O.N. Ilesanmi**
- MEDI 50.** Benzoflavone derivatives as potent antihyperuricemic agents. **H. Singh, J. Singh, A. Singh, P. Bedi**
- MEDI 51.** La-DOTA-melanocortin 1 receptor targeting ligand clearance route is controlled by linker polarity. **H. Kil, N. Tafreshi, D. Pandya, M. Doligalski, C. Tichacek, M. Budzevich, E. Moros, T. Wadas, D. Morse, M. McLaughlin**
- MEDI 52.** Purifying complex reaction mixtures via high-performance flash chromatography. **J.R. Bickler**
- MEDI 53.** Binding affinity of flavins to riboflavin binding protein using fluorescence spectrometry and isothermal titration calorimetry; and estimated binding energies using computational approaches. **A. Jenkins, M. McMillan, J.B. Ealy**
- MEDI 54.** Discovery of (3*S*,4*S*)-3-methyl-3-(4-fluorophenyl)-4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxyprop-2-yl)phenyl)pyrrolidines as novel ROR $\gamma$ t inverse agonists. **B. Jiang, J. Duan, C.A. Weigelt, S.M. Stachura, A. Karmakar, H. Hemagiri, D.K. Raut, A.K. Gupta, J. Khan, J.S. Sack, D. Wu, M. Yarde, D. Shen, M.A. Galella, Q. Zhao, L.M. Salter-Cid, P.H. Carter, T. Dhar**

**MEDI 55.** X-ray crystal structure determination of leukotriene A<sub>4</sub> hydrolase in complex with 4-methoxy-ARM1 and characterization of the aminopeptidase enzyme mechanism. **K. Lee**, G. Petruncio, Y. Shim, S. Noble, M. Paige

**MEDI 56.** Substrate-dependent hydrolysis by the leukotriene A<sub>4</sub> hydrolase in the presence of 4MDM. **K. Lee**, Y. Shim, S. Noble, M. Paige

**MEDI 57.** Novel 5-cyanopyrimidine derivatives induces inhibition EGFR signaling pathways in cancer cell lines. **D. Khochenkov**, Y. Khochenkova, **A.S. Bunev**

**MEDI 58.** Tip48/Tip49 inhibitors: Antipyrene derivatives with an oxadiazole ring as potential anticancer agents. **T. Tsukada**, M. Ebisawa, Y. Sugimoto, T. Taniguchi, S. Hirano, F. Muro, T. Suzuki, T. Hamada, T. Murata, S. Takechi, R. Motoki, Y. Kagoshima, M. Hirasawa, K. Hagihara, Y. Fujii, K. Hashimoto, T. Takata, R. Murakami, K. Iwanaga, N. Haginoya, K. Uoto

**MEDI 59.** Discovery and characterization of a novel allosteric binding site of HSP70 by fragment based screening. **S. O'Connor**, Y. Le Bihan, R. van Montfort, I. Collins

**MEDI 60.** 5-Cyanopyrimidine-based compounds inhibits migration in A549 lung cancer cells. **V. Dudanova**, D. Khochenkov, Y. Khochenkova, A.S. Bunev

**MEDI 61.** Methylphenidate (Ritalin<sup>®</sup>) and synthetic cathinones (bath salts): Are they similar?. **B.J. Yadav**, J. Eltit, R.A. Glennon

**MEDI 62.** Pharmacological analysis of 1,2,3-triazoles as amide bioisosteres in potentiators of the cystic fibrosis transmembrane conductance regulator protein. **J. Doiron**, G.W. Breton, L. Tang, W. Wang, S.M. Rowe, S.G. Aller, M.L. Turlington

**MEDI 63.** Development of potent GPR35 agonists with activity at human and rodent receptors. **L.L. Wendt**, D. Thimm, C.E. Muller

**MEDI 64.** Library of covalent, bifunctional small-molecule probes for the targeting of cysteine residues. **E. Altmann**, S. Numao, P. Ertl, L. McGregor, S. Renner

**MEDI 65.** FRAGNET: A European consortium to advance fragment-based drug discovery and educate its future advocates. **M. Wijtmans**, J. van Muijlwijk-Koezen, I. de Esch

**MEDI 66.** Aurora-A inhibitor alisertib potentiates VEGFR inhibitors in glioblastoma cell lines. **K. Smith**, C. Mifsud, C. Zumber, N. Lehman

**MEDI 67.** Nanokinib: A cyclic library of hinge binder and chemocentric approach for the discovery of selective kinases inhibitor. **N. George**, P. Benderitter, P. Blom, M. Fouchet, A. Denis, J. Hoflack

**MEDI 68.** Structural evolution of novel opioid peptidomimetics with reduced abuse liabilities. **S. Henry**, N. Griggs, J.P. Anand, B. Sears, J.R. Traynor, E. Jutkiewicz, K. Sobczyk-Kojiro, H.I. Mosberg

**MEDI 69.** Regioselective alkylation, arylation, and heteroarylation of 3-substituted pyrazoles. **A. Bao**, A. Huang

**MEDI 70.** Novel imidazobenzodiazepine GABA<sub>A</sub> receptor  $\alpha 2/\alpha 3$  selective PAM for the treatment of refractory/resistance epilepsy. **L.K. Golani**, J.M. Witkin, J.M. Cook

**MEDI 71.** Structure of membrane bound pyrophosphatase from *Thermotoga maritima* in complex with imidodiphosphate and *N*-[(2-aminobenzo[*d*]thiazol-6-yl)methyl]-1*H*-indole-2-carboxamide. K. Vidilaseris, A. Kiriazis, A. Turku, A. Khattab, **N.G. Johansson**, T.O. Leino, P.S. Kiuru, G. Boije af Gennäs, S. Meri, J.T. Yli-Kauhaluoma, H. Xhaard, A. Goldman

**MEDI 72.** Discovery of a novel olefin derivative as a highly potent and selective acetyl-CoA carboxylase 2 inhibitor. **Y. Nishiura**, A. Matsumura, N. Kobayashi, A. Shimazaki, S. Sakamoto, N. Kitade, Y. Tonomura, A. Ino, T. Okuno

**MEDI 73.** New organic photo CORM and the PCBA polymer nanoparticle incorporating it. **A. Elgattar**, **A. Alwagdani**, **T. Khalil**, **H. Pal**, **Y. Liao**

**MEDI 74.** First-generation structure-activity relationship studies of 2,3,4,9-tetrahydro-1*H*-carbazol-1-amines as CpxRA modulators. Y. Li, **J.J. Gardner**, K.R. Fortney, S. Spinola, A.S. Duerfeldt

**MEDI 75.** Targeting glioma progression: Human heparanase inhibition by a novel class of non-anticoagulant heparinoids. **S. Nadji**, R.K. Dhar

**MEDI 76.** Azulene-based compounds targeting orexin receptors. **T.O. Leino**, A. Turku, J.T. Yli-Kauhaluoma, J.P. Kukkonen, H. Xhaard, E. Wallen

**MEDI 77.** PPE51-mutation effect the sensitivity of *Tubercle bacilli* to selected thio-sugars. **Z.J. Witczak**, M. Korycka-Machala, A. Brzostek, P. Borowka, D. Strapagiel, J. Dziadek

**MEDI 78.** Progress towards orally bioavailable, potent, and selective small-molecule inhibitors of CD73 for immuno-oncology. R. Thomas-Tran, E. Lindsey, K. Lawson, **J. Beatty**, J. Jeffrey, J. Fournier, D. Mandal, X. Yan, S. Drew, N. Walker, S. Moschütz, N. Sträter, A. Chen, M. Reddy Leleti, J. Powers

**MEDI 79.** Discovery and characterization of potent and selective small-molecule inhibitors of ecto-nucleotidase CD73 for cancer immunotherapy. **E.U. Sharif**, K. Lawson, J. Kalisiak, E. Lindsey, E. Newcomb, B. Rosen, N. Walker, L. Jin, E.R. Scaletti, N. Sträter, A. Chen, M. Reddy Leleti, J. Powers

**MEDI 80.** Discovery of SAM competitive and non-nucleoside derivative PRMT5 inhibitors with potent antitumor activity. **X. Yang**, W. Zhou, C. Li

**MEDI 81.** Impact of automated supersaturation stability assay to differentiate poorly soluble compounds in Novartis drug discovery and development. **S. Skolnik**, S. Dodd, G. Geraci

**MEDI 82.** Phytochemical screening and antioxidant activities of *Irvingia gabonensis* and its effect on alloxan-induced diabetes rats. **O.E. Ogunjinmi**, I.A. Salaudeen, M.O. Abdulganeey

**MEDI 83.** *In-situ* single-step electrochemical detection of DL-methionine in human serum sample. **A.N. Kawde**

**MEDI 84.** Discovery of novel 6-aryl-2-benzoyl-pyridines as tubulin polymerization inhibitor with potent antiproliferative properties. **H. Chen**, S. Deng, N. Albadari, D.D. Miller, W. Li

**MEDI 85.** Design and development of novel selective D<sub>4</sub>-receptor ligands as CNS-therapeutics. **U. Gonela**, S.Y. Ablordeppey

**MEDI 86.** Antioxidant activity of eugenol derivatives. **E. Siech**, **V. Thurman**, A. Vummenthala

**MEDI 87.** Discovery of a novel second-site corrector for delF508 CFTR mutations. **P. Lam**, K.D. Boss, A.K. Cheung, R. Epple, S. Espinola, A. Honda, C. Lay, W. Li, H.A. Malik, L. Whitehead, B. Wu, W.G. Barnes, S.J. Patel

**MEDI 88.** Discovery and SAR studies of novel 2-anilinopyrimidine-based selective inhibitors against triple-negative breast cancer cell line. **J. Jo**, S. Kim, H. Kim, M. Jeong, Y. Jung, H. Yun

**MEDI 89.** Efficient synthetic methods of 7-trifluoromethyl-7-deazapurine ribonucleoside analogs and their phosphoramidate prodrugs. **J. Cho**, S. Choi, J. Kim, F. Amblard, L. Bassit, R. Schinazi

**MEDI 90.** *In silico* discovery of new small-molecule immune checkpoint inhibitors as an innovative approach to treat cancer. **S. Ferla**, S. Lanfredini, G. Patel, A. Brancale

**MEDI 91.** Delivering glutathione persulfide by an esterase-sensitive donor. **Z. Yuan**, Y. Zheng, B. Yu, S. Wang, X. Yang, B. Wang

**MEDI 92.** Highly advanced intermediate towards a macrocyclic ketone mimic of zampanolide. **Z. Jiang**, G. Chen, Q. Chen

**MEDI 93.** Development of a platform for resveratrol delivery: Functionalization of resveratrol-loaded nanoparticles and hypertrophy modulation in cardiac cells. **P. Garcia**

**MEDI 94.** Chromatography and fractionation of *Schinus terebinthifolius* extracts which inhibit breast cancer cell migration *in vitro*. **M. Pina**, **J.M. Brown**, A. Tapanes-Castillo

**MEDI 95.** Computational designed new inhibitors of xanthine oxidase for treatment of gout. **C. Dong**, V. Usanga

**MEDI 96.** Structure Activity Relationship (SAR) studies of a nucleotide reverse transcriptase inhibitors (NRTI) AZT (Zidovudine) analogs using Gaussian computational techniques. **S. Narayan**, K. Quirk, K. Baldwin

**MEDI 97.** Time-on-target: Easy method development for reverse phase preparative chromatography. **J.E. Silver**, C. Bailey, D. Johnson, R. Lewis

**MEDI 98.** Searching for sensitizers of bacteria toward existing antibiotics. **M. Roy Choudhury**, B. Yu, A. Kumar, M. Zhu, D.W. Boykin, B. Wang

**MEDI 99.** On-column dilution: A method to improve loading and resolution in chromatography. **J.E. Silver**, C. Bailey, D. Johnson, R. Lewis

**MEDI 100.** Optimization of structural features of the 4-anilinoquin(az)oline scaffold for chordoma utilizing an innovative toxicology profiling assay panel. **C.R. Asquith**, A.A. Bieberich, K. Maffuid, R. Fatig, G.J. Tizzard, T. Laitinen, M.P. East, C.D. Torrice, D. Drewry, G.J. Johnson, D.J. Crona, B. Calvin, D.C. Morris, W.J. Zuercher

**MEDI 101.** Biphenyl acid derivatives as APJ receptor agonists. **S. Su**, A. Clarke, Y. Han, H. Chao, J. Bostwick, W. Schumacher, T. Wang, M. Yang, M. Hsu, E. Simmons, Y. Hsiao, E.E. Luk, M. Dabros, M.A. Galella, J. Onorato, D. Gordon, R.R. Wexler, P.S. Gargalovic, M. Lawrence

**MEDI 102.** Using electrostatic complementarity to design compounds: A new approach to visualize and predict activity. **T. Cheeseright**, S. Sciammetta, M. Bauer, M.D. Mackey

**MEDI 103.** Cruentaren A analogs and their biological activities. **B. Patel**, M. Topinka, B.S. Blagg

**MEDI 104.** Potential correlation between chlorine-treated drinking water and cancer incidences. **A. Avalos**, S. Rodriguez

**MEDI 105.** Design and optimization of CDK4/6 and FLT3 dual inhibitors with a novel hinge binder. **K. Li**, L.R. McGee, J.E. Eksterowicz, D. Piper, Z. Wang, G. Alba, M. Ragains, R. Ngo, M. Lo, J. Ma, K. Keegan, C. Li, L. Liang, K. Dai

**MEDI 106.** Transporter informatics: Predicting substrates for transmembrane transporters. **G.F. Ecker**, S.M. Kohlbacher

**MEDI 107.** Discovery of a pan-mGluR PAM for the treatment of CNS disorders. **S. Mayer**

**MEDI 108.** Fisetin derivatives as anti-prostate cancer agents. **k.W. muthima**, Q. Chen, G. Chen, M. Lee

**MEDI 109.** Immuno-oncology (IO) drug conjugate concentrates at cells and tumors and enhances survival. **S. Kaulagari**, M. Doligalski, A.S. Cohen, H. Zheng, V. Estrella, A. Beg, D. Morse, M. McLaughlin

**MEDI 110.** Discovery and characterization of peptide inhibitors of RsmC function. **D.D. To**, K. GC, S. Abeyirigunawardena

**MEDI 111.** Implementation of vector analysis for the identification of potential KLK-6/PAR-1 dual inhibitors for the treatment of multiple sclerosis through molecular docking, molecular dynamics and chemoinformatic studies. **J. S. Tejada**, M.A. Loza-Mejia, S. Fuentes-Villegas, M. Salinas-Parra, V. Villegas-Gonzalez

**MEDI 112.** Molecular docking of torreyunlignans in phosphodiesterases 9A, 4B, and 8A: Computational analysis of torreyunlignan inhibition. **E.M. Bonett**, M. McEwan, K.E. Cole, J.M. Carney

**MEDI 113.** Molecular docking and lead optimization of torreyunlignans, phosphodiesterase 9A inhibitors. **E.M. Bonett**, K.E. Cole, J.M. Carney

**MEDI 114.** Cytosine-based TET enzyme inhibitors. **H. Sun**, N. Kuzio, M.J. Bennett, G. Chua, K.L. Wassarman, J.A. Alp, E.I. Jarczyk, B.G. Malachowsky, A. Kennedy

**MEDI 115.** Comparison of native ribose and conformationally-constrained (N)-methanocarba nucleosides for A<sub>1</sub> adenosine receptor agonists: Design and *in vivo* characterization. **D. Tosh**, H. Rao, A. Bitant, V. Salmaso, P. Mannes, D. Lieberman, J. Auchampach, A. Ciancetta, N. Liu, Z. Cui, Z. Gao, M. Reitman, O. GavriloVA, K.A. Jacobson

**MEDI 116.** Curcumin-metal complexes as inhibitors of beta-amyloid aggregation. **M. Dervisevic**, A. Vummenthala, **J. Brabant**

**MEDI 117.** Biochemical analysis of *Syzygium aromaticum* as potential agent in the treatment of diabetes. **G.W. Garcia**, A. Mar, H.M. Morales

**MEDI 118.** Structure-function studies of a novel allosteric site of the dopamine transporter as a target for alternative therapeutics against cocaine use disorder. **S. Aggarwal**, X. Liu, C. Rice, S. Kortagere, J. Salvino, O. Mortensen

**MEDI 119.** Cyclization-centered structure-activity relationship of a noncovalent inhibitor of the KEAP1-NRF2 interaction. **K.M. Booker**, T.W. Moore, B. David

**MEDI 120.** *In vivo* effect of PEG-tethered A<sub>2A</sub> adenosine receptor agonist-alendronic acid conjugates on induced bone degeneration. **K.S. Toti**, A. Larrañaga-Vera, A. Gadiano, E. Warnick, H. Rao, Z. Gao, B.N. Cronstein, K.A. Jacobson

**MEDI 121.** Treatment of sensorimotor gating deficits in neuropsychiatric disorders using deuterated  $\alpha$ 6-GABA<sub>A</sub>R subtype selective ligands. **D.E. Knutson**, R. Kodali, M. Treven, B.

Divovic, H. Lee, J. Chou, H. Chen, L. Chiou, M. Ernst, M.D. Mihovilovic, M.M. Savić, W. Sieghart, J.M. Cook

**MEDI 122.** Anti-glycation effect and advanced glycation end-products protein cross-links breaking ability of *Psidium guajava* leaf extracts. **O.I. Adeniran**, A. Mogale, L.J. Shai

**MEDI 123.** Renoprotective effects of hypoxylonol derivatives isolated from *Hypoxylon truncatum* against cisplatin-induced cytotoxicity. **J. Ham**, K. Kang, B. Hwang, D. Lee, P. Choi, T. Kim, Y. Park, S. Choi, B. Song, K. Cho

**MEDI 124.** Incarvillateine produces antinociceptive and motor suppressive effects via adenosine receptor activation. **J. Kim**, D.M. Bogdan, M.W. Elmes, M. Awwa, S. Yan, J. Che, G. Lee, D.G. Deutsch, R.C. Rizzo, M. Kaczocha, I. Ojima

**MEDI 125.** Study of the biochemistry of lemon grass: A widely used diabetes remedy. **N. Trejo**

**MEDI 126.** Investigation of effects of rigidity on kinase inhibitor selectivity. **C. Yu**, A. Assadieskandar, C. Zhang

**MEDI 127.** Androgen receptor degraders and transactivation domain inhibitors targeting castration-resistant prostate cancer. **D. N. G. Ralalage**, J. An, M.E. Jung, M.B. Rettig

**MEDI 128.** Discovery and SAR studies of novel non-toxic azacyclic derivatives for the treatment of type 2 diabetes mellitus. **H. Choi**, Y. Park, J. Kwak, E. Jung, M. Yang, K. Kang, H. Yun

**MEDI 129.** Optimization of 6-amino-3-methylpyrimidinones as potent, selective, and orally efficacious SHP2 inhibitors. **M.G. Palermo**, P.J. Sarver, M. Acker, J.T. Bagdanoff, Z. Chen, M. Fodor, J. Garcia-Fortanet, H. Hao, M. Kato, R. Koenig, L. LaBonte, G. Liu, S. Liu, C. Liu, M. Mohseni, M. Sendzick, T. Stams, R.B. Tichkule, C. Towler, H. Wang, P. Wang, S.L. Williams, B. Yu, M.J. Lamarche

**MEDI 130.** Optimizing the anti-proliferative activity of CJ-15,208 in prostate cancer cells. **R. Pescatore**, J.V. Aldrich

**MEDI 131.** Finding new molecules for treatment of neurological and metabolic disorders by *in silico* analysis of phytoconstituents from traditional Indian and Russian medicines. N. Ionov, P. Pogodin, A. Rudik, S. Ivanov, A. Lagunin, V. Poroikov, V. Luzhanin, M. Povydysh, R. Kumar Goel, G. Sastry, **D. Druzhilovskiy**

**MEDI 132.** Development of tumor-targeting, light-activated chemotherapy with vitamin B<sub>12</sub>-protein kinase inhibitor conjugates. **L.N. Gendron**, **C.G. Sheveland**, T.A. Shell, **J.R. Shell**

**MEDI 133.** Tagetnoic acid: A new lipoxygenase inhibitor peroxy fatty acid from *Tagetes minuta* growing in Saudi Arabia. **M.T. Khayat**, G.A. Mohamed, S.R. Ibrahim

- MEDI 134.** *In silico* assessment of cardiovascular adverse effects of drug-drug interactions. S. Ivanov, A. Lagunin, D. Filimonov, V. Poroikov, **D. Druzhilovskiy**
- MEDI 135.** Novel macrocyclic tetrapeptide kappa opioid receptor ligands: Cytochrome P450 metabolism and interactions. **T. Khaliq, J.V. Aldrich**
- MEDI 136.** AI-driven design of dual-pharmacophore libraries. **C.S. Bury**, J.P. Overington, A. Pannifer
- MEDI 137.** Development of potent and specific inhibitors for oncogenic kinase FGFR4. **R. Rezende Miranda**, C. Zhang
- MEDI 138.** Flexibility at different stages of mechanism of activation of the GPCR-prototype agrees with local motions explored by molecular dynamics simulations. **K. Gonzalez Ponce**, A. Madariaga, K. Martinez Mayorga
- MEDI 139.** Drug delivery of xanthohumol to adipocytes using ultrasmall superparamagnetic iron oxide nanoparticles. I. Khaki Najafabadi, J. Samuels, R. Dansby-Sparks, T. Fields, A. Singh, S. Raylam, R. Deshmukh, **V.V. Mody**
- MEDI 140.** Nonracemic prodrugs of a butyrophilin ligand. **N.A. Lentini**, C.C. Hsiao, A.J. Wiemer, D.F. Wiemer
- MEDI 141.** Structural optimization of pyrrolopyrimidine RET kinase inhibitors. **V. Garcia**, S. Toenjes, S.M. Maddox, G. Dawson, M.M. Cardenas, J.L. Gustafson
- MEDI 142.** Discovery and optimization of imidazoisoindole-based IDO/TDO dual inhibitors. **R. Pastor**, B. Parr, Y. Liu
- MEDI 143.** Multi-approach strategy to improve the spectrum of ClpP activators. **Q. Avila**, A.S. Duerfeldt
- MEDI 144.** Development and characterization of hiPSC cortical neurons and their application to drug evaluation in CNS disease models. **K. Autar**, X. Guo, A. Goswami, M. Jackson, J. Rumsey, C. Long, J.J. Hickman
- MEDI 145.** Effect of lithium at therapeutic and subtherapeutic doses in GSK3beta autonomous pathways at primary hippocampal neurons cell culture. **V. De-Paula**, A. Barbosa, O. Forlenza, H. Brentani
- MEDI 146.** Anti-diabetic activity of *Cissus rotundifolia* plant growing in Saudi Arabia. **S. Alshehri**, F.T. Halaweish
- MEDI 147.** Development of a thermal shift assay for evaluating inhibitor candidates targeting viral hemagglutinin and neuraminidase. **A. de Moya**, S.A. Whitney, L. Offermann, **N.L. Snyder**

**MEDI 148.** Identifying of the molecular target for the potent antimicrobial agent TI-I-100 to treat drug resistance bacteria. **V. Tiruveedhula**, R. Kodali, L. Han, L. Arnold, J.M. Cook

**MEDI 149.** Pharmacophore generation of  $\mu$ -opioid receptor biased-ligands: Uncovering structural features from molecular modeling analysis. **B. Hernández**, A. Madariaga, K. Martinez Mayorga

**MEDI 150.** Nucleic acid nano-vehicles designed form flexible tetra-U/T helix linking motif. **E.F. Khisamutdinov**

**MEDI 151.** Drug development on chemical therapeutics/antidote for chemical and biological warfare agents/toxic agents. **S.N. Olatunji**

**MEDI 152.** Next-generation bedaquiline for the treatment of tuberculosis. **P.J. Choi**, H. Sutherland, A. Tong, D. Conole, A. Blaser, C.B. Cooper, S.G. Franzblau, A.M. Upton, W.A. Denny, B.D. Palmer

**MEDI 153.** Inhibition of Dengue virus protease by chemical constituents of a clove: From food ingredient to medicine. **M. Saeed**

**MEDI 154.** Development of novel C3-analogs of galeterone for prostate cancer therapy. **P. Puranik**, F.N. Murigi, A.K. Kwegyir-Afful, S. Ramalingam, V.P. Ramamurthy, V.C. Njar

**MEDI 155.** Design, synthesis, and evaluation of quinazoline derivatives as FAK inhibitor with antiproliferative and antiangiogenic activity on cancer induced chick embryo. **A. Verma**, P. Pathak, p.K. Shukla, V. Kumar

**MEDI 156.** Pharmacoinformatic-based structural exploration, synthesis, and bioevaluation of selective Gly/NMDA antagonists: Potential ligands to treat intractable epilepsy. **V.G. Ugale**, S. Bari

**MEDI 157.** Identification of dibutyrate prodrug of antiviral deoxynojirimycin derivative IHVR-19029. **Y. Du**, H. Lu, G. Guo, H. Luo, Q. Su, N. Hwang, J. Ma, X. Zhang, S. Bixler, T. Warren, S. Bavari, J. Guo, T. Block, J. Chang

**MEDI 158.** Multiple quantitative structure-activity relationships (QSARs) analysis for  $\gamma$ -secretase inhibitors. **V. Patil**, N. Masand

**MEDI 159.** Potent, non-carboxylesterase-labile pro-drugs of the enolase inhibitor HEX for the treatment of ENO1-deleted glioblastoma. **V.C. Yan**, E.S. Ballato, K.L. Yang, D.K. Georgiou, K. Arthur, P. Shrestha, S. Khakha, J. Ackroyd, F.L. Muller

**MEDI 160.** Rational design, synthesis, and *in-vitro* screening of novel tankyrase inhibitors for the treatment of cancer. **B.D. Patel**, A. Patel, H.G. Bhatt

**MEDI 161.** Novel diphenylbutylpiperidine analogs to treat lung cancer. **M. Ashraf Uz Zaman**, M. Sajib, C.M. Mikelis, N. German

**MEDI 162.** Discovery of novel toll-like receptor 7 antagonists. **S. Jiang**, H. Chen, H.H. Yin

**MEDI 163.** Green synthetic approach to access thiazetidin-2-imine and thiazolidin-2-imine fused pyrazolo-pyrimidine scaffold as hybrid bifunctional molecules: Structure-based optimization and evaluation of calcium dependent protein kinase1(CDPK1) inhibition. **N. Rao**

**MEDI 164.** Development of inhibitors of the pore forming protein perforin for the treatment of leukaemia. **J. Jose**, J. Spicer, C.K. Miller, P.D. O'Connor, A. Giddens, H. Akhlaghi, J. Trapani, W.A. Denny

**MEDI 165.** Design and synthesis of macrocyclic CREBBP bromodomain ligands. **M. Moroglu**, M.D. Selby, J. Reuberson, W. Pitt, J. Clayton, S.J. Conway

**MEDI 166.** Design and synthesis of novel benzoxazole derivatives as B-Raf kinase inhibitor for the treatment of skin cancer. **J.P. Chavda**, K.V. Shah, H.G. Bhatt

**MEDI 167.** Photopharmacology for GPCR receptor proteins: 1<sup>st</sup> and 2<sup>nd</sup> generation chemical biology tools. **M. Wijtmans**

**MEDI 168.** Inhibitors for Asp-proteases: Anchor-based virtual screening, innovative chemistry, and protein crystallography. **M. Konstantinidou**, F. Magari, F. Sutanto, M. Unver, V. Jumde, C.J. Camacho, G. Klebe, A. Hirsch, A. Doemling

**MEDI 169.** Designing and synthesis of novel scaffold by adopting ligand- and structure-based approaches as HIV-1 entry inhibitor specially targeting to viral glycoprotein Gp120. **K.V. Shah**, J.P. Chavda, H.G. Bhatt

**MEDI 170.** Developing a chemical probe: Thieno[3,2-*d*]pyrimidines, selective and potent inhibitors of protein kinase DRAK2/STK17B. **A. Picado**, C. Wells, D. Drewry

**MEDI 171.** PROTAC small-molecule degraders of AR protein. **X. Han**, C. Wang, C. Qin, W. Xiang, E. Fernandez-Salas, C. Yang, M. Wang, L. Zhao, T. Xu, J. Stuckey, S. Wang

**MEDI 172.** Design, synthesis, and application of GLP1 agonist-ASO conjugates to gene silencing in pancreatic beta cells. **L. Knerr**, A. Hayen, M. Ölwegård-Halvarsson, P.P. Seth, T.P. Prakash, W.J. Drury, C. ämmälä, I. Ahlstedt, P. Stillemark-Billton, C. Wennberg-Huldt, E. Andersson, E. Valeur, R. Jansson-Löfmark, D. Janzén, L. Sundström, J. Meuller, J. Claesson, P. Andersson, C. Johansson, R.G. lee, B.P. Monia, S. Andersson, A. Björkbom, E. Cavallin, X. Li

**MEDI 173.** Synthetic efforts towards the preparation of 2'-dihalogenated nucleotide prodrugs. **S.P. Mengshetti**, L. Zhou, O. Sari, C. De Shutter, S. Zhou, Z. Chen, H. Zhang, A. Khalil, H. Li, R. Ovadia, M. Kasthuri, F. Amblard, R.F. Schinazi

**MEDI 174.** Design, synthesis, and biological evaluation of novel oxadiazole- and thiazole-based histamine H<sub>3</sub>R ligands. **M.A. Khanfar**, H. Stark

**MEDI 175.** Design and optimization of a first-in-class NACK inhibitor: A novel path to notch inhibition. **T.T. Kelley**, X. Zhu, A.J. Capobianco, S. Schürer

**MEDI 176.** Anthrax antitoxin lead optimization via bioisosteric replacement and other *in silico* strategies. **C. McDermott**, E.A. Ambrose

**MEDI 177.** Radioiodinated aromatic choline analog tracers. **P. Svec**, Z. Novy, J. Kucka, M. Petrik, O. Sedlacek, M. Hajduch, M. Hruby

**MEDI 178.** Evolution of commercially available compounds for HTS. **D. Volochnyuk**, S. Ryabukhin, Y. Moroz

**MEDI 179.** Chemical tools to probe the role of bromodomains in the parasite *Trypanosoma cruzi*. **C. Laurin**, M. Schiedel, A.K. Chan, P.G. Humphreys, J.T. Seal, S.J. Conway

**MEDI 180.** PAMAM-half-dendron-based drug conjugates as efficient tumor-targeted drug-delivery system for a new-generation taxoid. **Y. Sun**, L. Wei, Y. Zhang, I. Ojima

**MEDI 181.** *In-silico* designing and synthesis of novel and selective hits as Poly ADP-Ribose Polymerase 1 (PARP1) inhibitors for treatment of solid tumours. **P.G. Jain**, B.D. Patel

**MEDI 182.** Ligand-based drug design and synthesis of novel phosphoinositide 3-kinase (PI<sub>3</sub>K) beta inhibitors for the treatment of lung cancer. **S.R. Mehta**, M. Ghate, P. Parikh

**MEDI 183.** Targeting membrane-bound dimer of cRaf kinase in search of anti-cancer drugs. **P. Srivastava**, J. Hancock, A. Gorfe Abebe

**MEDI 184.** Green synthesis of a synergetic structure of tellurium nanowires and metallic nanoparticles for biomedical applications. **A. Vernet Crua**, D. Medina Cruz, T. Webster, B. Zhang

**MEDI 185.** Intracellular paired agent imaging enables personalized medicine for cancer patients. **L. Wang**, E. Schultz, A. Solanki, K. Tichauer, K.S. Samkoe, S.L. Gibbs

**MEDI 186.** Catalytic allylic oxidation of cyclic enamides and 3,4\_dihydro\_2H\_pyrans by TBHP. **R. Humeidi**, Y. Yu, M. Doyle

**MEDI 187.** Exploring novel E3 ligase binders for targeted protein degradation. **Y. Tomata**, K. Gamo, N. Kitamoto, Y. Tominari

**MEDI 188.** BD2-selective BET inhibition induces cell death in pediatric tumor cell lines. **P.J. Slavish**, N. Martinez, A. Shelat

**MEDI 189.** Development of polymer-based nanoparticulate intranasal lipopeptide vaccine constructs against group A streptococcus. **R. Nevagi**, W. Dai, Z. Khalil, W. Hussein, R. Capon, M. Skwarczynski, I. Toth

**MEDI 190.** SAR of novel anti-fungal agents targeting the synthesis of fungal GlcCer. **K. Haranahalli**, C. Lazzarini, Y. Sun, M. Del Poeta, I. Ojima

**MEDI 191.** Encapsulation and controlled release of antimetabolite drug 6-thioguanine from aluminum metal-organic framework. C. Grinnell, R. Lapidus, **A. Samokhvalov**

**MEDI 192.** Modification of hydroxynaphthoquinone scaffold in search of antimicrobial and antineoplastic agents. E. Smith, T. Maloney, M. Humphrey, C. Ray, **I.N. Nawarathne**

**MEDI 193.** Design, syntheses, and SAR studies of carbasugar SGLT2 inhibitors. **W. Ng**, H. Li, V. Lau, A.K. Chan, J. Chan, C. Lau, T.K. Shing

**MEDI 194.** Synthesis and characterization of NIR dye-doped nanoparticles for *in vivo* medical imaging. **C. Schneider**, S. Dembski, F. Miller, T. Riess, J. Jose

**MEDI 195.** Dynamic DNA-encoded library technology: Discovery of kinesin-1 activators and inhibitors. **M. Thompson**, F. Reddavid, S. Heiden, M. Cui, Y. Zhang

**MEDI 196.** Design and synthesis of quinazolinone derivatives lacking toxicity producing attributes as glucokinase activators. **S.C. Khadse**

**MEDI 197.** Novel, odorranalectin-based, opioid-like peptides: Synthesis, intranasal delivery to brain, and activity against opioid receptors. **R. Rayala**, B. Williams, S. Majumder, J.P. McLaughlin, P. Cudic

**MEDI 198.** Binary metal-containing nanoparticles for CT imaging and radiosensitization of peritoneal metastatic tumors. **R. Kashfi Sadabad**, L. Gonzalez-Fajardo, M. Jay, X. Lu

**MEDI 199.** Rapid screening of synergistic combinations of group IB metals and antibiotics for *E. coli* inactivation. **O. Conroy-Ben**, D.E. Novoa, S. Key, M. Tran

**MEDI 200.** Design and synthesis of metabolically stable endocannabinoid analogs by reversing ester and amide group. **L. Ji**, S. Nikas, Y. Liu, A. Korde, A. Ciesielski, A. Straiker, O. Benchama, A.S. Dhopeswarkar, C. Honrao, K. Mackie, L.M. Bohn, A. Makriyannis

**MEDI 201.** Synthesis and structure activity relationship studies of cystargolides based beta-lactones as potent proteasome inhibitors and anti-cancer agents. **D. Niroula**, R. Tello-Aburto

**MEDI 202.** Surface functionalization of polyethylenimine coated iron oxide nanoparticles for dual delivery of doxorubicin and ADAM10 siRNA for prostate cancer treatment. **R. Panday**, A.M. Abdalla, G. Yang

**MEDI 203.** Design and synthesis of peptidomimetics with attenuated reactivity for the treatment of neurodegenerative diseases. **A. Jastaniah**, R. Knopp, I. Gaisina, M. Siklos, G.R. Thatcher

**MEDI 204.** Design, synthesis, and biostudy of bifunctional platinum complexes: Anti-cancer activity through DNA binding and HDAC inhibition. **C. Feng**, Y. Huang, D. Chen, A. Franz, X. Guo, Y. Chen, Q. Zhao

**MEDI 205.** Solvent-free synthesis and activity of new derivatives of hexylaryl piperazines as 5-HT<sub>7</sub> receptors ligands. **J.M. Jaskowska**, P. Sliwa, P. Zareba, D. Kulaga, A. Drabczyk

**MEDI 206.** Development of a new structural family of microbial choline trimethylamine lyase inhibitors for the treatment and prevention of cardiovascular disease. **A. Duzan**

**MEDI 207.** Search of the sirtuin 2 inhibitor as antichagasic candidate by structure-based drug design. **G.H. Trossini**, G.M. Ferreira, V.M. Almeida, S.R. Marana, F.D. Emery

**MEDI 208.** Phytochemical screening, metal concentration determination, and antibacterial evaluation of *Drymaria diandra* plant. **A. Phuyal**

**MEDI 209.** Efforts in redesigning the antileukemic drug 6-thiopurine: Decreasing toxic side effects while maintaining efficacy. **A.X. Torres Hernandez**, C.J. Weeramange, P. Desman, A. Fatino, O. Haney, R. Rafferty

**MEDI 210.** Biological and structural studies of some new Schiff's bases: Computational and experimental approach. **A. Altaf**, A. Badshah

**MEDI 211.** Total synthesis of a potent antimicrobial compounds griseoleuteins, pelagiomicins and alanylgriseoluteic acid. **S. Dighe**, P. Katavic, T. Collet

**MEDI 212.** Targeting Alzheimer's disease: A virtual screening protocol to discover new central-acting BACE1 inhibitors. **J. Coimbra**, S.J. Baptista, A.E. Santos, P.I. Moreira, M.M. Silva, T.C. Dinis, J.A. Salvador

## **Metal-Mediated Reactions & Syntheses**

Sponsored by ORGN, Cosponsored by MEDI<sup>‡</sup>

## **MONDAY MORNING**

Section A

Orange County Convention Center  
Room W414AB

## Synthetic Technologies to Enable Medicinal Chemistry

A. El Marrouni, L. M. Suen, J. Tucker, Y. Wang, *Organizers, Presiding*

**8:15** Introductory Remarks.

**8:20 MEDI 213.** Leveraging high-throughput experimentation and cutting-edge synthetic chemistries to improve the quality and speed of the drug discovery design cycle. **S.W. Krska**

**9:05 MEDI 214.** Acceleration of medicinal chemistry research enabled by high-throughput technologies. **Y. Wang**

**9:50 MEDI 215.** Development of flow reactions to enable synthesis and medicinal chemistry. **A.B. Beeler**, G. Fleming, R. Telmesani, A.L. Courtney, Y. Corre

**10:35 MEDI 216.** Going faster and leaner: Automated microscale reaction screening in flow. **P. Richardson**, N. Sach, J. Tucker, W.P. Farrell, C.J. Helal, D. Perera

**11:20 MEDI 217.** Mapping reaction space with machine learning. **A.G. Doyle**

**12:05** Concluding Remarks.

Section B

Orange County Convention Center  
Room W331A

## Therapeutic Developments in Health Disparities

S. Y. Ablordeppey, K. K. Bagga, *Organizers, Presiding*

**8:30 MEDI 218.** Current status of drug development for health disparity diseases: Cryptococcal meningitis. **S.Y. Ablordeppey**

**9:10 MEDI 219.** Development of drugs for the treatment of tuberculosis. **J.K. Sello**

**9:40 MEDI 220.** Developing peptides and peptidomimetics as potential treatments for substance abuse. **J.V. Aldrich**, J.P. McLaughlin

**10:10 MEDI 221.** Current approaches to anticancer drug development. **J.K. Buolamwini**

**10:40 MEDI 222.** Prostate cancer health disparities in African-American men: Possible targets for race specific drug development. **S. Khan**

**11:10 MEDI 223.** New approach to regenerative cartilage tissue engineering using temperature-sensitive therapeutic hydrogels. **J. Mendenhall**

### **LGBTQ+ Graduate Student & Postdoctoral Scholar Research Symposium**

Sponsored by PROF, Cosponsored by AGFD, ANYL, BIOL, BIOT, CARB, CELL, CHED, CMA, COLL, COMP, ENVR, GEOC, I&EC, MEDI, MPPG, NUCL, ORGN, PHYS, PMSE, POLY, PRES, WCC and YCC

### **Nucleic Acids-Based Therapeutics**

Sponsored by CARB, Cosponsored by BIOL and MEDI

### **MONDAY AFTERNOON**

Section A

Orange County Convention Center  
Room W414AB

### **Small Molecule Therapeutics for Neuro-oncology**

T. P. Heffron, *Organizer, Presiding*

**2:00** Introductory Remarks.

**2:10 MEDI 224.** Brain-penetrant kinase chemotherapeutics: Learning from CNS space. **M. Mader**, Y. Shi

**2:40 MEDI 225.** Mechanisms of ALK acquired resistance and the discovery of lorlatinib (PF-06463922), a macrocyclic ALK/ROS1 inhibitor for the treatment of resistant and metastatic NSCLC. **T.W. Johnson**

**3:10 MEDI 226.** Discovery of the clinical candidate AZD1390: A high-quality, potent and selective inhibitor of ATM kinase with the ability to cross the blood-brain barrier. **K. Pike**

**3:40 MEDI 227.** Discovery of entrectinib: A novel and potent inhibitor of ALK, ROS1, and Pan-TRKs kinases active in multiple molecularly defined cancer indications. **P. Orsini**

**4:10 MEDI 228.** Discovery of GDC-0084: A BBB penetrating PI3K/mTOR inhibitor. **T.P. Heffron**

Orange County Convention Center  
Room W331A

**Besides Off Rate: The Importance of On Rate & Target Rebinding**

Y. Pan, *Organizer, Presiding*

**2:00** Introductory Remarks.

**2:05 MEDI 229.** Drug-target residence time: A misleading concept. **R. Folmer**

**2:35 MEDI 230.** *In vitro* and *in vivo* target life for immucillin transition-state analogs. **V.L. Schramm**

**3:05 MEDI 231.** Kinetic profiling in drug discovery: A case study with EED hit-to-lead program. **Y. Wang**

**3:35 MEDI 232.** Importance of binding kinetics on *in vivo* target occupancy. **E. de Lange**

**4:05 MEDI 233.** Role of free ligand conformations in ligand binding kinetics: AstraZeneca case studies. **A. Balazs**

**LGBTQ+ Graduate Student & Postdoctoral Scholar Research Symposium**

Sponsored by PROF, Cosponsored by AGFD, ANYL, BIOL, BIOT, CARB, CELL, CHED, CMA, COLL, COMP, ENVR, GEOC, I&EC, MEDI, MPPG, NUCL, ORGN, PHYS, PMSE, POLY, PRES, WCC and YCC

**Chemistry in Space: Future Directions**

Sponsored by YCC, Cosponsored by AGFD, ANYL, BIOT, BMGT, CHAS, ENVR, FLUO, GEOC, HIST, I&EC, MEDI, POLY and PROF

**Nucleic Acids-Based Therapeutics**

Sponsored by CARB, Cosponsored by BIOL and MEDI

## **Undergraduate Research Posters**

### **Medicinal Chemistry**

Sponsored by CHED, Cosponsored by MEDI and SOCED

### **MONDAY EVENING**

Section A

Orange County Convention Center  
West Hall C

#### **Sci-Mix**

J. B. Schwarz, *Organizer*

**8:00 - 10:00**

**43, 52, 54, 59, 69, 72, 80-81, 97, 100, 105, 127, 130, 134, 142, 152, 160, 167, 170-171, 176, 178, 187, 195, 203, 205, 219.** See Previous Listings.

**313, 330, 340, 344, 351, 355, 357, 360, 362, 364, 378, 381.** See Subsequent Listings.

### **TUESDAY MORNING**

Section A

Orange County Convention Center  
Valencia Ballroom A

#### **MEDI Awards Symposium**

Cosponsored by BIOL

J. B. Schwarz, *Organizer*

A. Stamford, *Presiding*

**8:30 MEDI 234.** Design of antibiotics for tuberculosis. **C.C. Aldrich**

**9:05 MEDI 235. Award Address** (ACS Award for Creative Invention sponsored by the ACS Corporation Associates). Antimalarial ozonides. **J.L. Vennerstrom**

**9:50 MEDI 236.** Modulating host proteostasis to restrict viral adaptation. **M. Shoulders**

**10:25 MEDI 237.** Small-molecule modulation of HSP60/10 chaperonin systems: A therapeutic strategy over 100 years in the making? M. Stevens, S. Abdeen, A. Ray, A. Washburn, S. Chitre, J. Sivinski, Y. Park, Q. Hoang, E. Chapman, **S. Johnson**

**11:00 MEDI 238.** Targeting protein-protein interactions to treat misfolding diseases. **J.E. Gestwicki**

**11:35 MEDI 239. Award Address** (E. B. Hershberg Award for Important Discoveries in Medicinally Active Substances sponsored by the Merck Research Laboratories). Adapting the chemistry and/or biology of proteostasis to ameliorate aggregation-associated degenerative diseases. **J.W. Kelly**

Section B

Orange County Convention Center  
Room W331A

### **Recent Advances in Targeting Oncogenic KRAS**

E. Altmann, V. Cee, *Organizers, Presiding*

**9:00** Introductory Remarks.

**9:05 MEDI 240.** Ras proteins in normal cells and in human disease. **F.P. McCormick**

**9:40 MEDI 241.** Small-molecule inhibitors of mutant RAS-effector protein interactions derived using an intracellular antibody fragment. **T. Rabbitts**

**10:15 MEDI 242.** Discovery of small-molecule inhibitors of GTP bound KRAS<sup>G12C</sup>. **A.L. Gill**

**10:50 MEDI 243.** Use of chemotype evolution to discover novel, potent, irreversible inhibitors of the oncogenic G12C mutant form of KRAS. **D.A. Erlanson**, T. Arvedson, V. Cee, R. Fucini, S. Hansen, J. Iwig, J. Jeong, J. McCarter, S. Sabet, A. Sawayama, S. Sethofer

**11:25 MEDI 244.** Structure-based drug discovery of MRTX1257: A selective, covalent KRAS G12C inhibitor with oral activity in animal models of cancer. **M.A. Marx**, B.R. Baer, J.K. Ballard, J.F. Blake, K. Bouhana, D. Briere, L.E. Burgess, M. Burkhard, H. Chiang, M.J. Chicarelli, J.G. Christensen, J.P. Fischer, J. Hallin, M.J. Mejia, P. Olson, P. Savechenkov, N. Sudhakar, T.P. Tang, G.P. Vigers, J.B. Fell

### **TUESDAY AFTERNOON**

Section A

Orange County Convention Center  
Room W414AB

**Ions Count: Acids, Bases & Zwitterionics in Drug Design (Medicinal Chemists' Toolbox Series)**

N. A. Meanwell, *Organizer*  
P. M. Scola, K. Yeung, *Organizers, Presiding*

**2:00** Introductory Remarks.

**2:05 MEDI 245.** Utility of acidic and basic compounds in medicinal chemistry. **P. Walters**, P. Charifson

**2:35 MEDI 246.** Toxicity arising from amine-containing drugs: Where do we draw the line?.  
**A.S. Kalgutkar**

**3:05 MEDI 247.** Use of a pH-dependent conformational switching mechanism to enable the discovery of potent, selective and orally bioavailable CCR2 antagonists. M. Yang, Z. Xiao, R.J. Cherney, A.J. Tebben, D.G. Batt, G.D. Brown, J. Chen, M.E. Cvijic, M. Dabros, J.V. Duncia, M.A. Galella, D.S. Gardner, P. Khandelwal, S.S. Ko, M.F. Malley, R. Mo, J. Pang, A.V. Rose, J.B. Santella, H. Shi, A. Srivastava, S.C. Traeger, R. Vuppugalla, B. Wang, S. Xu, R. Zhao, J.C. Barrish, S. Mandlekar, Q. Zhao, **P.H. Carter**

**3:35 MEDI 248.** Carboxylic acids and their isosteres. **D.M. Huryn**

**4:05 MEDI 249.** Design and evaluation of surrogate structures of the carboxylic acid and other acidic functional groups as possible candidates for isosteric replacements. **C. Ballatore**

**4:35 MEDI 250.** Challenges with zwitterions: Discovery of zwitterionic CCR3 antagonist clinical candidates. **M.W. Perry**

Section B

Orange County Convention Center  
Room W331A

**Academic Drug Discovery**

E. A. Ambrose, C. Haskell-Luevano, *Organizers, Presiding*

**1:30 MEDI 251.** *In vitro* selection assays: On-DNA medicinal chemistry optimization of peptidomimetic ligands to chromodomains. **C.J. Krusemark**, S. Wang, K. Denton

**2:05 MEDI 252.** Development of novel transformations and structural templates to fuel medicinal chemistry discovery and optimization. **J.E. Golden**

**2:40 MEDI 253.** Allosteric targeting of the Parkinson's-related protein LRRK2. **E.J. Kennedy**

**3:15 MEDI 254.** Molecule-driven discovery for the identification of therapeutic leads. **J.G. Pierce**

**3:50 MEDI 255.** Caspase-2 inhibitors for the treatment of tauopathy-related cognitive decline. **K.M. Nelson**, J. Strasser, G. Singh, B. Smith, K. Ashe, M.A. Walters

**4:25 MEDI 256.** Novel genetically encoded cyclic and bicyclic architectures: Towards *de novo* discovery of bioavailable drugs. **R. Derda**

### **LGBTQ+ Graduate Student & Postdoctoral Scholar Research Symposium**

Sponsored by PROF, Cosponsored by ENVR, GEOC, I&EC, MEDI, MPPG, NUCL, ORGN, PHYS, PMSE, POLY, WCC and YCC

### **WEDNESDAY MORNING**

Section A

Orange County Convention Center  
Valencia Ballroom A

#### **First Time Disclosure of Clinical Candidates**

E. F. DiMauro, *Organizer, Presiding*

**8:30** Introductory Remarks.

**8:35 MEDI 257.** Discovery of AB680: A potent and selective CD73 inhibitor for cancer immunotherapy. **K.V. Lawson**, J. Kalisiak, E. Lindsey, E. Newcomb, E.U. Sharif, D. Miles, J. Jeffrey, M. Reddy Leleti, A. Chen, L. Jin, J. Tan, U. Schindler, S. Young, J. Jaen, J. Powers

**9:55 MEDI 258.** Identification and characterization of LHC165, a TLR7 agonist designed for localized intratumoral therapies. **G. Cortez**, S. Bender, J. Deane, N. Eifler, S. Kasibhatla, C. Li, S. Pan, N. Parikh, T. Wu

**10:35 MEDI 259.** Discovery of VNRX-7145: A broad-spectrum orally bioavailable beta-lactamase inhibitor (BLI) for highly resistant bacterial infections ("superbugs"). **C.J. Burns**, R.

Trout, A. Zulli, E. Mesaros, R. Jackson, S. Boyd, B. Liu, L. McLaughlin, C. Chatwin, J. Hamrick, D. Daigle, D. Pevear

**11:15 MEDI 260.** Discovery of TAK-981, a first-in-class inhibitor of Sumo Activating Enzyme (SAE) in phase 1 clinical trials. **S.P. Langston**, D. England, X. He, D. Huszar, P.D. Greenspan

**11:55** Concluding Remarks.

Section B

Orange County Convention Center  
Room W331A

### **Exploring Cryptic Pockets**

K. K. Liu, *Organizer, Presiding*

**9:00** Introductory Remarks.

**9:05 MEDI 261.** Exploring cryptic pockets formation in targets of pharmaceutical interest with enhanced sampling simulations. **F. Gervasio**

**9:40 MEDI 262.** Identifying and exploiting protein shape-shifting. **G. Bowman**

**10:15 MEDI 263.** Development of drug design methods and applications in first-in-class drug discovery. **J. Zhang**

**10:50 MEDI 264.** Remote control of a dynamic enzyme by leveraging small-molecule fragments. T. Skaist, S.M. Azeem, **D.A. Keedy**

**11:25 MEDI 265.** Selective FKBP51 inhibitors enabled by transient pocket binding. **F. Hausch**

Section C

Orange County Convention Center  
Room W414AB

### **Covalent Inhibition beyond Cysteine**

E. Altmann, R. Finlay, K. K. Liu, *Organizers, Presiding*

**8:45** Introductory Remarks.

**8:50 MEDI 266.** Targeted covalent inhibition: Review of the field and recent advances. **C.N. Rowley**

**9:25 MEDI 267.** Novel, boronic-acid-based, covalent lysine inhibitors. **T.A. McTeague**, N. Grimster, A. Hird, Q. Su

**10:00 MEDI 268.** Transition-metal-free, tryptophan-selective bioconjugation of proteins. **M. Kanai**

**10:35 MEDI 269.** Mapping of immunomodulatory receptor protein interactions via photocatalytic-based proximity labeling of the cell surface. **O. Fadeyi**

**11:10 MEDI 270.** Protein functionalization platform based on selective reactions at methionine residues. **M. Gaunt**

## **WEDNESDAY AFTERNOON**

Section A

Orange County Convention Center  
Valencia Ballroom A

### **First Time Disclosure of Clinical Candidates**

E. F. DiMauro, *Organizer, Presiding*

**2:00** Introductory Remarks.

**2:05 MEDI 271.** Discovery of AMG 510, a first-in-human covalent inhibitor of KRAS<sup>G12C</sup> for the treatment of solid tumors. **V. Cee**

**2:45 MEDI 272.** Discovery of ABBV-951 to enable continuous subcutaneous infusion of levodopa for the treatment of Parkinson's disease. **P. Kym**, E.A. Voight, R. Klix, P. Mayer, B. Enright, X. Lou, T. Moldovan, D. Stolarik, M.A. Matulenko, A. Hutters, J. Ji, M. Facheris, M. Rosebraugh, J. Benesh

**3:25 MEDI 273.** Structure guided discovery of S64315 (MIK665): a potent and selective MCL1 inhibitor. **A. Kotschy**, Z. Szlavik, O. Geneste, J. Murray, J. Davidson, R.E. Hubbard, M. Wood, M. Csekei, A. Paczal, Z.B. Szabo, S. Sipos, A. Prosenyak, B. Balint, A.L. Maragno, D. Demarles, G. Le Toumelin-Braizat, M. Chanrion, A. Bruno, A. Claperon, A. Surgenor, P. Dokurno, N. Matassova, I. Chen, B.J. Davis, H. Simmonite, A. Studeny, G. Lysiak-Auvity, A. Girard, F. Grave, G. Guasconi, N. Cauquil, F. Colland, J.A. Hickman

**4:05 MEDI 274.** Discovery of PF-06882961: A potent, orally bioavailable small molecule agonist of the GLP-1 receptor. **D.J. Edmonds**, D.A. Griffith, S.W. Bagley, C. Buckeridge, E.L.

Conn, J.M. Curto, D.R. Derksen, H. Eng, M.E. Flanagan, J. Fortin, M.C. Griffor, M.V. Jackson, A.S. Kalgutkar, J.B. Kuzmiski, M.S. Landis, D.J. Lettiere, C. Limberakis, S. Liras, P.M. Loria, A.M. Mathiowetz, D.W. Piotrowski, D. Price, L. Stevens, T.P. Rolph, R.B. Ruggeri, A.R. Saxena, A.H. Smith, D.A. Tess, L. Wei

**4:45** Concluding Remarks.

Section B

Orange County Convention Center  
Room W331A

### General Orals

J. B. Schwarz, *Organizer*  
C. Am Ende, *Presiding*

**1:30 MEDI 275.** Chemical biology impacting drug discovery. **C. Am Ende**

**1:50 MEDI 276.** Biological activity of ferrocenyl derivatives: Study of the effect of different core moieties and substituents on anticancer and antioxidant activity. **S.M. Delgado-Rivera**, S.A. Henriquez Lopez, G.E. Pérez-Ortiz, A. Baerga-Ortiz, I. Montes-Gonzalez, D.M. Pinero Cruz

**2:10 MEDI 277.** Structure-activity relationship of non-electrophilic naphthalene and isoquinoline based inhibitors of the KEAP1-NRF2 protein-protein interaction. **P. Lazzara**, B. Richardson, B. David, H.R. Potteti, K. Dye, S. Reddy, T.W. Moore

**2:30 MEDI 278.** Evolution-guided design of phosphatase inhibitors. M. Hjortness, L. Riccardi, A. Hongdusit, A. Ruppe, E. Kim, M. Zhao, P. Zwart, B. Sankaran, H. Arthanari, M. Sousa, M. Devivo, **J.M. Fox**

**2:50 MEDI 279.** Chemical tools to probe the function of TRIM33. **A. Scolah**, L. See, J. Bluck, J. Reynolds, W. McCoull, S.J. Conway

**3:10 MEDI 280.** Effects of phosphate linker modifications on 2',3'-cyclic dinucleotide STING agonists. **S.P. Walsh**, M.D. Altman, B.M. Andresen, W. Chang, A. Donofrio, T.J. Henderson, J.P. Jewell, C. Lesburg, J. Lim, H. Liu, M. Lu, R. Otte, J. Presland, D. Steinhuebel, B. Taoka, Q. Truong, W. Wu, S. Perera, S. Cemerski, W. Trotter, J. Cumming

**3:30 MEDI 281.** 2NDEP highlights allosteric activation of the  $\alpha 7$  nicotinic acetylcholine receptor. A. Gulsevin, C. Stokes, R.L. Papke, **M. Quadri**, N. Horenstein

**3:50 MEDI 282.** Discovery of selective FactorD inhibitors targeting the alternative complement pathway. **R.G. Karki**, J.J. Powers, D. Belanger, D. Liu, N. Ji, K. Jendza, C. Gelin, S. Flohr, E. Lorthiois, A. Vulpetti, A. Mac Sweeney, K. Anderson, M. Mogi, N. Mainolfi

**4:10 MEDI 283.** Multi-parameter optimization of isoform-selective dual Nav1.6/1.2 antagonists to balance CNS penetration with PK and *in vivo* efficacy in mouse models for epilepsy. **C.M. Dehnhardt**, K. Buford, J. Andrez, M.E. Grimwood, A. Zenova, M. Taron, W. Gong, S. Decker, S. Chowdhury, C. Higgs, P. Tari, R. Kwan, L. Sojo, R.J. Devita, C. Cohen, J. Johnson, S. Wesolowski, J. Empfield, T. Focken

**4:30 MEDI 284.** Enzymatic late-stage oxidation of lead compounds with solubilizing biomimetic docking/protecting groups. **U.E. Lange**

**4:50 MEDI 285.** Development and characterization of LHC165, a TLR7 agonist designed for localized intratumoral injection. **N. Eifler**

**5:10 MEDI 286.** Versatile C-H methylation reaction for late-stage functionalization. **S.D. Friis**, L. Ackermann, M.J. Johansson

Section C

Orange County Convention Center  
Room W414AB

### **The Messy Business of Target (In)Validation: Chemistry's Role & Challenges in Early Discovery**

M. Herold, B. A. Knapp-Reed, J. Shotwell, *Organizers*  
J. Shotwell, *Presiding*

**1:30** Introductory Remarks.

**1:35 MEDI 287.** Enzyme target pre-clinical (in)validation: The value of rational exploration of the unknown, and how application of target engagement principles can address key pharmacology questions. **T.B. Durham**

**2:05 MEDI 288.** Promoting illiteracy: Development of chemical probes for epigenetic reader domains to explore untapped targets. **L.I. James**

**2:35 MEDI 289.** Lessons learnt from the discovery of CDK8/19 protein kinase inhibitors: From phenotypic screen to selective chemical probes. **P.A. Clarke**

**3:05** Intermission.

**3:15 MEDI 290.** Small molecules from phenotypic screens: Looking for “a” target?. **S. Patnaik**

**3:45 MEDI 291.** Discovery of a novel kinetoplastid inhibitor for the treatment of human African Trypanosomiasis. **J. Jiricek**, S. Rao, S. B Lakshminarayana, C. Sarko, N. Aziz, F. Gu, T. Diagana

**4:15 MEDI 292.** SMYD3 target (in)validation from a medicinal chemistry perspective. **B.A. Knapp-Reed**

## **WEDNESDAY EVENING**

Section A

Orange County Convention Center  
West Hall C

### **General Posters**

Cosponsored by ORGN<sup>‡</sup>  
J. B. Schwarz, *Organizer*

#### **7:00 - 9:00**

**MEDI 293.** Discovery of KAG-308: A potent and orally available EP4 agonist for the treatment of inflammatory bowel disease. **Y. Ishibashi**, Y. Matsumura, Y. Miyake

**MEDI 294.** Synthesis and evaluation of linear and macrocyclic dolastatin 10 analogues containing heteroatoms on the amino acid side chains. **M. Akaiwa**, T. Martin, B.A. Mendelsohn

**MEDI 295.** Design, synthesis, and biological evaluation of bisphenol Z derivatives. **L.M. Stitzlein**, C.T. Stang, L.R. Inbody, R.A. Schneider, R.W. Dudley

**MEDI 296.** Saturated bioisosteres of benzene with improved solubility. **P. Mykhailiuk**, V. Levterov, O.O. Stepaniuk

**MEDI 297.** Conformationally restricted pyrrolidines for drug discovery. **P. Mykhailiuk**, V. Levterov, A. Cherepakha

**MEDI 298.** Synthesis and evaluation of thalassotalic acid A and analogs. J. Schulz, **J. Patrone**

**MEDI 299.** Synthesis of prodrugs from a quinazoline derivative to optimize its behavior against cancer cells. **L.C. Arenas Corona**, F. Hernández Luis

**MEDI 300.** Design and synthesis of a novel series of highly potent RAF kinase-inhibiting triarylpyrazole derivatives with potential antiproliferative activity against melanoma. **M. El-Gamal**, M. Khan, H. Tarazi, H. Choi, C. Oh

- MEDI 301.** Design, synthesis, and evaluation of biological properties of new 5-cyanopyrimidine-based compounds. **A.S. Bunev**, D. Khochenkov, Y. Khochenkova, E. Stepanova
- MEDI 302.** Novel imidazo[2,1-*B*]thiazoles as potential EGFR tyrosine kinase inhibitors: Synthesis and *in vitro* evaluation. **A.S. Bunev**, D. Khochenkov, Y. Khochenkova, E. Stepanova
- MEDI 303.** 4-Amino-5- (thiazol-2-yl) pyrimidine derivatives: New effective inhibitors of EGFR-dependent signal cascades. **A.S. Bunev**, D. Khochenkov, Y. Khochenkova, E. Stepanova
- MEDI 304.** Inhibition of pancreatic acinar ductal metaplasia by a novel STAT3 inhibitor LLL12B. L. Da Silva, **J. Song**, J. Matthews, J. Jiang, H. Luesch, C. Li, T. Schmittgen
- MEDI 305.** Structure-activity relationships of UDEPs as caseinolytic protease activators. **Y. Zhao**, E. Griffith, A. Arya, M. LaFleur, R.E. Lee
- MEDI 306.** Design, synthesis, and biological evaluation of flavones showing inhibitory effects on aurora kinases. J. Lee, **D. Koh**
- MEDI 307.** Synthesis and evaluation of novel multifunctional opioid peptidomimetics. **M.A. Baber**, D. Montgomery, J.P. Anand, L. Delong, J.R. Traynor, H.I. Mosberg
- MEDI 308.** Trifluoromethyl thiazine-based BACE1 Inhibitors: Synthesis, *in vivo* efficacy, cardiovascular side effects, and covalent binding burden. **T. Oguma**, K. Nakahara, K. Anan, Y. Isou, S. Suzuki, T. Yamamoto, Y. Kido, N. Kanegawa, T. Fukushima, Y. Tonomura, H. Ito, G. Sakaguchi, F. Bischoff, H. Gijzen, K. Kusakabe
- MEDI 309.** Medicinal chemistry and chemical biology approach in order to design and synthesize of TBK1/ IKK- $\epsilon$  small molecules inhibitors. **A. Assadieskandar**, C. Zhang
- MEDI 310.** Development of a new series of bacterial topoisomerase inhibitors for antibiotic-resistant infections. **L. Li**, S. Dellos-Nolan, A. English, J.C. Yalowich, D. Wozniak, M.J. Mitton-Fry
- MEDI 311.** Hydrazolyl linked hybrids of sulfonate esters and 4-thiazolidinone: Design, synthesis, and biological evaluation as potent  $\alpha$ -glucosidase inhibitors. **R. Kaur**, M. Kumar
- MEDI 312.** Design, synthesis, and antimicrobial evaluation of substituted urea derivatives containing alkyl/aryl moieties. M. Patil, N. Poyil, A. Bugarin, S. Joshi, S. Patil, **S. Patil**
- MEDI 313.** Recombinant expression of xenobiotic and steroidogenic cytochrome P450 enzymes. **L. Sanchez**, S. Brixius-Anderko, E. Scott
- MEDI 314.** Exploratory synthesis of novel cyclic and straight-chain 1,3-azaborines as potential HIV-1 protease inhibitors. **K. Hawley**, **R. Latsis**, **C. Suarez**, K. Norris, **A. Vulcano**, **S. Dawson**, **A. Williams**, A. Lanin, J. Murray, **L. Fabry-Asztalos**

**MEDI 315.** Examination of aminophenol-containing compounds designed as antiproliferative agents and potential atypical retinoids. **S. Altman**, M. Imai, N. Takahashi, T.R. Burke

**MEDI 316.** Synthesis and biological evaluation of 1,2,3-triazole analogs of CFTR corrector VX-809. **J. Brace**, S.J. Post, N.L. Thacker, L. Tang, S.M. Rowe, S.G. Aller, M.L. Turlington

**MEDI 317.** Discovery of novel anti-tubercular agent for the treatment of MDR/XDR TB. **J. Choi**, S. kang, Y. Kim, I. Choi, A. Lee, G. Jin, V. Delorme, **K. Park**

**MEDI 318.** Development of novel treatments against inherited blinding diseases *Retinitis pigmentosa* and Leber's congenital amaurosis. **E. Pileggi**, G. Pasqualetto, M. Rozanowska, A. Brancale, M. Bassetto

**MEDI 319.** Synthesis and biological activity of a new saccharine derivatives as a dual D<sub>2</sub>/5-HT<sub>1A</sub> receptor ligands. **D. Kulaga**

**MEDI 320.** New long-chain derivatives of 1-(1,2-benzisothiazol-3-yl)piperazine with high affinity for selected serotonin receptors. **P. Zareba**, J. Jaskowska, A. Drabczyk

**MEDI 321.** Structure-activity relationships of fragment-based inhibitors of *Trichomonas vaginalis* uridine nucleoside ribohydrolase. **J.K. Persaud**, S.F. Thuilot, S. Auletta, W. Caravan, A. Leonardo, T. Li, Z. Dulloo, N. Kabir, D.G. Brown, D.W. Parkin, M.A. Vanalstine-Parris, B.J. Stockman

**MEDI 322.** Novel applications of biocatalysis to late stage derivatization and stereochemistry determination of 2'3'-cyclic dinucleotide bisphosphorothioates. **J. Lim**, L. Nogle, H. Kim, J. Sauri, Y. Chen, J. Piesvaux, J. Cumming, W. Trotter

**MEDI 323.** (1-4)-*S*-thiodisaccharides induction of ER stress as possible mechanism of glioblastoma cells death. J. Sarnik, A. Maciejka, **Z.J. Witezak**, T. Poplawski

**MEDI 324.** Synthesis of 1,2,3-triazole analogs of CFTR potentiator VX-770. **B. Ody**

**MEDI 325.** Design, synthesis, and antimicrobial evaluation of dibenzothiophene sulfones derivatives. **S. Alelaiwi**

**MEDI 326.** Discovery of *in situ* click chemistry compatible analogs of F508del-CFTR corrector VX-809. **O.R. Brown**, M.L. Turlington

**MEDI 327.** Design, synthesis, and structural activity relationships of styrylquinoline derivatives as potent antimalarial agents. **G. Huang**, C. Solano, J. Kreisel, A.K. Arshadi, D. Chakrabarti, Y. Yuan

**MEDI 328.** NMR-based counter screens of fragment inhibitors of *Trichomonas vaginalis* uridine nucleoside ribohydrolase confirm reversible, target-specific inhibition. **S.F. Thuilot**, J.K. Persaud, D.G. Brown, D.W. Parkin, B.J. Stockman

**MEDI 329.** Molecular modeling and NMR-based counter screens of fragment inhibitors of *Trichomonas vaginalis* adenosine/guanosine nucleoside ribohydrolase. **A. Kaur**, J. Gonzalez, D.G. Brown, D.W. Parkin, B.J. Stockman

**MEDI 330.** Novel class of STING agonists that self-assemble into nanostructures are potent anti-cancer immuno-therapeutic agents. **A. Sheri**, S. Padmanabhan, G. Meher, R.H. Gimi, D. Cleary, S. Khedkar, S. Challa, S. Zhou, V. Nair, L. Suppiah, D. Schmidt, N. Afdhal, R. Iyer

**MEDI 331.** Synthesis of novel functionally selective and long-acting muscarinic antagonists. **L. Mesa**, **C. Martin**, J. Boulos

**MEDI 332.** Cyclooxygenase-2 inhibitory activity of metal-curcumin complexes. **J. Harder**, **A. Vummenthala**, **M. Vazquez**

**MEDI 333.** Synthesis of new  $\beta$ -benzyloxy-*N*-phenethylamines as biogenic amine neurotransmitter transporter blockers. S. Almendras, A. Fierro, J. Campusano, J. Eltit, **E.G. Pérez**

**MEDI 334.** Synthesis of  $\omega$ -hydroxy isoprenoid bisphosphonates as potential GGDPs inhibitors. **N. Bhuiyan**, M. Varney, S.A. Holstein, D.F. Wiemer

**MEDI 335.** Design, synthesis, and biological evaluation of water-soluble amino acid prodrugs of a rhein-derived anti-cancer agent. **A. Anifowose**, Z. Yuan, X. Yang, Y. Zheng, Z. Pan, Z. Zhang, B. Wang

**MEDI 336.** Synthesis and biological evaluation of selective tubulin inhibitors as anti-trypanosomal agents. **V. Bobba**

**MEDI 337.** Synthesis of triclosan derivatives that function as azo dyes. **S. Desmond**, P. Sibbald

**MEDI 338.** Synthesis and design of CRB, a resveratrol analog, reduces cell injury caused by surgery mimicking deep brain stimulation. **M. Lee**, S. Gallemore, A. Linberg, Z. DeBruine, B. Babu, K.A. Brien, G. Fraley

**MEDI 339.** Synthesis, optimization, and analysis of hexavalent sulfoglycodendrimers as anti-viral agents. **C. Vierra**, K.D. McReynolds

**MEDI 340.** Synthesis and biological evaluation of nitrogen containing marine natural products. **C. Martinez-Brokaw**, K.R. Robinson, J.G. Pierce

**MEDI 341.** 2-Amino-quinolin-4(*IH*)-ones as novel anti-coronavirus agents. **C. Park**, J. Song, J. Lee, J. Lee, S. Kim, H. Kim

**MEDI 342.** Translation of  $^1\text{H}$  and  $^{19}\text{F}$  NMR-based activity assays to *in vitro* characterization of nucleoside hydrolase activity in cell extracts and whole cells. **M. Canestrari**, M. Mahmood, S.F. Thuilot, B.J. Stockman

**MEDI 343.** Design, synthesis, and biological evaluations of next-generation taxoids, bearing *m*-OCF<sub>3</sub> and *m*-OCF<sub>2</sub>H groups at the C2 benzoate moiety. **L. Chen**, C. Wang, W. Guo, X. Wang, Y. Jing, Y. Sun, I. Ojima

**MEDI 344.** Improved synthetic approach to CA IX selective inhibitors featuring one-pot cyclization/deprotection. **H. Li**, A.B. Murray, M. Quadri, R. McKenna, N. Horenstein

**MEDI 345.** Synthesis, evaluation, and *in silico* study of structural analogs of colchicine as potential anticancer agents. **S. Yoganathan**, N. Karadkhelkar, P. Gupta, Z. Chen

**MEDI 346.** Synthesis of inhibitors of 1-deoxyulose- 5-phosphate reductoisomerase. **G. Mancini**, J.W. Tomsho

**MEDI 347.** Studies toward an amide core for zampanolide mimics as potential anti-prostate cancer agents. **M. Gonzalez**, G. Chen, Q. Chen

**MEDI 348.** Structure-based design, synthesis and evaluation of D-3,3-diphenylalanine-based tetrapeptides inhibitors of thrombin-activated platelets aggregation and potent anticoagulants. **C.C. Clement**, J. Gonzalez, A. Babinska, M.R. Gil

**MEDI 349.** Synthesis of 2-aminocyclobutanones as potential serine- and metalloprotease inhibitors. **T. Habeeb Mohammad**, C. Reidl, D.P. Becker

**MEDI 350.** Synthesis, *in silico*, and *in vitro* evaluation of long chain alkyl amides from 2-amino-4-quinolone derivatives as biofilm inhibitors. M.A. Loza-Mejia, **S. Borbolla-Alvarez**, **A.E. Delgado**, **M.P. Espinosa Valdes**, J. S. Tejada, A. Cerón-Nava, O. Quintana-Romero, A. Ariza-Castolo, D. García-del Río

**MEDI 351.** Synthesis of small molecules based on novobiocin and the biphenylcyclohexane system that inhibit the Hsp90 molecular chaperone. **A. Zuo**, P.N. Meka, B. Keegan, B.S. Blagg

**MEDI 352.** Synthesis of oxindole derivatives via C-H alkylation and intramolecular cyclization: Access to Hit compound for anti-tumor agent. **S. Han**

**MEDI 353.** Design, synthesis, and evaluation of resveratrol-NSAID hybrids as potential antioxidants and anti-inflammatories. **M.A. Enriquez-Pichardo**, **S.S. Medina-Rosas**, **G. Sánchez-Tejeda**, I. Rodríguez-Nuño, J. García-Ibarra, H. Mancilla-Díaz, J.R. Salazar, M.A. Loza-Mejia

**MEDI 354.** Design, synthesis, and structure-activity relationship studies of phthalimide-based sphingosine kinase inhibitors. **F. Afrin**, K. Obuch, Y. Kharel, W. Santos, K. Lynch, S. Pashikanti

**MEDI 355.** Design, synthesis, and biological evaluation of truxillic acid-based fatty acid binding protein 5 (FABP5) inhibitors as anti-nociceptive and anti-inflammatory agents. **T.S. Clement**,

M. Awwa, A. Taouil, A. Maharaj, J. Kim, Y. Sun, A. Pepe, H. Li, D.G. Deutsch, M.W. Elmes, M. Kaczocha, I. Ojima

**MEDI 356.** TB or not TB? That is not the only question. **J. Trant, N. Milligan, A. Ford, Z. Hodge, I.N. Nawarathne**

**MEDI 357.** Pharmacology and modeling of methcathinone (MCAT) isomers and achiral analogs at the monoamine transporters (MATs). **R.A. Davies, F. Sakloth, B. Ruiz, J. Eltit, R.A. Glennon**

**MEDI 358.** Design, synthesis, and evaluation of the anthranilic acid derivative HGA-01 as a potential multitarget drug for the management of metabolic syndrome. **H. González Álvarez, M. Bravo Jimenez, M.A. Loza-Mejia, R. Pinto-Almazán, K. Gallardo-Ignacio, L.A. González-Hernández, E. Chávez-Gutiérrez**

**MEDI 359.** Synthesis and bioevaluation of new pyrazino[2,3-*b*]quinolinones as potential antitumorals: Effect of the nature of alkyl substituents in position 5. **D.G. Juan Guadarrama, L.J. Jimenez Sanchez, J. Villalobos, J. Solano, A. Lira, L. Martino, M.A. Loza-Mejia**

**MEDI 360.** Synthesis of small molecules for protein control. **E. Bray, C. Alvarez, J. Leahy, M.W. White**

**MEDI 361.** Development of a selective phosphatase inhibitor for neurodegenerative disorders. **J. Nunziata, B.J. Eduful, Y. Chen, D. Kang, J. Leahy**

**MEDI 362.** Synthesis of rhodacyanine derivatives as Hsp70 inhibitors for improved tau degradation in tauopathies. **A. Lemus, S. Patel, R. Swonger, R. Blackburn, J. Koren, C. Dickey, L. Blair, J. Leahy**

**MEDI 363.** Design, synthesis, and SAR of matrix metalloprotease 9 inhibitors as anti-metastasis agents. **M. Awwa, V.M. Alford, X. Ren, J. Cao, N.S. Sampson, I. Ojima**

**MEDI 364.** Conformational constraint of aromatic residues of the kappa opioid receptor antagonist arodyn using ring closing metathesis. **S.A. Gisemba, J.V. Aldrich, T. Murray**

**MEDI 365.** Synthesis and QSAR study of novel NSAID hybrid conjugates as potential anti-inflammatory agents. **H.H. Honkanadavar, S.S. Panda**

**MEDI 366.** Design, synthesis, and characterization of new modulators of the leukotriene A<sub>4</sub> hydrolase aminopeptidase activity. **G. Petruncio, K. Lee, L. Jansen, S. Noble, Y. Shim, M. Paige**

**MEDI 367.** Structure-activity relationship-guided synthesis and identification of the GATA4 and NKX2-5 protein-protein interaction modulators. **M. Jumppanen, S. Kinnunen, M. Välimäki, S. Auno, G. Boije af Gennäs, H. Xhaard, V. Talman, H. Ruskoaho, J.T. Yli-Kauhaluoma**

**MEDI 368.** Atypically substituted carbapenem antibiotics with improved activity against OXA-23-producing *Acinetobacter baumannii*. N.M. Al-Kharji, **M. Alqurafi**, T. Nguyen, W. Chai, N.K. Stewart, M. Toth, J. Kim, N. Nformi, S. Solanki, K. Wong Wirth, M. Ardesna, A. Mehta, A. Jakubowski, B. Meshram, C. Varner, A. He, M. Pan, S.B. Vakulenko, J.D. Buynak

**MEDI 369.** Synthesis of new  $\beta$ -heteroarylmethoxy-*N*-phenethylamines as possible monoamine neurotransmitter transporter blockers. **I. Almodovar**, E.G. Perez, M. Madrid

**MEDI 370.** Identification, validation, and synthesis of small molecule inhibitors of the Lin28b/pre-Let-7 interaction in pancreatic ductal adenocarcinoma. **H. Ahamed**, **T. Aramburu**, R.L. Broadrup, R. Mostoslavsky

**MEDI 371.** Evaluation of the effects of differentially sulfated heparin/heparan sulfate analogs on MCF-7 cell migration. **A.M. Brown**, **N.L. Snyder**

**MEDI 372.** Synthesis and biological screening of praziquantel derivatives for use as pharmacological chaperones of arylsulfatase B. **K. Terpstra**, T.A. Russell

**MEDI 373.** Synthesis and computational study of pyrazinoic acid conjugates as potential anti-infective agents. **W.F. Littlefield**, S.S. Panda

**MEDI 374.** Design and synthesis of quinolone-based hybrid conjugates as potential anticancer agents. **R.M. Bokhtia**, T.S. Ibrahim, A.M. Al-Mahmoudy, E.H. Abdel-Aal, S.S. Panda

**MEDI 375.** Synthesis of indoles-based Schiff base complexes and spiro compounds as potential anticancer agents. **I. Selim**, T.S. Ibrahim, A.M. Al-Mahmoudy, Z.K. Abdel-Samii, S.S. Panda

**MEDI 376.** Synthesis of carbon nitride dots for target-specific biomedical applications. **P. Liyanage**, R. Graham, C.C. Chusuei, K.J. Mintz, Y. Zhou, J. Harper, R.M. Leblanc

**MEDI 377.** Heterocycle libraries based on natural anti-inflammatory. **B. Maki**

**MEDI 378.** New tools for targeting the asialoglycoprotein receptor. **N.L. Snyder**, **A. Strasser**, N. Fendler

**MEDI 379.** Trehalose-based photosensitizers targeting *Mycobacterium tuberculosis*. **L.A. Russell**, R.C. Steffens, M.B. Burch, D.G. Dennis, M. Parris, J.V. Ruppel, **N.L. Snyder**

**MEDI 380.** *In silico* models for predicting metabolism by Flavin-Containing Monooxygenases (FMOs). **G. KC**, M. Hassan, S. Sirimulla

**MEDI 381.** Synthesis, characterization and reactivities of a new HDAC inhibitor. **D. Shao**, E.S. Guo, C. Feng, Q. Zhao

**MEDI 382.** Design, synthesis, and structure-activity relationship of novel 1,2,4-triazine-3-one derivatives as multimodal compounds intended to treat schizophrenia. **B. Narasimha**, V.R. Middekadi, M. Rasheed, D.S. Sisodaya, V.R. Mekala, S. Petlu, R. Nirogi

**MEDI 383.** Design, synthesis, and structure-activity relationship of novel pyrazolo-pyrimidine carboxamides as Muscarinic<sub>1</sub> Positive Allosteric Modulators (M<sub>1</sub> PAM). **S.R. Gagginapally**, D.M. Kancharla, M. Dasoju, N.R. Mudanna, R. Subramanian, R. Nirogi

**MEDI 384.** Design, synthesis, and pharmacological characterization of novel series of 4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine derivatives as H<sub>3</sub> receptor antagonists. **P.K. Achanta**, S.K. Saraf, R.K. Badange, R. Subramanian, N.R. Mudanna, P. Jayarajan, R. Nirogi

**MEDI 385.** Design, synthesis, and pharmacological characterization of novel carboxamides as 5-HT<sub>4</sub> receptor agonists. **R.K. Badange**, P.K. Achanta, K.K. Kandukuri, V. Bhatta, V. Reballi, V.R. Mekala, G. Bhyrapuneni, V. Benade, R. Nirogi

### **Asymmetric Reactions & Syntheses**

Sponsored by ORGN, Cosponsored by MEDI<sup>‡</sup>

### **CH Activation**

Sponsored by ORGN, Cosponsored by MEDI<sup>‡</sup>

### **Heterocycles & Aromatics**

Sponsored by ORGN, Cosponsored by MEDI<sup>‡</sup>

### **Peptides, Proteins & Amino Acids**

Sponsored by ORGN, Cosponsored by MEDI<sup>‡</sup>

### **Total Synthesis of Complex Molecules**

Sponsored by ORGN, Cosponsored by MEDI<sup>‡</sup>

## MEDI 1

### Discovery of potent and structurally diverse IDO1 selective heme-displacing inhibitors from optimization of hits from a mass spectrometry based affinity (ALIS) screen

**Yongxin Han**<sup>4</sup>, *yongxin\_han@merck.com*, Abdelghani Achab<sup>4</sup>, **christine andrews**<sup>2</sup>, *christine.andrews@merck.com*, Jeanine Ballard<sup>3</sup>, **Indu Bharathan**<sup>4</sup>, *indu.bharathan@merck.com*, Xiaomei Cha<sup>2</sup>, Ping Chen<sup>7</sup>, Mangeng Cheng<sup>2</sup>, Dane Clausen<sup>7</sup>, Yongqi Deng<sup>4</sup>, Amy Doty<sup>1</sup>, Heidi Ferguson<sup>1</sup>, Xavier Fradera<sup>5</sup>, Craig Gibeau<sup>4</sup>, Warren Glaab<sup>6</sup>, Liangqin Guo<sup>7</sup>, Shuwen He<sup>7</sup>, Brett A. Hopkins<sup>4</sup>, Xianhai Huang<sup>7</sup>, Wen Kang<sup>6</sup>, Joseph A. Kozlowski<sup>7</sup>, Charles Lesburg<sup>5</sup>, Guoqing Li<sup>7</sup>, Jongwon Lim<sup>4</sup>, Kun Liu<sup>4</sup>, Min Lu<sup>4</sup>, Theodore Martinot<sup>4</sup>, Meredith A. McGowan<sup>4</sup>, J. R. Miller<sup>2</sup>, Elliot Nickbarg<sup>2</sup>, Jennifer O'Neil<sup>8</sup>, Karin Otte<sup>3</sup>, Qinglin Pu<sup>4</sup>, Sulagna Sanyal<sup>4</sup>, Nunzio Sciammetta<sup>4</sup>, Nadya Smotrov<sup>2</sup>, David Sloman<sup>4</sup>, Nicolas Solbar<sup>2</sup>, Xuelei Song<sup>2</sup>, Peter Spacciapoli<sup>2</sup>, Alan Bass<sup>6</sup>, Stella Vincent<sup>3</sup>, Catherine White<sup>4</sup>, Dong Xiao<sup>7</sup>, Wensheng Yu<sup>7</sup>, Hua Zhou<sup>4</sup>, Hongjun Zhang<sup>4</sup>, **Derun Li**<sup>4</sup>, *derun\_li@merck.com*, Alexander Pasternak<sup>4</sup>, David J. Bennett<sup>4</sup>. (1) Discovery Pharmaceutical Sciences, Merck & Co., Inc., Boston, Massachusetts, United States (2) Pharmacology, Merck & Co., Inc., Boston, Massachusetts, United States (3) PPDM, Merck & Co., Inc., West Point, Pennsylvania, United States (4) Discovery Chemistry Boston, Merck & Co., Inc., Boston, Massachusetts, United States (5) Structural Chemistry, Merck & Co., Inc., Boston, Massachusetts, United States (6) Systems Toxicology, Merck & Co., Inc., West Point, Pennsylvania, United States (7) Discovery Chemistry Kenilworth, Merck & Co., Inc., Kenilworth, New Jersey, United States (8) Biology, Merck & Co., Inc., Boston, Massachusetts, United States

Indoleamine-2,3-dioxygenase-1 (IDO1) and tryptophan 2,3-dioxygenase (TDO) are intracellular heme-containing enzymes which catalyze the first and rate-determining step in tryptophan (Trp) catabolism, producing immunosuppressive catabolites such as kynurenine (Kyn). Trp catabolism mediated by IDO1 is an important mechanism of peripheral immune tolerance contributing to tumoral immune resistance due to depletion of Trp levels in the tumoral microenvironment and the formation of immunosuppressive catabolites such as Kyn. Many human tumors are shown to constitutively express IDO1, and an increased level of IDO1 expression in tumor cells is correlated with poor prognosis for survival in several tumor types. Initial clinical POC for IDO1 inhibition in cancer was established with epacadostat, an IDO1 selective heme-binding inhibitor, in combination with anti-PD-1 antibodies in Phlb-II trials. However, in a PhIII confirmatory study (ECHO-301/KEYNOTE-252) in unresectable or metastatic melanoma, the epacadostat/pembrolizumab combo failed to show improved efficacy (PFS) over pembro monotherapy. While the underlying causes of the failure remain to be uncovered, there are a number of potential explanations, including insufficient tumor target engagement and the potential of AhR activation by epacadostat. In order to unequivocally test the clinical utility of IDO1 inhibition in combination with anti-PD-1 antibodies, it is highly desirable to discover exquisitely potent IDO1 inhibitors that are devoid of the potential for AhR activation, allowing an extremely high level of tumor

target engagement without the complication of tumor immunosuppression *via* AhR activation.

In this presentation, we will describe the identification of a number of heme-displacing IDO1 inhibitor hits from an ALIS screen, and subsequent structure based optimization of these hits to highly potent and structurally diverse IDO1 inhibitors with an excellent overall profile. We will also discuss the PK/PD behavior of representative inhibitors in a rodent tumor model in which a number of these inhibitors achieve unprecedented levels of IDO1 inhibition at low drug concentrations.

## **MEDI 2**

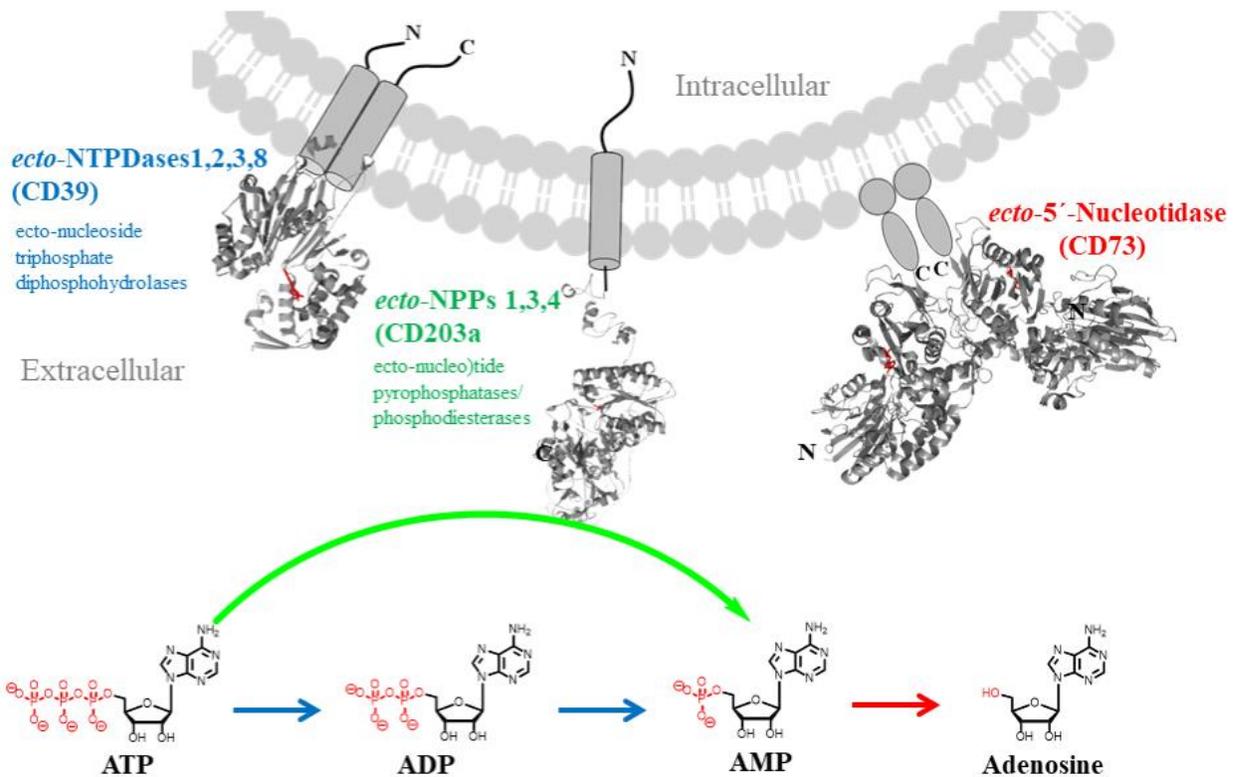
### **Small molecule ectonucleotidase inhibitors for the immunotherapy of cancer**

**Christa E. Muller**<sup>1,2</sup>, [christa.mueller@uni-bonn.de](mailto:christa.mueller@uni-bonn.de). (1) *Pharmaceutical Chemistry, University of Bonn, Bonn, Germany* (2) *PharmaCenter Bonn, Bonn, Germany*

Adenosine is one of the strongest immunosuppressant agents of the innate immune system. Cancer cells and tissues can release large amounts of ATP which is immediately hydrolyzed by ectonucleotidases. These ecto-enzymes, including ectonucleotide pyrophosphatase/phosphodiesterase 1 (NPP1, CD203a), ectonucleoside diphosphohydrolase 1 (NTPDase1, CD3), and ecto-5'-nucleotidase (CD73), are upregulated on many cancer cells leading to the production of adenosine. NPP1 has been found to be overexpressed in some brain tumors, such as glioblastoma, and expression levels were reported to be correlated with tumor grade. The cloud of adenosine formed around cancer tissues contributes to immune escape by interacting with adenosine A<sub>2A</sub> and A<sub>2B</sub>receptor subtypes (A<sub>2A</sub>AR, A<sub>2B</sub>AR) on immune cells. In addition, activation of A<sub>2B</sub>ARs by adenosine enhances cancer cell proliferation and angiogenesis.

In contrast to CD39 and CD73, NPP1 is a highly promiscuous ectonucleotidase. In addition to nucleoside triphosphates (most importantly ATP), it also hydrolyzes cyclic nucleotides, such as cAMP and the cyclic dinucleotide 2',3''-cGAMP (cGAMP). cGAMP is formed through condensation of ATP and GTP by the cyclic cAMP-cGMP synthase (cGAS) and activates STING (stimulator of interferon gene). NPP1 inhibitors may therefore not only block the hydrolysis of proinflammatory ATP, but also the hydrolysis of cGAMP, both activities leading to enhanced immune responses.

Our work has been focused on the identification and optimization of small molecule inhibitors of ectonucleotidases, including NPP1, CD39 and CD73 inhibitors, as novel therapeutics in immuno-oncology.



### MEDI 3

#### Identification of BAY-218: A potent and selective small molecule AHR inhibitor, as a new modality to counteract tumor immunosuppression

**Norbert Schmees**<sup>3</sup>, [norbert.schmees@bayer.com](mailto:norbert.schmees@bayer.com), **Ilona Gutcher**<sup>2</sup>, **Ulrike Roehn**<sup>1</sup>, **Horst Irlbacher**<sup>3</sup>, **Benjamin Bader**<sup>3</sup>, **Christina Kober**<sup>2</sup>, **Lars Roesse**<sup>2</sup>, **Rafael Carretero**<sup>2</sup>, **Iris Oezen**<sup>4</sup>, **Ludwig Zorn**<sup>3</sup>, **Michael Platten**<sup>4</sup>, **Ingo Hartung**<sup>3</sup>, **Bertolt Kreft**<sup>2</sup>, **detlef stoeckigt**<sup>5</sup>, **Hilmar Weinmann**<sup>3</sup>. (1) Medicinal Chemistry, Bayer AG, Berlin, Germany (2) TRG Oncology, Bayer AG, Berlin, Germany (3) SMI, Bayer AG, Berlin, Germany (4) DKFZ Heidelberg, Heidelberg, Germany (5) Research DMPK, Bayer AG, Berlin, Germany

Re-constitution of anti-tumor T-cell responses by clinically-approved immune checkpoint inhibitors (ICI) targeting CTLA4 or PD-1/PD-L1 represents a breakthrough cancer therapy. Nevertheless, a substantial number of patients do not benefit from these new therapeutic modalities chiefly due to local immunosuppression in the tumor microenvironment. The long circulation time of ICIs restricts options to modify dosing regimens for management of adverse effects. Oral small molecule inhibitors as next

generation immune-oncology agents may – in contrast to antibodies – allow targeting of intracellular targets for a defined duration of time. This will permit a fine-tuning of efficacy versus tolerability in single-agent treatment as well as in combination with approved ICIs. The overexpression of indole dioxygenase (IDO1) and tryptophan dioxygenase (TDO2) by many tumors results in increased metabolism of tryptophan (TRP) into kynurenine (KYN), which induces immunosuppression via activation of the aryl hydrocarbon receptor (AHR). Inhibition of AHR was proposed to restore T-cell function and induce tumor rejection. However, it was expected that identification of selective lead candidates for AHR inhibition would be challenging due to the known affinity of the AHR ligand binding site for polyaromatic, non-drug-like ligands. A library of 4 million compounds was screened in a cell based HTS campaign. A thorough hit reduction process was performed based on stringent filter parameters for lead-likeness. This process delivered a hit set of significant chemical diversity. Out of several compound classes with drug-like properties, 1,3-diaryl-pyrazin-6-one-5-carboxylic amides were selected as a preferred lead series. A comprehensive SAR exploration, including mechanistic and functional validation, was performed. Lead optimization was strongly emphasized on improving lipophilicity efficiency (LLE) to balance potency with a viable PK and CYP450 interaction profile. Several candidates suitable for *in vivo* profiling were identified and BAY-218 was advanced to in depth pharmacodynamic and pharmacokinetic *in vivo* assessment. BAY-218 showed *in vivo* mono-therapeutic efficacy that was comparable to ICI treatment and further therapeutic improvement was achieved by combination with an aPD-L1 antibody. We characterized 1,3-diaryl-pyrazin-6-one-5-carboxylic amides as an unprecedented class of AHR inhibitors and identified the key substitutions that contribute to the overall compound profile.

## MEDI 4

### Discovery of novel cyclic dinucleotide STING agonists for cancer treatment

**Wonsuk Chang**<sup>1</sup>, [wonsuk.chang@merck.com](mailto:wonsuk.chang@merck.com), Michael D. Altman<sup>2</sup>, Brian M. Andresen<sup>2</sup>, Saso Cemersk<sup>2</sup>, Matthew Childers<sup>2</sup>, Andrew Haidle<sup>2</sup>, Timothy J. Henderson<sup>2</sup>, James P. Jewell<sup>2</sup>, Rui Liang<sup>1</sup>, Jongwon Lim<sup>2</sup>, Hong Liu<sup>1</sup>, Min Lu<sup>2</sup>, Alan Northrup<sup>2</sup>, Ryan Otte<sup>2</sup>, Samantha A. Perera<sup>2</sup>, Jeremy Presland<sup>2</sup>, Tony Siu<sup>2</sup>, Quang Truong<sup>1</sup>, Shawn Walsh<sup>1</sup>, Kake Zhao<sup>1</sup>, Jared Cumming<sup>2</sup>, Wes Trotter<sup>2</sup>. (1) Merck Research Laboratories, Kenilworth, New Jersey, United States (2) Merck Research Laboratories, Boston, Massachusetts, United States

Activation of the Stimulator of Interferon Genes (STING) pathway is a central innate immune sensing mechanism that leads to production of type I interferons and pro-inflammatory cytokines, maturation of antigen-presenting cells and priming of tumor antigen-specific CD8+ T-cells. Stimulation of this pathway in a tumor microenvironment therefore holds promise for generating an anti-tumor immune response. Accordingly, in various syngeneic mouse tumor models, STING agonists demonstrate robust tumor and plasma cytokine upregulation and strong anti-tumor activity, alone or in combination with anti-PD-1 monoclonal antibodies. Intratumoral injection of STING agonists thus represents a promising cancer treatment approach that is currently under investigation

in human clinical trials in combination with recently approved checkpoint inhibitors. This talk will review synthetic chemistry approaches at Merck that enabled rapid exploration of the structurally and stereochemically complex cyclic dinucleotide (CDN) class of STING agonists. A variety of potent STING agonists were identified, many of which demonstrated greater than 100-fold improvements in efficacious dose in vivo when compared to the endogenous human CDN STING ligand, 2',3'-cGAMP. Details in synthetic preparations of the diverse CDN STING agonists and their precursors, as well as structure activity relationships of these STING agonists will be discussed.

## **MEDI 5**

### **Discovery of JNJ-787: An Hpk1 inhibitor that enhances the anti-tumor immunity of anti-PD1 in mice**

*Laurence MEVELLEC<sup>2</sup>, lmevelle@its.jnj.com, Sophie Descamps<sup>2</sup>, Christophe Adeline<sup>2</sup>, Berthold Wroblowski<sup>1</sup>, Veronique Vreys<sup>1</sup>, Annemie Valckx<sup>1</sup>, Inge Boeckx<sup>1</sup>, Nele Van Slycken<sup>1</sup>, Caroline Paulussen<sup>1</sup>, Laurent Leclercq<sup>1</sup>, Tinne Verhulst<sup>1</sup>, Bas-jan Van der Leede<sup>1</sup>, Patrick Angibaud<sup>2</sup>, Lieven Meerpoel<sup>1</sup>, James P. Edwards<sup>3</sup>, Sylvie Laquerre<sup>3</sup>, Matt Lorenzi<sup>3</sup>, Jorge Vialard<sup>1</sup>. (1) Janssen Research & Development, a division of Janssen Pharmaceutica NV, Beerse, Belgium (2) Janssen Research & Development, a division of Janssen-Cilag, Val de Reuil, France (3) Janssen Research & Development, Spring House, Pennsylvania, United States*

The serine/threonine Hpk1 kinase is a negative regulator of T cell, B cell and dendritic cell function that has been shown to limit the immune response to tumors. Hpk1 disrupts T cell receptor (TCR)-mediated signaling at least partially through phosphorylation of SLP76, an essential component of the TCR signalosome. An Hpk1 kinase inactivating mutation was shown to increase T cell activation and enhance tumor growth inhibition in mice.

Here we report a structure-based drug design approach starting from a macrocyclic azaindole high-throughput screening hit that led to the generation of a novel chemical series of bioavailable Hpk1 inhibitors. It resulted in identification of JNJ-787, a selective Hpk1 inhibitor that increased T cell activity in vitro and enhanced the inhibitory effect of a-PD1 treatment on MC-38 tumor growth in mice. The anti-tumoral effect was associated with an enhanced immune response. To our knowledge, it will be the first disclosure of an Hpk1 inhibitor with anti-tumoral properties through immune modulation. In addition to potency and selectivity, we will also discuss Structure Property Relationships (SPR) for specifically improving cardiovascular safety and reducing phospholipidosis-inducing potential in this chemical series.

## **MEDI 6**

### **Antiviral innate immunity through small molecules for protection against RNA viruses**

**Michael Gale**, *mgale@uw.edu*. Immunology, University of Washington, Seattle, Washington, United States

Innate immune defenses are essential for restricting virus replication and for programming the adaptive immune response against infection. Our studies are focused on defining the pathogen recognition receptor interactions and signaling events triggered by viral pathogen associated molecular patterns (PAMPs) to drive innate antiviral immunity and program/enhance the adaptive immune response to RNA virus infection and vaccination. This work has defined the RIG-I-like receptors, including RIG-I, MDA5, and LGP2, as critical factors in the recognition of RNA virus infection and immune protection against infection and disease. We have identified distinct PAMP/RLR interactions that serve to program the outcome of infection and immunity. We are now applying the principles of PAMP/RIG-I interactions to target RIG-I and RLR signaling through small molecule therapeutics aimed at suppressing virus infection through robust induction of innate antiviral immunity, and to serve as vaccine adjuvants to enhance the immune response to vaccination for lasting protection against RNA virus infection. Our preclinical studies demonstrate that targeting RIG-I and RLR signaling offers broad-spectrum antiviral actions. Moreover, small molecule activation of RIG-I serves to greatly enhance the adaptive immune response induced by specific RNA virus vaccines. Thus, RLRs are critical mediators of innate immunity wherein their functions are essential for protection against RNA virus infection. Targeting RLRs through small molecules provides a host-based regimen of antiviral therapy through the actions of PAMP/RIG-I intracellular and tissue response gene expression networks, and offers strong vaccine adjuvant activity through RLR signaling of innate immunity.

## **MEDI 7**

### **GS-4361: A novel IDO1 Inhibitor**

**Rao V. Kalla**<sup>1</sup>, *rao.kalla@gilead.com*, **Kristy Elbel**<sup>1</sup>, **Mark Bartlett**<sup>1</sup>, **Jennifer Cosman**<sup>1</sup>, **Thao D. Perry**<sup>1</sup>, **Elfatih Elzein**<sup>1</sup>, **Xiaofen Li**<sup>1</sup>, **Dmitry O. Koltun**<sup>1</sup>, **Eric Q. Parkhill**<sup>1</sup>, **Jeff A. Zablocki**<sup>1</sup>, **Mike Clark**<sup>1</sup>, **Heather Maecker**<sup>2</sup>, **Sudhamsu Jawahar**<sup>2</sup>, **Deborah Hendricks**<sup>2</sup>, **Alex Shornikov**<sup>3</sup>, **David Koditek**<sup>3</sup>, **Brian Stafford**<sup>4</sup>, **Daniel Soohoo**<sup>4</sup>, **Johannes Voigt**<sup>5</sup>, **Eric Lansdon**<sup>5</sup>, **Richard Mackman**<sup>1</sup>, **Britton Corkey**<sup>1</sup>. (1) Medicinal Chemistry, Gilead Sciences, Foster City, California, United States (2) Oncology Biology, Gilead Science, Foster City, California, United States (3) High Throughput Biology, Gilead Sciences, Foster City, California, United States (4) Drug Metabolism, Gilead Sciences, Foster City, California, United States (5) Structural Chemistry, Gilead Sciences, Foster City, California, United States

Indoleamine 2,3-dioxygenase 1 (IDO1) is an inducible, heme-containing enzyme that catabolizes the essential amino acid tryptophan to kynurenine. Low levels of tryptophan result in suppression of cytotoxic T cell (CTL) proliferation, and elevated levels of downstream kynurenine metabolites have a cytotoxic effect on T cells. IDO1 is elevated in the tumor microenvironment of multiple cancers and correlates negatively with prognosis. Early clinical studies suggest that IDO1 inhibitors enhance the efficacy of

anti-PD1 and anti-CTLA4 checkpoint inhibitors in melanoma and lung cancer. We initiated an IDO1 inhibitor program and during the course of our research, a novel mechanism of inhibition was discovered wherein binding of the heme cofactor to IDO1 is prevented by our inhibitors. Here in we describe our efforts towards the discovery of GS-4361, which had excellent potency, selectivity, and pharmacokinetic properties.

## **MEDI 8**

### **Discovery and optimization of inhibitors of the autophagy E1 enzyme, ATG7**

**Shih-Chung Huang**, *sampson.huang@mpi.com*, Sean J. Harrison, Alexandra E. Gould. Takeda Pharmaceuticals International Co., Cambridge, Massachusetts, United States

Autophagy is postulated to be required by cancer cells to survive periods of metabolic and/or hypoxic stress. ATG7 is the E1 enzyme that is required for activation of Ubl conjugation pathways involved in autophagosome formation. Herein, we describe the design and optimization of pyrazolopyrimidine sulfamate compounds as potent and selective inhibitors of the ATG7. Cellular levels of the autophagy markers, LC3B and NBR1, are regulated following treatment with these compounds.

## **MEDI 9**

### **Development of water soluble, brain permeable EP2 receptor antagonist: Lead-optimization and *in vitro* proof-of-concept studies**

**Radhika Amaradhi**, *radhika\_laghuvarapu@yahoo.com*, Avijit Banik, Shabber Mohammed, Vidyavathi Patro, Asheebo Rojas, Wenyi Wang, Ray Dingledine, Thota Ganesh. Pharmacology, Emory University-School of Medicine, Decatur, Georgia, United States

Neuroinflammation is a key driver of several neurodegenerative diseases including Epilepsy, Parkinson's diseases, Amyotrophic lateral sclerosis and Alzheimer' diseases. Prostaglandin-E<sub>2</sub> (PGE<sub>2</sub>) receptor EP2 has emerged as an important target for therapeutic discovery. The EP2 receptor exacerbates the vicious inflammatory signaling during the progression of these central nervous system diseases. EP2 is a Gs-coupled receptor, when activated by the endogenous ligand PGE<sub>2</sub>, stimulates adenylate cyclase resulting in elevation of cytoplasmic cAMP concentration, which initiates downstream events via protein kinase A (PKA) or exchange protein activated by cAMP (Epac) mediated cell signaling pathways. We developed a cAMP-driven TR-FRET assay in C6-glioma cell line overexpressed with EP2 receptor, and initially screened a small molecule library 262,370 compounds of to identify novel class of antagonists of the EP2 receptor. The first-generation compounds displayed high EP2 potency, but they showed low selectivity against other prostanoid receptors (e.g. DP1 and IP receptors) (*Ganesh et al., J. Med. Chem. 2014*). Then, we developed second-generation derivatives with high EP2 potency and selectivity, but aqueous solubility and brain permeability

properties must be optimized within the class (*Ganesh et al., Eur. J. Med. Chem. 2014*). For a chronic oral dosing into animal models of Alzheimer's disease, we needed a compound with good aqueous solubility and brain permeability properties. Recently, we synthesized > 100 novel derivatives and conducted lead-optimization studies within the class to identify a novel compound with water solubility and good brain permeability. This novel compound will enable to test proof-of-concept in a variety of animal models of chronic neurodegenerative diseases where EP2 receptor plays deleterious roles. The lead optimization strategies, potency and selectivity (structure activity relationships, SAR), aqueous solubility, ADME and pharmacokinetics data of the novel compounds including the optimized lead compound along with in vitro proof-of-concept that EP2 antagonism is beneficial, will be presented in the meetings.

## **MEDI 10**

### **SAR studies in the sulfonyl carboxamide class of core protein modulators of the hepatitis B virus**

**Scott D. Kuduk**, *skuduk@its.jnj.com. Janssen R&D, Spring House, Pennsylvania, United States*

Hepatitis B virus infection is a common cause of severe liver disease and liver cancer. Current treatment options cannot fully suppress viral replication in the majority of patients and only show very low cure rates. Accordingly, the identification of antivirals with a new mechanism of action should allow for the intensification of HBV suppression towards fully blocking HBV production in the liver and thus improve treatment outcomes toward the identification of a cure. The HBV core capsid protein has multiple essential functions in the HBV life cycle to enable chronic HBV infection. It is therefore an important target for antiviral drug development. NVR 3-778 is a first-in-class sulfonyl carboxamide-based HBV capsid assembly modulator (CAM) that has demonstrated proof of mechanism in a Phase I clinical trial. Herein we describe SAR efforts in the sulfonyl carboxamide series to identify next generation CAMs beyond NVR 3-778.

## **MEDI 11**

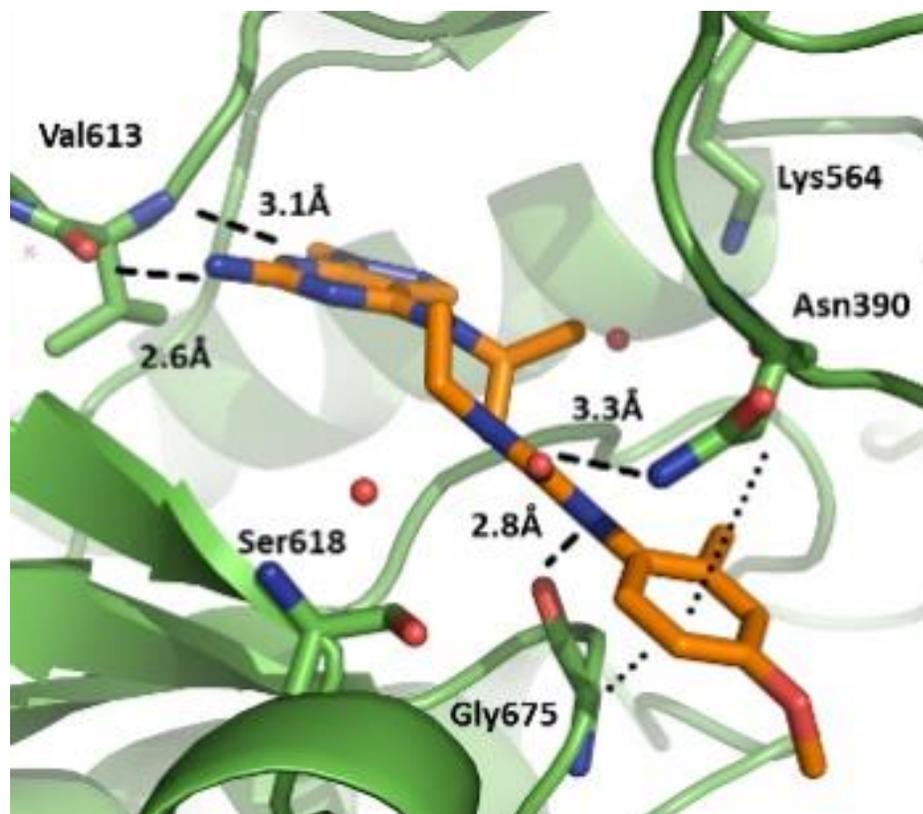
### **Discovery and development of PI4KIII $\beta$ inhibitors as immunosuppressive agents for the prolongation of allogeneic organ engraftment**

**James Reuberson**, *James.Reuberson@UCB.com. UCB Pharma, Slough, United Kingdom*

Recently we confirmed the target of a novel series of immunosuppressive piperazine urea's was the lipid kinase PI4KIII $\beta$  and that a clear link between inhibition of PI4KIII $\beta$  and the suppression of immune responses both *in vitro* and *in vivo* was emerging. Development of this series led to the discovery of UCB9608, a pyrazolopyrimidine analogue with an excellent *in vivo* profile and an ideal tool compound to fully establish the link between PI4KIII $\beta$  inhibition and modulation of immune responses in a variety of

pre-clinical models.

In this talk we shall expand upon the structural activity relationships established within the UCB9608 series, discuss in more detail the effect of UCB9608 in a range of disease models and further discuss the insights gained from the crystal structure of UCB9608 and close analogues that enabled us to design a range of conformationally locked urea surrogates that could mitigate potential genotoxicity concerns inherent in molecules containing embedded anilines.



## MEDI 12

### Target identification studies of a utrophin modulator for treatment of Duchenne muscular dystrophy

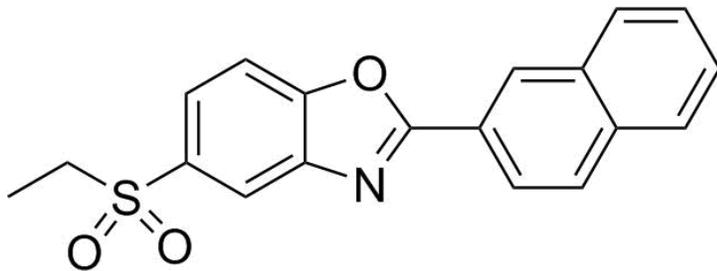
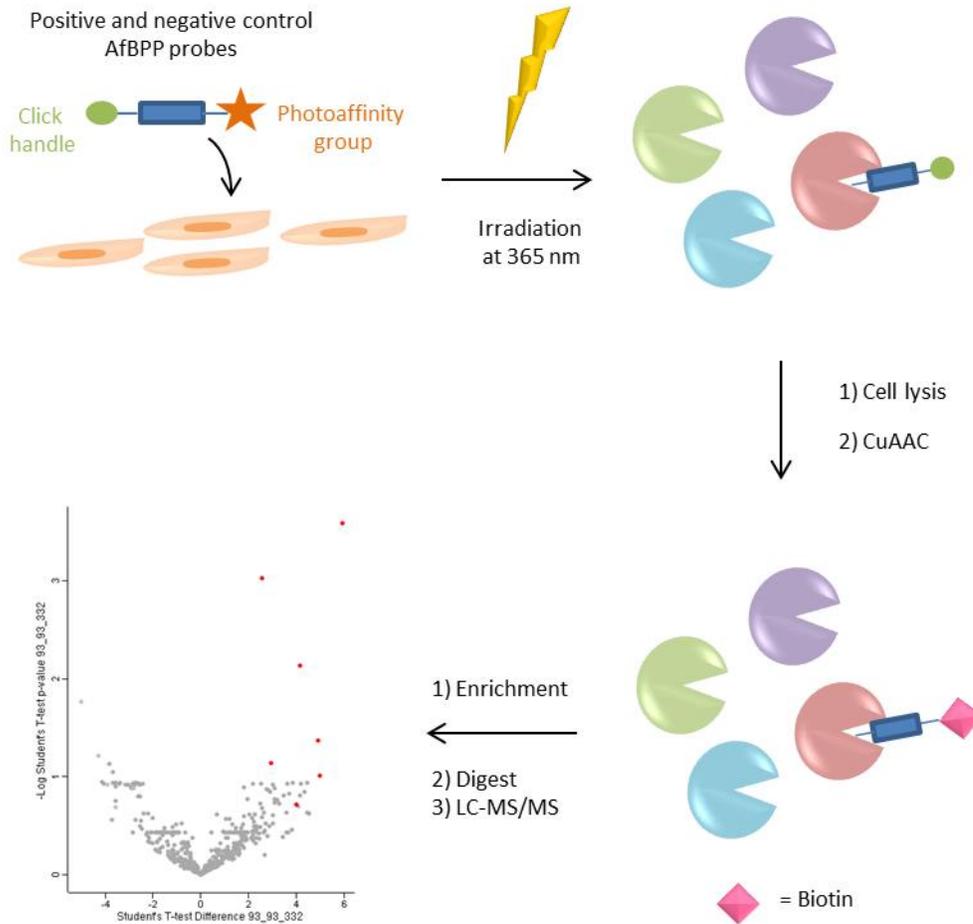
**Isabel Wilkinson**<sup>1</sup>, [isabel.wilkinson@dtc.ox.ac.uk](mailto:isabel.wilkinson@dtc.ox.ac.uk), Aini Vuorinen<sup>1</sup>, Jessica Reynolds<sup>1</sup>, Kelly Perkins<sup>2</sup>, Hannah Dugdale<sup>2</sup>, Sarah Squire<sup>2</sup>, Anne-Sophie Casagrande<sup>7</sup>, Marcus Geese<sup>8</sup>, Francis Wilson<sup>3</sup>, Graham Wynne<sup>1</sup>, Shabaz Mohammed<sup>1,4</sup>, Kilian Huber<sup>5</sup>, Kay Davies<sup>2</sup>, Angela Russell<sup>1,6</sup>. (1) Department of Chemistry, University of Oxford, Oxford, United Kingdom (2) Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, United Kingdom (3) summit plc, Abingdon, United Kingdom (4) Department of Biochemistry, University of Oxford, Oxford, United Kingdom (5) Target

*Discovery Institute, University of Oxford, Oxford, United Kingdom (6) Department of Pharmacology, University of Oxford, Oxford, United Kingdom (7) Evotec, Toulouse, France (8) Evotec, Göttingen, Germany*

Duchenne muscular dystrophy (DMD) is a muscle wasting disease arising from mutations in the dystrophin gene, affecting about 1 in 3500 boys. Whilst there is currently no available cure for DMD, a number of therapeutic strategies are under development. One such therapy aims to promote expression of utrophin, an autosomal paralogue of dystrophin. A novel small molecule utrophin modulator, ezutromid (Summit Therapeutics; formerly SMT C1100), which was identified using a phenotypic screen, progressed to Phase II clinical trials in DMD patients. Interim 24-week data demonstrated reduced muscle fibre damage and increased levels of utrophin, providing the first evidence of ezutromid target engagement and proof of mechanism. However, these effects were not seen after the full 48 weeks of the trial. This work aims to define the mechanism of ezutromid in order to help understand the trial results, and to aid development of new generations of utrophin modulators.

Target identification through affinity based protein profiling (AfBPP) has been carried out in this work alongside CETSA and broad -omics profiling studies. AfBPP requires bioactive analogues suitable for affinity purification. Photoaffinity-labelled analogues of ezutromid designed to be positive and negative controls have been synthesised and tested in RT-qPCR and Western blot assays. These probes were used in AfBPP experiments followed by LC-MS/MS. Integration of the hits identified by these strategies has led to a shortlist of targets which are currently being validated.

## Affinity based protein profiling



Ezutromid

## MEDI 13

### **Synthesis and biological evaluation of a new class of aryl isonitriles as antimicrobial agents**

**Kwaku Kyei-Baffour**<sup>1</sup>, [kyeichem@gmail.com](mailto:kyeichem@gmail.com), Haroon Mohammad<sup>2</sup>, Mohamed N. Seleem<sup>2,3</sup>, Mingji Dai<sup>1,3</sup>. (1) Chemistry, Purdue University, West Lafayette, Indiana, United States (2) Department of Comparative Pathobiology, College of Veterinary Medicine, Purdue University, West Lafayette, Indiana, United States (3) Purdue Institute for Inflammation, Immunology, and Infectious Diseases, Purdue University, West Lafayette, Indiana, United States

Infectious diseases caused by bacteria and fungi are a huge problem affecting millions of people worldwide that necessitates continuous discovery of antimicrobial agent, particularly those utilizing new scaffolds. A novel class aryl isonitriles that exhibits potent inhibitory activity against several clinically relevant MRSA and VRSA isolates as well as species of *Candida* and *Cryptococcus* have been discovered. Beyond exhibiting good safety profile, metabolic stability analysis of the most potent compounds have showed stability to hepatic metabolism and have a long half-life. These agents have also been shown to exhibit *in vivo* efficacy in MRSA skin and thigh infections.

## MEDI 14

### **Hit-to-lead evolution of small-molecule PPAR $\alpha$ agonists: Working towards non-invasive options for retinal diseases**

**Adam S. Duerfeldt**, [adam.duerfeldt@ou.edu](mailto:adam.duerfeldt@ou.edu). Chemistry & Biochemistry, University of Oklahoma, Norman, Oklahoma, United States

More than 40% of patients with retinal inflammatory diseases are refractory to the standard of care treatment, direct intraocular injection of anti-VEGF antibodies. The inability to effectively treat ocular diseases, especially those associated with diabetes mellitus like diabetic retinopathy (DR), accounts for >20% of healthcare expenditures and threatens the quality of life of >30 million people in the United States alone. Considering population growth rates and aging demographics, the diabetes epidemic and prevalence of disease related comorbidities continue to worsen. Frontline approaches require frequent injections, are destructive, demand specialized facilities, suffer from poor response rates, and produce significant burdens on the healthcare system.

Our studies have revealed that agonism of peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ) with genetic or pharmacological tools in diabetic retinopathy ameliorates inflammation, vascular leakage, neurodegeneration, and neovascularization in diabetic animal models. Recently, we identified a novel PPAR $\alpha$  agonist that exhibits efficacy in DR animal models after systemic administration. Since this discovery, we have advanced this hit into leads which exhibit improved PPAR $\alpha$  potency and selectivity and exhibit efficacy in a vascular leakage DR animal model. PPAR $\alpha$  is now a clinically

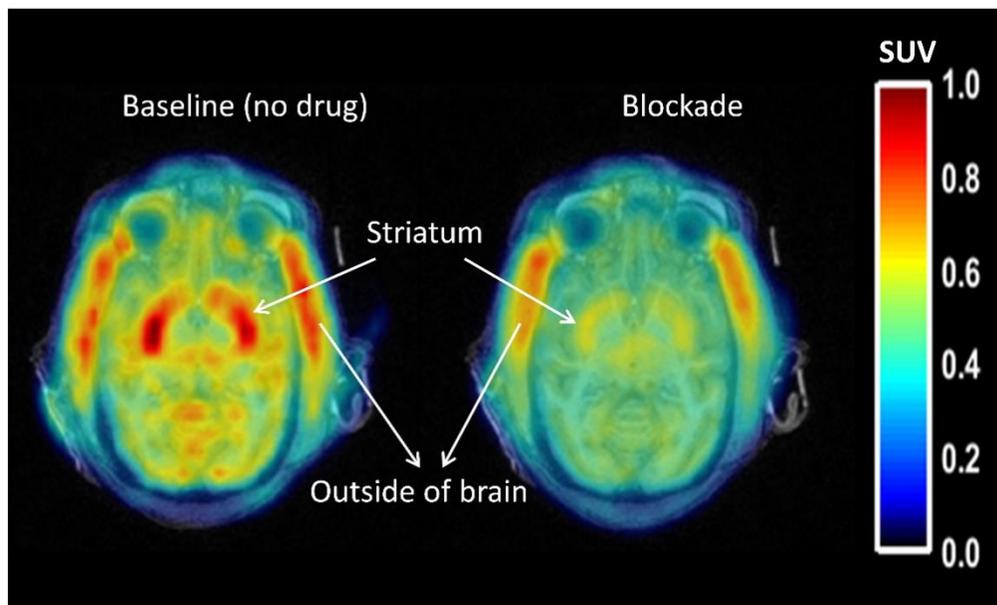
proven yet unexploited therapeutic target for DR. This talk will summarize our recent progress towards developing small molecule PPAR $\alpha$  agonists as first-in-class therapies for the treatment of DR and related diseases. The work showcases a strategic cross-campus collaboration between the University of Oklahoma (OU) and the University of Oklahoma Health Sciences Center (OUHSC).

## MEDI 15

### Discovery of [ $^{11}\text{C}$ ]MK-6884: A positron emission tomography (PET) imaging agent for M4 PAM

**Ling Tong**<sup>2</sup>, [ling.tong@merck.com](mailto:ling.tong@merck.com), **Wenping Li**<sup>1</sup>, **Xiaolei Gao**<sup>7</sup>, [xgao@njcu.edu](mailto:xgao@njcu.edu), **Michael Lo**<sup>7</sup>, **Jenny M. Wa**<sup>2</sup>, **Michael T. Rudd**<sup>3</sup>, **David M. Tellers**<sup>2</sup>, **Zhizhen Zeng**<sup>1</sup>, **Patricia Miller**<sup>1</sup>, **Cristian Salinas**<sup>1</sup>, **Kerry A. Riffel**<sup>4</sup>, **Hyking Haley**<sup>1</sup>, **Mona Purcell**<sup>1</sup>, **Marie Holahan**<sup>1</sup>, **Tjerk Bueters**<sup>5</sup>, **Jason Uslaner**<sup>6</sup>, **John Morrow**<sup>6</sup>, **Rob Mazzola**<sup>7</sup>. (1) *Translational Biomarkers*, Merck & Co., Inc., West Point, Pennsylvania, United States (2) *Discovery Chemistry*, Merck & Co., Inc., West Point, Pennsylvania, United States (3) *WP14-3*, Merck Co Inc, West Point, Pennsylvania, United States (4) *Wp 44d-2*, Merck Co Inc, West Point, Pennsylvania, United States (5) *PPDM*, Merck & Co., Inc., West Point, Pennsylvania, United States (6) *Discovery Biology*, Merck & Co., Inc., West Point, Pennsylvania, United States (7) *Discovery Chemistry*, Merck, Kenilworth, New Jersey, United States

The muscarinic acetylcholine receptor M4 has been implicated in several CNS disorders. It possesses an allosteric binding site for which ligands modulating the affinity or efficacy of acetylcholine may be exploited for selective receptor targeting. This positive allosteric modulator (PAM) approach has led to the discovery of compounds that potentiate the efficacy of acetylcholine. To facilitate the identification and clinical development of a therapeutic M4 PAM, a devoted effort has focused on the development of a positron emission tomography (PET) tracer. The early clinical development of an allosteric-site PET ligand is proposed to generate data informing on several potential developmental challenges that the M4 PAM team has identified arising from the dependence of M4 PAM binding to the cholinergic tone *in vivo*. The focus of this presentation will be the SAR development leading up to the discovery of M4 PAM PET tracer [ $^{11}\text{C}$ ]MK-6884. The *in vitro* and *in vivo* characterizations of [ $^{11}\text{C}$ ]MK-6884 and its utility in preclinical species to advance the chemical matter (Figure 1) will be discussed. The full structure of tracer [ $^{11}\text{C}$ ]MK-6884 will be disclosed at conference.



**Figure 1:** Co-registered transverse PET/MRI summed image (0-90 min) of [ $^{11}\text{C}$ ]MK-6884 in rhesus monkey highlighting tracer uptake in the striatum. The left panel is [ $^{11}\text{C}$ ]MK-6884 baseline, and the right panel includes blockade with a M4 PAM compound. The scale is shown in Standardized Uptake Value (SUV) units, which are normalized for the injected dose and mass of the monkey.

## MEDI 16

### Discovery and optimization of potent, selective, and bioavailable USP7 inhibitors to target tumor growth

*Paul Leger, leger.paul@gmail.com, Dennis X. Hu, Betty Abraham, Lavanya Adsusmilli, Berenger Biannic, Delia Bradford, Gene Cutler, Xinping Han, Scott Jacobson, Aparna Jorapur, Paul Kassner, Deepika Kaveri, John Ketcham, Andrea Kim, Jack Maung, Jenny McKinnell, Yamini Ohol, Akinori Okano, Leanne Peiser, Deepa Pookot, Payal Rana, Nick Shah, Grant Shibuya, Michael Sun, Silpa Suthram, Oezcan Talay, Kyle Young, Jacob B. Schwarz, David J. Wustrow. FLX Bio, Inc., Oakland, California, United States*

USP7 is a deubiquitinase (DUB) that has been reported to regulate the levels of multiple proteins with roles in cancer progression and immune response, including MDM2 and p53. Inhibition of USP7 is expected to decrease function of oncogenes, increase tumor suppressor function, and enhance immune function. Using structure-based drug design, we have designed a series of reversible USP7 inhibitors that are highly potent in biochemical and cellular assays and are selective for USP7 over other DUBs. Additionally, potent USP7 inhibitors have been identified which display good oral bioavailability and low clearance across species. The discovery of cyclic imides as an

important potency-driving motif, properly positioned through the utilization of a thienopyridine core structure will be described.

## MEDI 17

### **New ruthenium Formate catalyst MCAT-53™ for C-H activation useful for the synthesis of medicinally relevant molecules**

**Anita Mehta**, *amehta@chicagodiscoverysolutions.com*, **Biswajit Saha**, *ali.koohang@chicagodiscoverysolutions.com*, **Mukund Chorghade**, *chicagodiscoverysolutions.com*, Plainfield, Illinois, United States

A new water friendly MCAT-53 [Ru<sub>2</sub>Cl<sub>2</sub>(HCOO)<sub>3</sub>(*p*-cymene)] Na (sodium η-6-*p*-cymene dichloro diruthenium triformate complex) has been developed as a catalyst to effect aromatic C–H bond activation and C–C coupling reactions in water. **MCAT-53™** allows directed C–H functionalization with high levels of positional selectivity control for the synthesis of API intermediate of Anacetrapib a CETP inhibitor (OPRD, 2018, 22,9, 1119-1130). **MCAT-53™** catalyst is now commercially available in 40 countries. The catalyst has been proven to be useful for the synthesis of substituted phenyl pyridines, phenyl pyrazoles, phenyl oxazolines and Benzo[h]quinolones and others through N-directed C-H functionalization.

## MEDI 18

### **Discovery of a novel α7 nAChR positive allosteric modulator for the treatment of cognitive disorders**

**Brendan M. Crowley**<sup>1</sup>, *brendan.crowley@gmail.com*, **Jaume Balsells-Padros**<sup>2</sup>, **Jianming Bao**<sup>3</sup>, **Brian T. Campbell**<sup>1</sup>, **Chris J. Daley**<sup>4</sup>, **Deodial Guiadeen**<sup>1</sup>, **Belinda C. Huff**<sup>5</sup>, **Joe Della Rocca**<sup>6</sup>, **Elizabeth M. Joshi**<sup>7</sup>, **Kenneth J. Leavitt**<sup>1</sup>, **Dharam Paul**<sup>5</sup>, **John M. Sanders**<sup>8</sup>, **Spencer Tye**<sup>9</sup>, **Xiaohai Wang**<sup>10</sup>, **Sue M. O'Connor**<sup>5</sup>, **Andrew J. Harvey**<sup>5</sup>, **Jason Uslander**<sup>10</sup>, **Joseph L. Duffy**<sup>11</sup>, **Ian M. Bell**<sup>1</sup>. (1) Discovery Chemistry, Merck, West Point, Pennsylvania, United States (2) Discovery Process Chemistry, Merck, West Point, Pennsylvania, United States (3) External Discovery Chemistry, Merck, Shanghai, China (4) In Vitro Pharmacology, Merck, West Point, Pennsylvania, United States (5) Bionomics, Adelaide, South Australia, Australia (6) Discovery Pharmaceutical Sciences, Merck, West Point, Pennsylvania, United States (7) Pharmacokinetics, Pharmacodynamics, and Drug Metabolism, Merck, Kenilworth, New Jersey, United States (8) Modeling & Informatics, Merck, West Point, Pennsylvania, United States (9) In Vivo Pharmacology, Merck, West Point, Pennsylvania, United States (10) Neuroscience Discovery, Merck, West Point, Pennsylvania, United States (11) Discovery Chemistry, Merck, Rahway, New Jersey, United States

The alpha 7 nicotinic acetylcholine receptor (α7 nAChR) is a ligand-gated ion channel that is highly expressed in regions of the brain associated with cognition, where it is thought to play a key role in learning and memory. Genetic data and clinical studies with α7 agonists support the hypothesis that activating this target will provide therapeutic

benefit to patients with cognitive disorders, such as Alzheimer's disease (AD). Orthosteric agonists, however, lack selectivity over related receptors, often cause receptor desensitization, and appear to be effective over only a limited exposure range. In contrast, preclinical data suggest that a positive allosteric modulator (PAM) of the alpha 7 receptor should provide improved selectivity, be more resistant to desensitization, and provide efficacy over a broader exposure range. Thus, the goal of our effort was to identify an alpha 7 PAM that was suitable for clinical development. The previous lead molecule, BNC375, demonstrated robust efficacy in preclinical cognition models across a wide exposure range and had a good overall profile, but had suboptimal physicochemical properties and a relatively high projected clinical dose. Lead optimization efforts were guided by CNS multi-parameter optimization scoring and resulted in significant improvements to the pharmacokinetics, off-target selectivity profile, and physicochemical properties of the series. Ultimately, this work led to the identification of a novel, highly potent, orally bioavailable  $\alpha 7$  nAChR PAM with an excellent overall profile and a low projected clinical dose.

## **MEDI 19**

### **Design of clinical candidate eFT226, a first-in-class inhibitor of the RNA helicase eIF4A**

*Christian Nilewski, christian.nilewski@gmail.com, Justin T. Ernst, Peggy A. Thompson, Alan X. Xiang, Chinh V. Tran, Garrick K. Packard, Theodore D. Michels, Paul A. Sprengeler, Boreth Eam, Nathan P. Young, Sarah Fish, Joan Chen, Maria Barrera, Haleigh Howard, Ana Parra, Eric Sung, Jocelyn Staunton, Ivy N. Hung, Gregory S. Parker, Gary G. Chiang, Christopher J. Wegerski, Andres Nevarez, Jeffrey Clarine, Samuel Sperry, Kevin R. Webster, Siegfried H. Reich. eFFECTOR Therapeutics, San Diego, California, United States*

Dysregulated translation of specific mRNAs is an important driver of uncontrolled growth, immune evasion and metastasis in many types of cancer. eIF4A (eukaryotic initiation factor 4A), an ATP-dependent DEAD-box RNA helicase and a key component of the eIF4F complex, plays a crucial role in translational regulation of several oncogenes, rendering it a promising therapeutic target for the treatment of cancer. Flavagline natural products have been shown to inhibit eIF4A by RNA-sequence specific formation of a stabilized eIF4A/RNA/flavagline ternary complex; however, these compounds generally display suboptimal drug-like properties. This presentation describes the design of and physicochemical property optimization in novel flavagline cores to support intravenous delivery, culminating in clinical candidate eIF4A inhibitor eFT226.

## **MEDI 20**

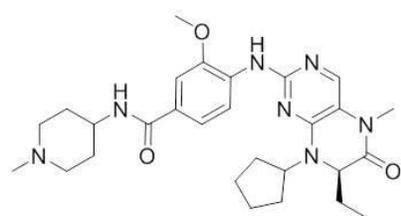
### **Design and synthesis of a dual kinase-bromodomain inhibitor targeting ALK and BRD4**

**Ellen Watts**<sup>1</sup>, [ellen.watts@icr.ac.uk](mailto:ellen.watts@icr.ac.uk), **David Heidenreich**<sup>2</sup>, **Elizabeth Tucker**<sup>1</sup>, **Benjamin Bellenie**<sup>1</sup>, **Stefan Knapp**<sup>2</sup>, **Louis Chesler**<sup>1</sup>, **Swen Hoelder**<sup>1</sup>. (1) The Institute of Cancer Research, London, United Kingdom (2) Goethe University of Frankfurt, Frankfurt, Germany

Neuroblastoma is a paediatric cancer of neural crest origin and is the most common extracranial solid tumour in childhood. In high-risk patients with poor clinical outcome, mutations within the kinase domain of anaplastic lymphoma kinase (ALK), such as ALK<sup>F1174L</sup>, co-segregate with amplification of the *MYCN* gene. Transcription of *MYCN* is directly upregulated by ALK<sup>F1174L</sup>, whilst BRD4, a member of the BET family of transcriptional co-regulators is essential for *MYCN* expression.

Our hypothesis is that a dual ALK-BRD4 inhibitor is beneficial compared with single inhibitors of ALK and BRD4, avoiding the need for combinatorial trials and treatment. The aim of the project is to generate dual ALK-BRD4 inhibitors that target both oncogenic mutations as an effective treatment for high-risk neuroblastoma patients. We chose BI-2536 a known dual PLK-1-BRD4 inhibitor with modest potency against ALK as our starting point. Using structure based design, we prepared and tested analogues with the aims of increasing ALK activity, decreasing PLK-1 activity and maintaining BRD4 activity. The testing of these compounds has provided SAR on how the potency can be modulated at ALK, BRD4 and PLK-1.

This work has led to a series of compounds with significantly improved dual ALK-BRD4 profiles, favourable kinase and bromodomain selectivity and on-target activity in cells. Furthermore our work highlights the challenges of designing and developing dual inhibitors; in particular balancing dual inhibition with the physicochemical properties whilst maintaining selectivity against other bromodomains and kinases.



**BI-2536**

ALK<sup>F1174L</sup> IC<sub>50</sub> = 190 nM

BRD4 K<sub>d</sub> = 37 nM

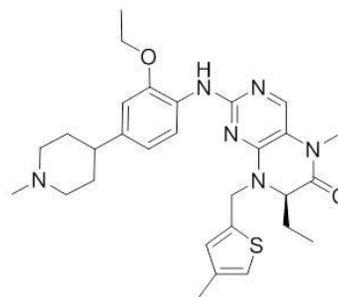
PLK-1 IC<sub>50</sub> = < 2.6 nM



*Improve ALK<sup>F1174L</sup> Potency*

*Maintain BRD4 Potency*

*Decrease PLK-1 Potency*



**CCT368408**

ALK<sup>F1174L</sup> IC<sub>50</sub> = 17 nM

BRD4 K<sub>d</sub> = 44 nM

PLK-1 IC<sub>50</sub> = 130 nM

## MEDI 21

### Design, synthesis, and optimization of 2'2'-cyclic dinucleotides as STING agonists

*Min Lu<sup>1</sup>, szlucifer@gmail.com, Michael D. Altman<sup>2</sup>, Adam Beard<sup>2</sup>, Frank Bennett<sup>2</sup>, Tim Cernak<sup>6</sup>, Wonsuk Chang<sup>2</sup>, Matthew Childers<sup>2</sup>, Spencer Dreher<sup>3</sup>, Chip Lesburg<sup>2</sup>, Chaomin Li<sup>7</sup>, Rui Liang<sup>8</sup>, Jongwon Lim<sup>2</sup>, Hong Liu<sup>2</sup>, Lisa Nogle<sup>2</sup>, Tony Siu<sup>2</sup>, Dietrich Steinhuebel<sup>4</sup>, Brandon Taoka<sup>2</sup>, Quang Truong<sup>2</sup>, Shawn Walsh<sup>2</sup>, Jeremy Presland<sup>2</sup>, Samantha Perera<sup>2</sup>, Saso Cemerski<sup>9</sup>, Jared Cumming<sup>5</sup>, Wes Trotter<sup>2</sup>. (1) Global Chemistry, Merck Research Labs, Boston, Massachusetts, United States (2) Merck, Princeton, New Jersey, United States (3) Process Chemistry, Merck, Metuchen, New Jersey, United States (4) Mail stop BMB 2-136, Merck Co Inc, Boston, Massachusetts, United States (5) K15-MN208, Merck Research Laboratories, Kenilworth, New Jersey, United States (6) Chemistry, University of Michigan, Ann Arbor, Michigan, United States (7) Chemistry, Biogen, Cambridge, Massachusetts, United States (8) Tri-Institutional Therapeutics Discovery Institute, New York City, New York, United States (9) Cue Biopharma, Cambridge, Massachusetts, United States*

Cyclic dinucleotide (CDN) agonists of the adaptor protein STING (Stimulator of Interferon Genes) have recently attracted intense interest due to their structural complexity and their dramatic anti-tumor effects in preclinical mouse models. Similar to the endogenous STING ligand 2'3'-cGAMP, the isomeric CDN 2'2'-cGAMP has been reported to bind STING and induce conformational changes that lead to production of type-I interferons and pro-inflammatory cytokines. Herein we present the team's efforts in design, synthesis and optimization of novel 2'2'-CDNs as a promising class of STING agonists. We demonstrate that, similar to 2'3'-CDNs, intratumoral delivery of a prototype 2'2'-cGAMP analog effects complete tumor regression in a syngeneic mouse tumor model. To enable broad SAR exploration in this series, we sought alternatives to the well-documented, lengthy total syntheses required to prepare CDNs. Employing high throughput experimentation (HTE) techniques, we have discovered and developed novel cyclo-dimerization processes to streamline the synthesis of 2'2'-CDNs, leading to a significantly accelerated design-synthesis-test cycle. Employing molecular modeling and X-ray crystallography, we have elucidated similarities and differences in the binding of 2'2'- and 2',3'-CDNs to STING. Structure based drug design (SBDD) in combination with our improved cyclo-dimerization chemistry further accelerated discovery of structurally differentiated 2'2'-CDNs with favorable in vitro and in vivo activities.

## MEDI 22

### Geopharmaceuticals: New drug scaffolds from Baltic amber

*Elizabeth A. Ambrose, ambrose@umn.edu, Connor McDermott. Medicinal Chemistry, University of Minnesota, Minneapolis, Minnesota, United States*

Amber is a fossilized tree resin produced primarily as an exudate from various species of pine, specifically extinct conifers of the Sciadopityaceae family from the Eocene (~44 million years ago). Although amber has been valued since the Neolithic for its colors and inclusions, and also as a fossilization system for animal and plant species of interest, it may also be a rich source of therapeutic chemical matter – in the emerging field of geopharmaceuticals. Amber has a longstanding tradition of medicinal use over thousands of years, as an analgesic, anti-infective, antifungal, wound healing, anti-inflammatory, anticancer, and immune-boosting agent, especially in the Baltic countries of Lithuania, Latvia and Estonia. Subject to a complex maturation process over many years, in which polymerization, volatile component formation, transformation and evaporation, isomerization, crosslinking, and cyclization all occur, compounds in amber may serve as novel drug scaffolds occupying unexplored chemical space. Yet, very little research has been conducted to identify the bioactive principles in Baltic amber; a comprehensive study of molecules, mechanisms and therapeutic effects is yet to be done. Here we report the results of extraction, analytical, and modeling experiments to isolate and identify such bioactives in Baltic amber samples from Lithuania. In addition to pinpointing molecular targets and mechanisms, we seek to identify new drug scaffolds to meet critical clinical needs, particularly new anti-inflammatory and analgesic therapeutics.

## **MEDI 23**

### **Discovery of a novel series of small molecule modulators of TNF alpha binding and signalling through a novel mechanism of action**

*Tim Norman<sup>1</sup>, tim.norman@ucb.com, Fabien Lecomte<sup>1</sup>, Jeff Kennedy<sup>1</sup>, Bruce Carrington<sup>1</sup>, John Porter<sup>1</sup>, James O'Connell<sup>1</sup>, Alistair Lawson<sup>1</sup>, Rachel Davis<sup>1</sup>, Stephen Rapecki<sup>1</sup>, Boris Kroeplien<sup>1</sup>, Alex Burgin<sup>2</sup>, Tracey Arakak<sup>2</sup>. (1) UCB, Slough, United Kingdom (2) Emerald BioStructures, Bainbridge Island, Washington, United States*

TNF alpha is a cell signalling protein involved in numerous autoimmune disorders. Antibody biologics that bind to TNF alpha have for some time demonstrated the clinical utility of anti-TNF therapy. Despite the clear clinical benefit demonstrated by TNF alpha inhibition, to date no small molecule inhibitor of TNF alpha has entered clinical development. The discovery and development of small molecule inhibitors of TNF alpha has therefore long been considered one of the holy grails of drug discovery. Here we describe the discovery of a novel series of small molecule modulators of TNF alpha binding and signalling with a novel mechanism of action. Fragment screening by SPR initially identified TNF alpha binders which were shown to weakly inhibit binding to TNFR1. The stoichiometry of binding was shown by mass spectrometry to be one small molecule per TNF alpha trimer and this was confirmed by X-ray crystallography. These fragment hits were elaborated to improve binding affinity and function. This initial chemistry, that ultimately formed the foundation for a full medicinal chemistry programme, will be described.

## MEDI 24

### Structure-based drug design towards small molecule interleukin-6 inhibitors

**Daniel Schultz**<sup>1</sup>, *dschultz13@ufl.edu*, Liguang Mao<sup>1</sup>, Guqin Shi<sup>1</sup>, Wei Zhou<sup>2</sup>, Robert Huigens<sup>1</sup>, Chenglong Li<sup>1,2</sup>. (1) Medicinal Chemistry, University of Florida, Gainesville, Florida, United States (2) Biochemistry and Molecular Biology, University of Florida, Gainesville, Florida, United States

Interleukin-6 (IL-6) is a pleiotropic cytokine responsible for the regulation of many different cellular processes, including acute-phase response, cell proliferation, and T and B cell proliferation and differentiation. IL-6 is upregulated in many different disease states, including autoimmune diseases, chronic inflammatory diseases, and cancers, which makes it a desirable target for the treatment of these diseases. Currently, the only approved drug for treating this pathway is tocilizumab, which is a monoclonal antibody. While tocilizumab performs well, it must be given intravenously or via an injection. This, combined with its status as a biologic drug, makes it an unattractive treatment in terms of cost and administration. Therefore, it would be considered advantageous to produce a small molecule inhibitor drug of IL-6, which would decrease the cost and increase the ease of drug administration.

To pursue this end, the Li lab has endeavored to utilize a structure-based approach to design and synthesize a class of small molecule inhibitors. Through docking and molecular dynamics simulations, key pockets and residues in glycoprotein 130 (GP130), to which IL-6 must bind for signaling, have been identified. From this finding, several generations of IL-6 pathway-selective inhibitors have been developed, with the most recent generation possessing single-digit micromolar affinity. The most recent developments have been towards the optimization of the synthesis of these selective inhibitors as well as towards the development of the next generation of inhibitors that will ideally possess sub-micromolar affinity. Cellular studies have confirmed their targeting efficacy and selectivity.

## MEDI 25

### Design and synthesis of novel central nervous system penetrant metabotropic glutamate receptor subtype 2 (mGlu<sub>2</sub>) negative allosteric modulators (NAMs) via scaffold hopping

**Elizabeth S. Childress**<sup>1,2</sup>, *elizabeth.s.childress@vanderbilt.edu*, Joshua M. Wieting<sup>1,2</sup>, Andrew S. Felts<sup>1,2</sup>, Megan M. Breiner<sup>1,2</sup>, Madeline F. Long<sup>1</sup>, Vincent B. Luscombe<sup>1,2</sup>, Alice L. Rodriguez<sup>1,2</sup>, Hyekyung P. Cho<sup>1,2</sup>, Anna L. Blobaum<sup>1,2</sup>, Colleen M. Niswender<sup>1,2,3</sup>, P. J. Conn<sup>1,2,3</sup>, Craig W. Lindsley<sup>1,2,4</sup>. (1) Vanderbilt Center for Neuroscience Drug Discovery, Nashville, Tennessee, United States (2) Pharmacology, Vanderbilt University, Nashville, Tennessee, United States (3) Vanderbilt Kennedy Center, Nashville, Tennessee, United States (4) Chemistry, Vanderbilt University, Nashville, Tennessee, United States

Metabotropic glutamate receptors (mGlu) are a class of g-protein coupled receptors (GPCRs) that signal throughout the central nervous system (CNS) when activated by the neurotransmitter L-glutamic acid (glutamate). This class of GPCRs contains eight members that are divided into three groups according to their gene sequence, agonist selectivity, synaptic localization, and mode of g-protein coupling – group I (mGlu<sub>1</sub> and mGlu<sub>5</sub>), group II (mGlu<sub>2</sub> and mGlu<sub>3</sub>), and group III (mGlu<sub>4</sub>, mGlu<sub>6</sub>, mGlu<sub>7</sub>, and mGlu<sub>8</sub>). Group II mGlu are presynaptic and highly expressed within the brain, particularly in regions associated with cognition and emotion, including the prefrontal cortex, striatum, thalamus, hippocampus, and amygdala. Consequently, mGlu<sub>2</sub> and mGlu<sub>3</sub> have become desirable targets for the treatment of schizophrenia, anxiety, depression, Alzheimer's disease, and Parkinson's disease. While there has been extensive work in the development of selective and drug-like mGlu<sub>2</sub> positive allosteric modulators (PAMs) and mGlu<sub>3</sub> NAMs, with biological studies validating these therapeutic approaches, there is a dearth of examples of selective and drug-like mGlu<sub>2</sub> NAMs within the literature to validate this target's therapeutic potential. Herein, we report the design, synthesis, and biological evaluation of two heterobicyclic series based on either a functionalized pyrazolo[1,5-*a*]pyrimidine-5-carboxamide core or a thieno[3,2-*b*]pyridine-5-carboxamide core. These compounds were developed through a scaffold-hopping approach. This exercise resulted in the development of potent and selective mGlu<sub>2</sub> NAMs with good CNS penetration ( $K_p$ ). In particular, the DMPK profiles of VU6014900 and VU6002035 will be discussed.

## **MEDI 26**

### **Beyond the "Rule of 5" (bRo5): The evolution of efficient drug discovery**

*Christopher A. Lipinski, chris44@aol.com. Melior Discovery, Waterford, Connecticut, United States*

In 1997, we published a very simple computational test to "estimate solubility and permeability in drug discovery and development settings." Our rule of 5 (Ro5) is widely adopted in the pharmaceutical industry to evaluate a molecule's likelihood of poor solubility or poor permeability—and to decrease failure probability in oral drug discovery. However, in the 20 years since the Ro5 came to prominence, drug discovery has undergone significant changes. As targets gradually shift from monomeric protein cavities towards protein-protein interactions (PPI), small molecules that were once the industry mainstay are slowly giving way to larger bRo5 compounds. Accordingly, the Ro5 should not limit ligand chemical space exploration in the new targets. To what extent will medicinal chemistry data search and SAR analysis principles developed for Ro5 targets work for the newer bRo5 targets is an unanswered question.

## **MEDI 27**

### **Use of heterobifunctional molecules that direct targeted protein degradation to explore signaling pathways**

**Christine Loh**, *christine@kymeratx.com*, Joseph Kelleher, Matt Weiss, Veronica Campbell, Karen Yuan, Christine Klaus, Nello Mainolfi. R&D, Kymera Therapeutics, Cambridge, Massachusetts, United States

Targeted protein degradation combines the power of eliminating a disease-causing protein with the advantages of small molecule circulation in the body. Kymera is pioneering and advancing this technology by designing novel heterobifunctional molecules that engage the target protein and the E3 ligases, to direct the target protein to be selectively degraded by the ubiquitin-proteasome system. We have utilized this technology to successfully degrade several protein targets of disease interest. This talk will describe the investigation of the pharmacology of degraders, and the use of degraders and small molecule inhibitors to elucidate the multiple roles of proteins in signaling pathways, that can lead to distinct functional outcomes.

## **MEDI 28**

### **Design, characterization, and function of PROTACs targeting B-cell lymphoma 6 (BCL6)**

**William McCoull**, *William.McCoull@astrazeneca.com*. AstraZeneca, Macclesfield, United Kingdom

B-cell lymphoma 6 (BCL6) inhibition is a promising mechanism for treating haematological cancers but high quality chemical probes are necessary to evaluate its therapeutic potential. Here we report the discovery of potent BCL6 inhibitors that demonstrate cellular target engagement and exhibit exquisite selectivity for BCL6 based on mass spectrometry analyses following chemical proteomic pulldown. The subsequent design of proteolysis-targeting chimeras (PROTACs) targeting BCL6 will be described leading to an optimized BCL6 PROTAC which was shown to significantly degrade BCL6 across a number of diffuse large B-cell lymphoma (DLBCL) cell lines. Furthermore, a sub-cellular compartment analysis will be presented to illustrate how sub-cellular concentrations of both PROTAC and inhibitor relate to observed function.

## **MEDI 29**

### **Co-opting and degrading IAPs**

**Steven T. Staben**, *sstaben@gmail.com*. Genentech Inc, South San Francisco, California, United States

The invention of modalities that promote degradation of target proteins remains an exciting area of academic and industrial research. Proteolysis targeting heterobifunctional molecules that direct non-native proximity of an E3-ubiquitin ligase (most typically CRL2<sup>VHL</sup> and CRL4<sup>CRBN</sup>) to a target protein have received much recent attention. We hypothesize the ability to co-opt additional E3-ubiquitin ligases will expand the utility and applicability of this approach. In this presentation, we will describe

utilization of single-protein E3-ubiquitin ligases XIAP and cIAP. We will show that treatment of cells with heterobifunctional small molecules incorporating highly selective XIAP-BIR2-domain binders and dual XIAP/cIAP-BIR3-domain binders results in rapid and complete degradation of targeted proteins. In addition, the results from these studies led us to invent an unprecedented approach to promoting degradation of the E3s themselves (XIAP or XIAP/cIAP). SAR studies and mechanistic characterization of these novel modalities will be presented in detail.

### **MEDI 30**

#### **Harnessing bioPROTACs to achieve rapid and robust protein knockdown**

**Shuhui Lim**, *shuhui.lim@merck.com*, Jeff Chang, Anthony Partridge. Pharmacology, MSD International GmbH (Singapore), Singapore, Singapore

To tackle historically intractable targets, we have developed a platform employing targeted degradation. Specifically, we have engineered fusion constructs involving two components I) mini-proteins/peptides with high-affinity against therapeutic targets linked to II) truncated E3 ligase receptors. These 'bioPROTACs' have proven broadly successful with many constructs showing robust degradation activity. Currently, we aim to apply this technology as research tools and therapeutically by pursuing delivery strategies of bioPROTAC mRNAs.

### **MEDI 31**

#### **Targeting the undruggable: PROTAC approach to target transcriptional factors**

**Shaomeng Wang**, *shaomeng@umich.edu*. Medicinal Chemistry, Internal Medicine and Pharmacology, Univ of Michigan, Ann Arbor, Michigan, United States

The proteolysis targeting chimera (PROTAC) has gained momentum for the discovery and development of completely new classes of therapeutics for the treatment of human diseases. In this lecture, I will present our latest advancement in the discovery and development of PROTAC molecules to target gene transcriptional factors. I will focus on targeting those traditionally undruggable targets such as STAT3 protein. I will present our major findings in terms of key differences between small-molecule inhibitors and PROTAC degraders in terms of regulation of gene transcriptional and the major advantages for PROTAC degraders over traditional small-molecule inhibitors for transcriptional factors.

### **MEDI 32**

#### **Lead optimisation of a series of RIPK2 PROTACs: Ripping up the rule book**

**John D. Harling**, *john.d.harling@gsk.com*. GlaxoSmithKline, Stevenage, United Kingdom

Targeted protein degradation using proteolysis targeting chimeras (PROTACs) is a rapidly emerging technology in drug discovery. PROTACs are heterobifunctional molecules that simultaneously bind to a target protein and an E3 ligase. The ternary complex formed from this simultaneous binding promotes transfer of ubiquitin proteins from the E2-E3 complex onto surface lysine residues of the target protein. This tags it for recruitment to the proteasome where it is unfolded and proteolysed into small peptide fragments. This mechanism of action physically removes the protein from cells and constitutes a post-translational chemical knock-down.

Many reviews of the area have highlighted potential advantages PROTACs might bring over traditional small molecules, namely:

*Target all protein functions, including scaffolding;*

*Extended PD, disconnected from PK due to protein resynthesis rates*

*Achieve low clinical dose from catalytic action*

*Unlocking 'undruggable' targets via affinity binder*

*Tissue selective pharmacology via E3 ligase distribution*

Evidence to support these potential advantages in the literature has however remained noticeably scant to date. This presentation will describe the lead optimisation of a series of RIPK2 PROTACs. RIPK2 is a serine/threonine kinase that sits downstream of the pattern-recognition receptor NOD2 and is implicated in a number of autoinflammatory diseases. From this lead optimisation campaign, we will highlight data to support the catalytic nature of PROTAC action as well as disconnects that are observed in the PK/PD relationships for slowly resynthesised proteins such as RIPK2. Collectively, these attractive features can lead to low predicted human doses.

## **MEDI 33**

### **Tip48/Tip49 inhibitors: Antipyrene derivatives with diamide linker as potential anticancer agents**

**TOMOAKI HAMADA**<sup>1</sup>, hamada.tomoaki.s6@daiichisankyo.co.jp, Masayuki Ebisawa<sup>1</sup>, Takashi Suzuki<sup>1</sup>, Takeshi Murata<sup>1</sup>, Tomoharu Tsukada<sup>1</sup>, Rie Motoki<sup>1</sup>, Yoshiko Kagoshima<sup>1</sup>, Makoto Hirasawa<sup>1</sup>, Katsunobu Hagihara<sup>1</sup>, Yoshimine Fujii<sup>2</sup>, Ryo Murakami<sup>1</sup>, Takehiko Takata<sup>1</sup>, Koichi Iwanaga<sup>1</sup>, Noriyasu Haginoya<sup>1</sup>, Kouichi Uoto<sup>1</sup>. (1) Daiichi-Sankyo, Tokyo, Japan (2) Daiichi-Sankyo RD Novare, Tokyo, Japan

Tip48 and Tip49 are two related and highly conserved eukaryotic AAA+ proteins (ATPases associated with various cellular activities) with an essential biological function and a critical role in major pathways that are closely linked to cancer. Small molecule inhibitors of Tip48/Tip49 are therefore considered attractive for anticancer drug discovery.

Here we describe our efforts leading to the discovery of the first inhibitors. Hit to lead chemistry identified compound 4 showing potent inhibition of the ATPase activity of Tip48/Tip49 and potent growth inhibitory activity against Ramos cells (human Burkitt's lymphoma) (Figure 1). However, oral administration of compound 4 showed a poor PK profile as well as poor PD response in subcutaneous models of Burkitt's lymphoma probably due to its poor aqueous solubility. As such, our approach is to introduce a

basic group into the molecule so as to improve solubility while maintaining potency. After extensive medicinal chemistry efforts, we finally discovered potent Tip48/Tip49 inhibitors DS71290859 and DS31540255 bearing a solubilizing amino group. Oral dosing of these compounds resulted in a robust tumor growth inhibition associated with clear upregulation of p21 mRNA level in subcutaneous models of Burkitt's lymphoma without any severe toxicity profile at tested dose levels. In addition, they demonstrated acceptable ADME profile and drug-like properties including metabolic stability and solubility.

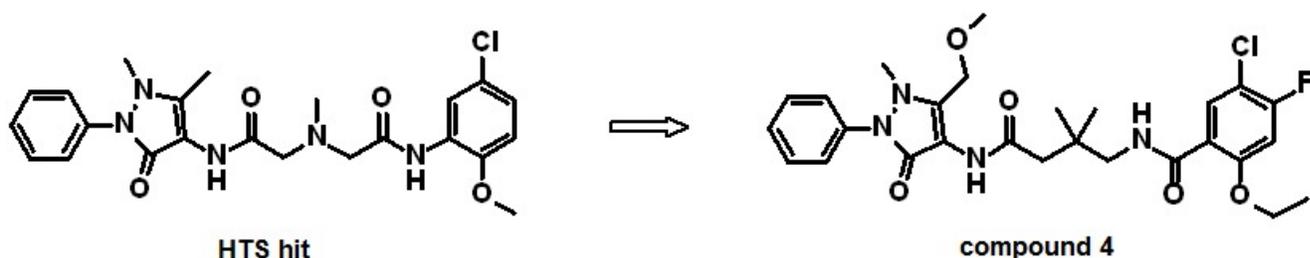


Figure 1. Hit to lead chemistry

## MEDI 34

### Using small molecule adjuvants to combat antibiotic resistant bacteria in cystic fibrosis

**Veronica B. Hubble**, *veronica.hubble@gmail.com*, Christian Melander. Chemistry, University of Notre Dame, Mishawaka, Indiana, United States

Cystic fibrosis (CF) is a life-threatening disease inherited by approximately one in 2,500 American children each year. CF is diagnosed by defects in the *cystic transmembrane conductance regulator* gene, which causes an over-accumulation of thickened mucus that coats the lungs and acts as an ideal breeding ground for bacterial infections. The main cause of fatality in CF patients is directly related to infection with a deadly bacterial pathogen, *Pseudomonas aeruginosa*. Antimicrobials are the main treatment focus for CF due to the patient's vulnerability to infection. The highly adaptive nature of *P. aeruginosa*, in addition to the intrinsic resistance to many antibiotics exhibited by most Gram-negative bacteria, means that multi-drug resistant strains are increasingly prevalent. This results in eradication of pseudomonal lung infections becoming nearly impossible once the infection becomes chronic. New methods to treat pseudomonal infections by both lowering inflammation within the respiratory tract and eradicating the bacteria responsible for this inflammation are greatly needed to better the quality of life for CF patients. Azithromycin is a macrolide antibiotic currently prescribed to CF patients as an anti-inflammatory agent due to its well-documented ability to lower inflammation in patients with known respiratory diseases. However, *P.*

*aeruginosa* exhibits intrinsic resistance to macrolide antibiotics, including azithromycin, making this antibiotic ineffective in eradicating infections caused by this bacterium. Herein, we describe a novel approach for combatting pseudomonal infections through the use of nonmicrobicidal bis-2-aminoimidazole (bis-2-AI) adjuvants that suppress azithromycin resistance in a highly resistant strain of *P. aeruginosa*. Our lead bis-2-AI exhibits a 1024-fold reduction in the minimum inhibitory concentration of azithromycin *in vitro* and increases survival rates in a *Galleria mellonella* model of infection, demonstrating the potential dual use of azithromycin not only as an anti-inflammatory agent, but also as an antibiotic for CF treatment regimens.

## **MEDI 35**

### **Pt-Mal-LHRH attenuates breast cancer tumor growth and metastasis by targeting overexpression of the LHRH receptor**

**Margaret Ndinguri**, [mndinguri@gmail.com](mailto:mndinguri@gmail.com), Carrie Black, Joseph Rollins, Lindsay Calderon. Eastern Kentucky University, Richmond, Kentucky, United States

For 2018, there are an estimated 1,735,350 new cancer cases diagnoses and 609,640 projected cancer death in the United States, of which 268,670 are attributed to breast cancer with 41,400 deaths. Patient survival rate and prognosis depends on the type of cancer, in which, highly aggressive and invasive carcinomas promote the most mortality. In men, prostate cancer is the leading cause of all cancer among men (19%), followed by lung cancer (14%), and colon and rectum cancer (9%). In women, breast cancer is the forefront leading cause of all cancer among women (30%), followed by lung cancer (13%), and colon and rectum cancer (7%). Additionally, in the United States, breast cancer afflicts 1 in 8 women during their lifetime, this high prevalence provides evidence for the need to foster new therapeutic interventional research. While many approved drugs are well-tolerated by most biological systems, numerous drugs could utilize advanced delivery systems to direct them where needed and minimize breakdown as they circulate through the body. A major problems in cancer chemotherapy is the deleterious side effects of anticancer drugs designed to destroy rapidly dividing cells, including those found in healthy tissues. Due to these severe side effects, doctors often resort to dose reduction, treatment delay or discontinuance of therapy. To combat this problem, we have explored targeted delivery of various chemotherapeutics using Luteinizing hormone-releasing hormone (LHRH). We have synthesized Pt-Mal-LHRH, a Carboplatin analog which selectively targets cancer cells and attenuates breast cancer tumor growth. Data on potency and selectivity of Pt-Mal-LHRH will be discussed.

## **MEDI 36**

### **Quinazoline derivatives as potential tubulin polimerization inhibitors**

**Frida Herrera-Vázquez**<sup>1</sup>, [herrerafrida@hotmail.com](mailto:herrerafrida@hotmail.com), Rodrigo Aguayo-Ortiz<sup>2</sup>, Laura Dominguez<sup>2</sup>, Francisco Hernández-Luis<sup>1</sup>. (1) Pharmacy, National Autonomous

*University of Mexico, Mexico, Mexico (2) Physical Chemistry, National Autonomous University of Mexico, Mexico City, Mexico*

Quinazoline is a privileged structure due to its presence in multiple approved drugs and its related biological activities. Analogues of this structure have been associated as potential leads for certain targets inhibitors such as: dihydrofolate reductase and tyrosine kinase receptors, among others. For the latter mentioned, quinazoline is an interesting scaffold structure for the treatment of certain types of cancer. Our research group had previously synthesized quinazoline-2,4,6-triamine derivatives with acceptable cytotoxic activity against different cancer cell lines. Based on these studies, we performed molecular docking studies of our *in-house* compounds in the nocodazole binding site of the  $\beta$ -tubulin and designed 12 novel quinazoline derivatives as potential tubulin polymerization inhibitors.

In this work, we synthesized a set of 10 quinazoline derivatives varying the C6 position with poly-substituted quinolinyl, naphthyl and *meta or disubstituted*-phenyl groups. Our set of compounds were obtained by conventional and microwave aided methods, comparing their differences in terms of reaction yield, time, and chemical reactions involved. Currently, evaluation of these compounds is being determined in 5 different types of cancer cell lines such as: PC-3, HCT-15, MCF-7, MDAMB231 and SKLU. Appraising cellular viability, as a result of this biological assay, several compounds were identified to be very potent against these tumor cellular lines. Therefore, further biological assays will be carried out to determine the half maximal inhibitory concentrations (IC<sub>50</sub>) for the most potent compounds in only a few cell lines. To determine their possible mechanism as potential tubulin depolymerization activity, different experimental assays will be accomplished.

## **MEDI 37**

### **Discovery of DS-6930: A potent selective PPAR $\gamma$ modulator**

*Kunihiko Fujii<sup>2</sup>, fujii.kunihiko.a2@daiichisankyo.co.jp, Tsuyoshi Shinozuka<sup>2</sup>, Tomoharu Tsukada<sup>2</sup>, Eri Tokumaru<sup>2</sup>, Kousei Shimada<sup>2</sup>, Yoshiyuki Onishi<sup>2</sup>, Yumi Matsui<sup>1</sup>, Satoko Wakimoto<sup>2</sup>, Masanori Kuroha<sup>2</sup>, Tsuneaki Ogata<sup>2</sup>, Kazushi Araki<sup>2</sup>, Jun Ohsumi<sup>2</sup>, Ryoko Sawamura<sup>2</sup>, Nobuaki Watanabe<sup>2</sup>, Hideki Yamamoto<sup>2</sup>, Kazunori Fujimoto<sup>1</sup>, Yoshiro Tan<sup>2</sup>, Makoto Mori<sup>2</sup>, Jun Tanaka<sup>2</sup>. (1) Daiichi-Sankyo RD Novare, Tokyo, Japan (2) Daiichi Sankyo Co Ltd, Tokyo, Japan*

The world is suffering from an epidemic of type 2 diabetes mellitus (T2DM). Currently, it is estimated 425 million people get involved diabetes, of which around 90% have T2DM. Such epidemic of T2DM is making a critical impact on healthcare budgets in each country. Thiazolidinedione (TZD) based PPAR $\gamma$  full agonists, pioglitazone (Actos<sup>TM</sup>) and rosiglitazone (Avandia<sup>TM</sup>) proved their utility to improve insulin sensitivity by restoring plasma insulin and glucose levels in T2DM patients. However, they gained considerable attention for their adverse effects such as weight gain, peripheral edema, hepatotoxicity, bone fracture, carcinogenicity and cardiovascular risks. These adverse effects limit the usage of this class of compounds. If such adverse effects are avoided, there is still room

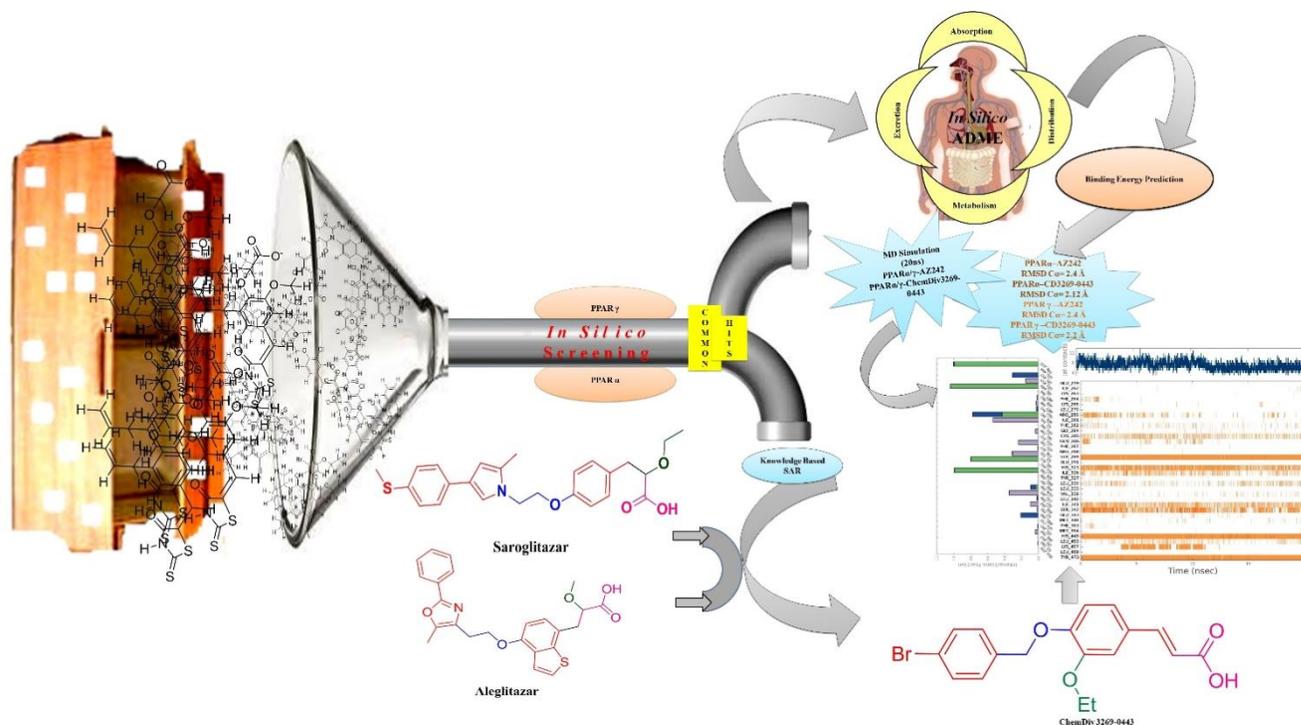
for the development of PPAR $\gamma$  modulators because PPAR $\gamma$  modulation is one of the most attractive therapeutic targets. Based on such concept, the potent selective PPAR $\gamma$  agonist, DS-6930 has been identified. In preclinical studies, DS-6930 demonstrated potent selective PPAR $\gamma$  agonist activity in vitro with potent plasma glucose reduction in vivo. DS-6930 maintained diminished PPAR $\gamma$ -related adverse effects in toxicological evaluation in vivo.

## **MEDI 38**

### **Identification of novel PPAR $\alpha/\gamma$ dual agonist by *in silico* screening and molecular dynamics simulations**

**Virendra Nath**, *vnsrivastav3@gmail.com*, Vipin KUMAR. Department of Pharmacy, Central University of Rajasthan, Ajmer, RAJASTHAN, India

The high incidence of mortality and morbidity due to type 2 diabetes mellitus in the world as well as the increasing risk about the undesirable effects of the current medications have prompted the researcher to develop more potential drug(s) against the disease. The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptors family and take part in a vital role in the regulation of metabolic equilibrium. They can induce or repress genes associated in adipogenesis, lipid and glucose metabolism. In this study, the PPAR $\alpha/\gamma$  agonistic hits were screened by hierarchical virtual screening followed by molecular dynamics simulation and knowledge-based structure-activity relation analysis. The key amino acid residues of binding pockets of both targets PPAR $\alpha/\gamma$  were acknowledged as essential and were found to be associated in the key interactions with the most potential dual hit (ChemDiv-3269-0443). Obtained potential hit have comparable binding energy and ADME. Stability studies using molecular dynamics (MD) simulation of PPAR $\alpha$  and  $\gamma$  complex was performed with the most promising hit. Further, comparative analysis of approved PPAR $\alpha/\gamma$  agonists was done for knowledge-based SAR, which may useful for designing of PPAR $\gamma$  agonistic candidates with hyperlipidemic potential.



Graphical Abstract

## MEDI 39

### Dual CDK4/ARK5 inhibition by ON 123300 for targeting metastatic colorectal cancer

**M Reddy**<sup>1,2</sup>, [dr.reddy@msn.com](mailto:dr.reddy@msn.com), Stephen Cosenza<sup>1</sup>, Saikrishna Divakar<sup>1</sup>, Balireddy Akula<sup>2</sup>, Muralidhar R. Mallireddigar<sup>2</sup>, Premkumar Reddy<sup>1</sup>. (1) Oncological Sciences, Icahn School of Medicine at Mount Sinai, New York, New York, United States (2) Department of Medicinal Chemistry, Onconova Therapeutics Inc., Newtown, Pennsylvania, United States

ARK5 is an AMPK-related kinase often elevated in metastatic colorectal cancers. ARK5 plays an important role in regulating metabolism in colorectal cancers and their ability to metastasize. This study explores the activity of ON 123300, a first in class dual kinase inhibitor targeting CDK4 and ARK5, in various colorectal cell lines.

We examined the effects of ON 123300 on RB and PI3K/AKT pathways in comparison with Palbociclib (PD 0332991) (a CDK4/6 inhibitor that does not have anti-ARK5 activity) in various colorectal cancer cell lines. Comparative analysis showed that ON 123300 and Palbociclib could effectively block CDK4/6 at similar concentrations, while ARK5 pathway was inhibited by ON 123300 only. ARK5 is also known to mediate metabolic changes in tumor cells. Treatment of ON 123300 in ARK5 expressing cells blocked glutamine uptake and ATP production. These metabolic changes are not

seen in cells treated with ON 123300 in non-ARK5expressing cells. These results demonstrate the specificity of ON 123300 to block metabolic changes mediated by ARK5.

We have developed a first in class dual inhibitor of CDK4 and ARK5 which can block proliferation and survival of metastatic colorectal cancers as a single agent. Using ON 123300, we could also block metabolic changes in glutamine uptake and ATP production, and promote tumor cell apoptosis under the clinically relevant conditions. Thus, dual targeting strategy appears to be an effective approach for treating metastatic colorectal cancers.

## **MEDI 40**

### **Activity landscape modeling and molecular dynamics of dual inhibitors of DNMT1 and G9a**

*Edgar Lopez<sup>1</sup>, edgar.lopez.593@hotmail.com, Fernando D. Prieto-Martínez<sup>2</sup>, José L. Medina-Franco<sup>2</sup>. (1) Clinical Chemistry, Veracruzana University, Veracruz, Mexico (2) Department of Pharmacy, School of Chemistry, National Autonomous University of Mexico, Mexico City, Mexico*

Using the concept SMART (structure multiple-activity relationships), herein we analyze 50 compounds synthesized as dual inhibitors of the enzyme lysine methyltransferase (G9a) and DNA methyltransferase 1 (DNMT1). Both enzymes are epigenetic targets with therapeutic interest for the treatment of hematological neoplastic diseases. The SMART analysis was performed with Structure-Activity Similarity Maps and Dual-Activity Difference maps implemented in the server Activity Landscape Plotter (freely available at [www.difacqim.com/d-tools/](http://www.difacqim.com/d-tools/)). Results led to the identification of single target and multi-target activity cliffs. The results were further analyzed at the molecular level using docking and molecular dynamic simulations leading to the identification of structural features that are associated with the dual epigenetic target activity.

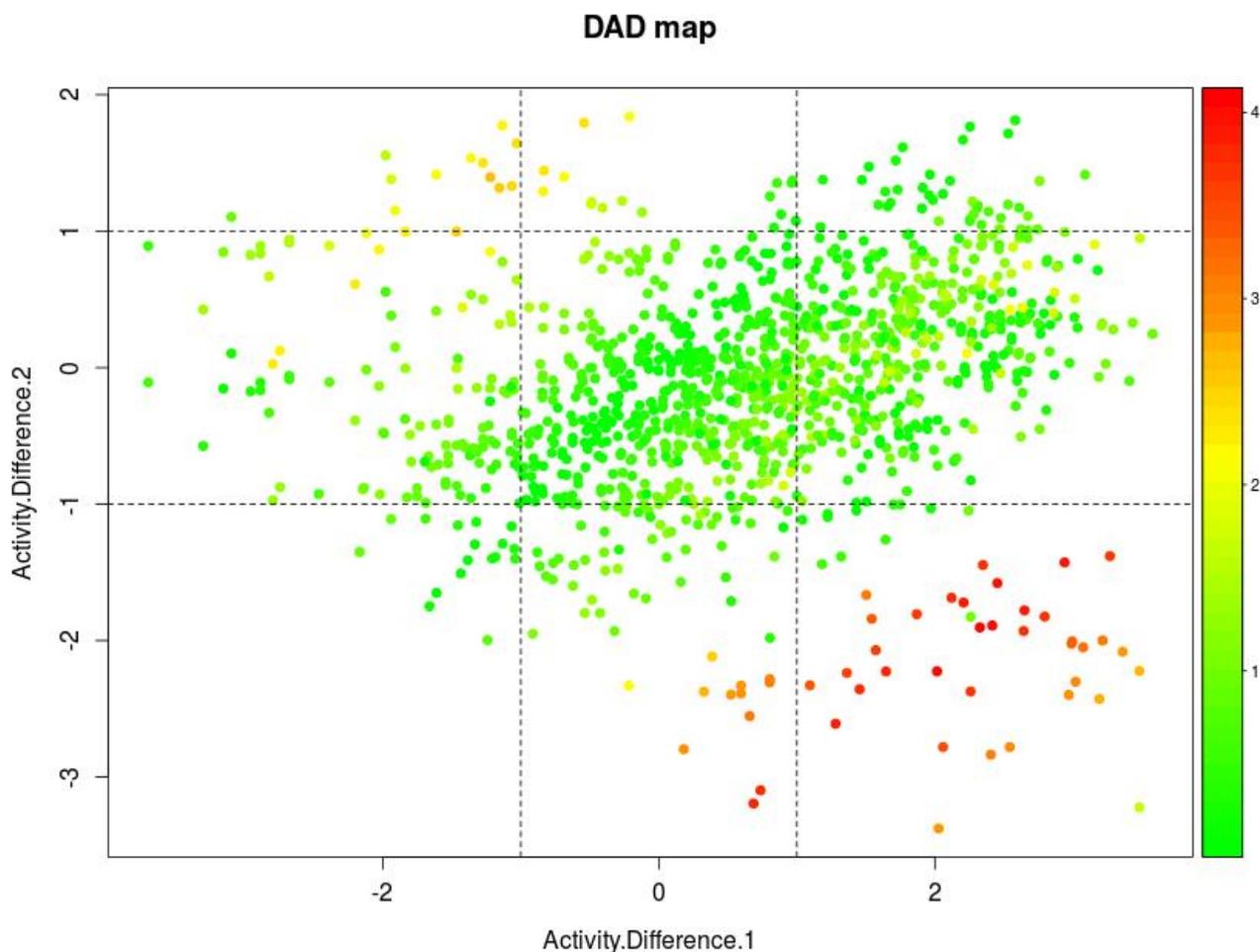


Figure. Dual Activity-Difference (DAD) map of data set. The compounds are colored by their selectivity value, the scale goes from Red (high) to Green (low).

## MEDI 41

### 4-Hydroxybenzthiazole inhibitors of catechol-O-methyltransferase

**Pablo J. De Leon**<sup>1</sup>, [p.deleon@rocketmail.com](mailto:p.deleon@rocketmail.com), James Barrow<sup>1,2</sup>. (1) Drug Discover Division, Lieber Institute for Brain Development, Baltimore, Maryland, United States (2) Pharmacology, Johns Hopkins University, Arnold, Maryland, United States

Catechol-O-methyltransferase (COMT) plays an important role in the termination of dopamine signaling in brain regions such as the prefrontal cortex and hippocampus, making it an important regulator of a number of cognitive and behavioral processes. Therefore, central inhibition of COMT may be useful in the treatment of a variety of conditions associated with dysregulated cortical dopaminergic function like schizophrenia, ADHD, and traumatic brain injury. COMT has two isoforms encoded from the same gene—a membrane-bound form (MB-COMT) and a soluble form (S-

COMT). Genetic and pharmacological studies have demonstrated that the membrane-bound form is especially important in the human brain. Though S-COMT expression predominates in the periphery, MB-COMT has higher expression in the brain. In addition, MB-COMT has a greater affinity for catechol substrates than S-COMT and is likely to metabolize catecholamines at the physiologically relevant concentrations found in the brain. The known brain penetrant COMT inhibitor tolcapone, a nitrocatechol structured compound, requires close liver monitoring due to idiosyncratic hepatotoxicity thus preventing widespread use in psychiatric disorders. Accordingly, we have developed potent and selective non-nitrocatechol COMT inhibitors based on the benzthiazole scaffold and evaluated their pharmacokinetic and brain penetration properties. Small substituents at the 5-position of the benzthiazole were found to increase metabolic stability without sacrificing potency. Compounds with good pharmacokinetics and low P-gp efflux ratios were identified; however, brain penetration was unexpectedly poor. An X-ray co-crystal structure of compound X in the S-COMT active site shows chelation of the active site magnesium similar to catechol-based inhibitors.

## **MEDI 42**

### **MOEsaic: Application of matched molecular pairs to interactive SAR exploration**

*Alain Ajamian, aajamian@chemcomp.com. Chemical Computing Group, Montreal, Quebec, Canada*

SAR analysis can be a huge challenge in a medicinal chemistry program. Often multiple chemical series are pursued in parallel. The number of assays involved in a screening cascade (selectivity, physico-chemical and ADME assays) can lead to the generation of hundreds to thousands of data points for each chemical series. The difficulty in managing the data means the analysis of historical results is seldom done or left to expert users.

- Review what has been made / not made
  - Explore effects of structural change at a certain position
  - Investigate if a trend is general or scaffold dependent
  - Rationalise trends based on calculated or measured properties
  - Determine if different series share the same SAR
  - Is the SAR additive and/or transferable
- These workflows are very difficult to perform with the existing analysis tools available.

## **MEDI 43**

### **Exploiting solvent effects in drug design and optimization**

*Alain Ajamian, aajamian@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 44**

### **Scaffold replacement and 3D ligand optimization applied to the discovery of tyrosine kinase inhibitors**

*Alain Ajamian, aajamian@chemcomp.com. Chemical Computing Group, Montreal, Quebec, Canada*

Point mutations within the BCR-ABL tyrosine kinase domain give rise to imatinib-resistant mutants. Designing next generation ligands to counteract TK inhibitor resistance remains a challenging problem. Scaffold replacement is applied to the imatinib framework where the 2-amino-pyrimidine fragment is exchanged through a scaffold screen to produce a number of related congeneric series. 3D ligand optimization is subsequently performed on one of the hits yielding a structurally related isomer of ponatinib, a known selective high affinity tyrosine kinase inhibitor.

## **MEDI 45**

### **Protocol for validating small molecule structure assignment using calculated <sup>13</sup>C NMR chemical shifts with quantum mechanics and MOE**

*Alain Ajamian, aajamian@chemcomp.com. Chemical Computing Group, Montreal, Quebec, Canada*

Structural assignment of newly synthesized compounds or validation of newly assigned natural products with close isomeric relationships can be quite challenging, especially when the variations in the carbon framework configuration or stereochemistry is epimeric. Here we present a streamlined protocol for calculating and analyzing <sup>13</sup>C chemical shifts of close structurally related compounds. The calculated chemical shifts are then compared with experimental <sup>13</sup>C NMR values to determine and validate the correct structural assignment. The steps in the protocol are as follows: 1) conduct conformational search using LowModeMD, 2) refine conformations using a QM method (e.g. Gaussian), 3) calculate shieldings for each conformation with Gaussian and convert to chemical shifts, 4) determine the weighted Boltzmann distribution for <sup>13</sup>C chemical shifts, 5) compare the calculated <sup>13</sup>C NMR chemical shifts of multiple compound candidates with experimentally derived <sup>13</sup>C values to identify the best match using the NMR Spectral Analysis application in MOE.

## MEDI 46

### First investigation of the antibacterial activity of the combination of 2-hexadecynoic acid and ciprofloxacin against multi-drug resistant *Staphylococcus aureus*

**Solymer Medina**<sup>1</sup>, *medinasoly@gmail.com*, **Tomas Pereles-De-Leon**<sup>1</sup>, *tpereles@yahoo.com*, **Carlimar Ocasio-Malave**<sup>1</sup>, **Damarith Diaz**<sup>1</sup>, **Nestor M. Carballeira**<sup>2</sup>, **David J. Sanabria Rios**<sup>1</sup>. (1) Department of Natural Sciences, Inter American University of Puerto Rico-Metropolitan Campus, San Juan, Puerto Rico, United States (2) Department of Chemistry, University of Puerto Rico, Rio Piedras, San Juan, Puerto Rico, United States

Methicillin-resistant *Staphylococcus aureus* (MRSA) represent a major public health problem worldwide. This bacterium is associated with increased morbidity and mortality when compared with other pathogenic bacteria. The increase of its colonization rate affords the incrimination of infection rates in the population and hospitals leading significant rise in treatment cost. This situation become more complex when MRSA is acquiring resistance towards ciprofloxacin (Cipro), a broad-spectrum antibiotic commonly prescribed for treating bacterial infections. Recently, it was discovered that the 2-hexadecynoic acid (2-HDA) effectively inhibited the antibacterial activity of Gram-positive and Gram-negative bacteria as well as clinical isolates of MRSA (CIMRSA). In the present study, it was investigated whether 2-HDA, in combination with Cipro, improves the antibacterial activity of Cipro in CIMRSA strains. To perform this study, antibacterial activity of either 2-HDA or Cipro in six CIMRSA strains were tested by using broth-dilution susceptibility tests. Subsequently, Cipro-resistant CIMRSA strains were identified in those strains that displayed MIC values higher than 2 µg/mL. Once Cipro-resistant CIMRSA strains were identified, these bacteria were treated with equimolar concentrations of 2-HDA and Cipro. Preliminary results reveal that the combination of 2-HDA and Cipro were 2- to 16-fold more effective than Cipro in inhibiting the growth of five Cipro-resistant CIMRSA strains. In addition, results from *S. aureus* DNA gyrase inhibitory tests suggest that the combination of 2-HDA and Cipro increase the inhibitory effect on the DNA gyrase supercoiling activity when compared with Cipro alone. Results from this study will impact broadly the field by providing the first combinatorial study between Cipro and 2-HDA.

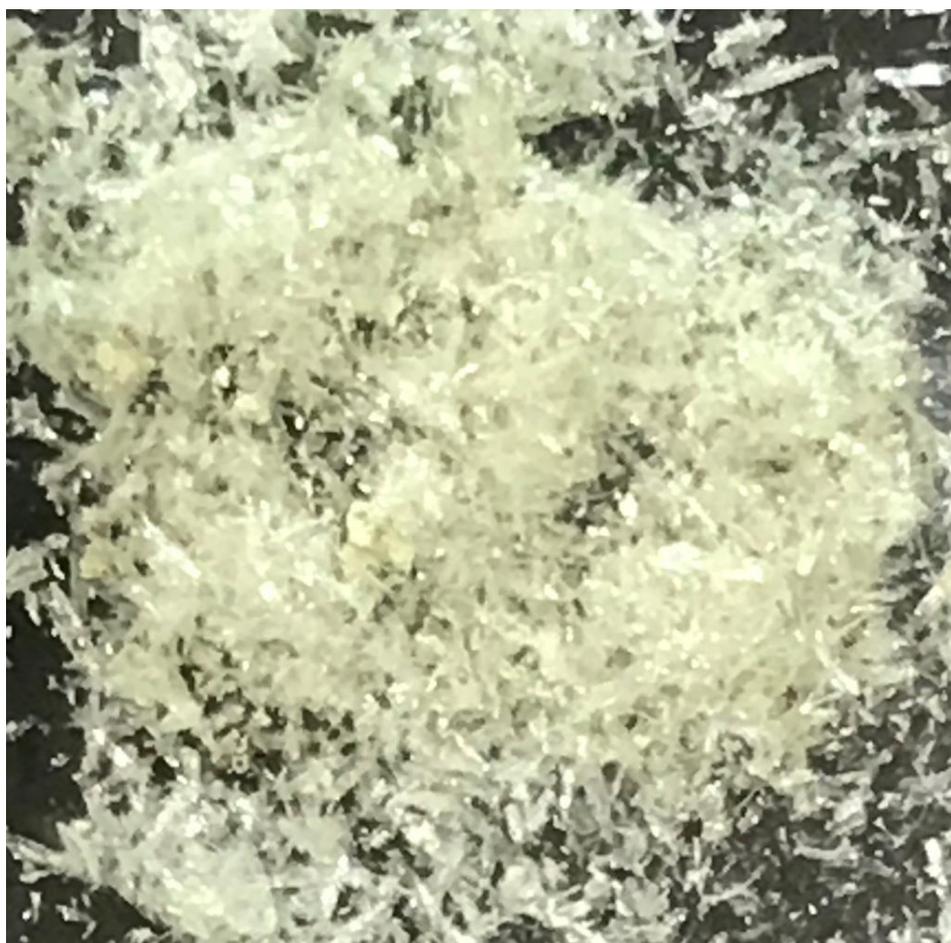
## MEDI 47

### α-Glucosidase inhibition natural products from *Chromolaena odorata*

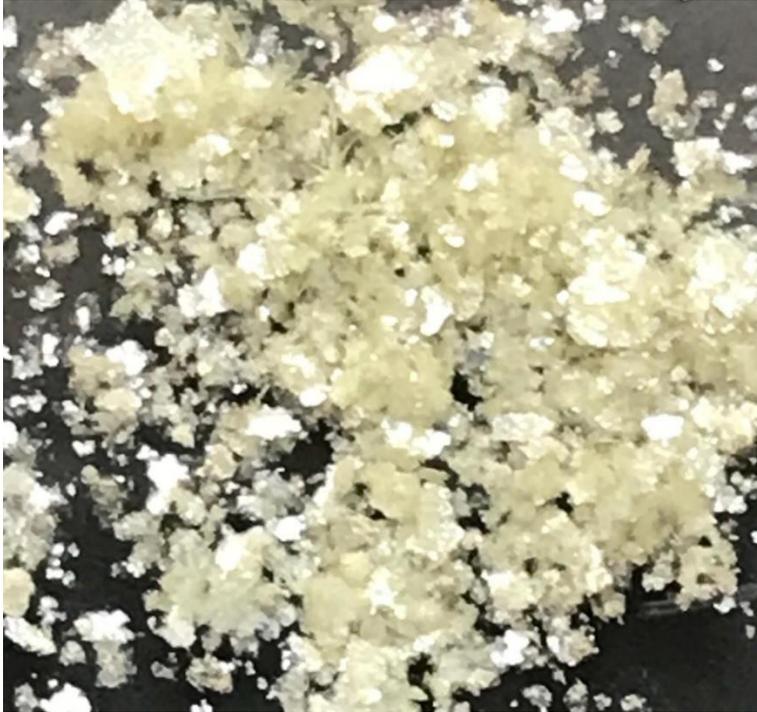
**Chukwuebuka T. Onyema**<sup>2,1</sup>, *ct.onyema@unizik.edu.ng*, **Vincent I. Ajiwe**<sup>1</sup>, **Athar Ata**<sup>2</sup>. (1) Pure and Industrial Chemistry, Nnamdi Azikiwe University, Awka, Awka, Nigeria (2) Chemistry, University of Winnipeg, Winnipeg, Manitoba, Canada

Regardless of the alarming and persistent increase in the number of people globally

affected by the Type II diabetes, there seems to be less natural curative measures except insulin and oral hypoglycaemic drugs (such as acarbose and magillitol) available to assist in tackling this issue. Both of these drugs work by inhibiting the activity of  $\alpha$ -glucosidase, an enzyme involved in type II diabetes. *Chromolaena Odorata*, a medicinally important plant, is used to treat type II diabetes symptoms by traditional healers in Nigeria. The crude extract of this plant was active against  $\alpha$ -glucosidase in our bioassay. Our recent phytochemical investigation of this plant resulted in the identification of flavonoids. In this presentation, isolation and structure elucidation of isolated compounds with the aid of detailed one - and two dimensional NMR spectroscopy will be discussed. Additionally, we will also discuss the bioactivity of these phytochemicals.



Chromolane A from *Chromolaena odorata*



Chromolane B from *Chromolaena odorata*

## **MEDI 48**

### **Polyhydroxyalkanoate-celecoxib nanoparticles for systemic lupus erythematosus therapy with enhanced efficacy and reduced side effects**

*Jin Hu, ncuskhujin@163.com. Research Department, Peking Union Medical College Hospital, Beijing, China*

Autoimmune disorder is a kind of common chronic disease, which is difficult to cure throughout life. Small chemical drugs such as glucocorticoids, immunosuppressors and non-steroidal anti-inflammatory drugs have been widely used for the treatment of autoimmune disorders. However, these small chemical drugs suffer from poor solubility, short circulating half-life and adverse side effects, which lead to poor compliance to patients and limit the widely clinical use. One of the most effective strategies to extend the circulating time is loading drugs into nanocarriers to form nanomedicines, which is of particular interest for cancer and viral diseases therapy but seldom applied in autoimmune disorder treatment. Furthermore, current carriers have many drawbacks such as poor biocompatibility, low stability and over-complicated design. In this study, we developed an easy but general drug delivery platform based on the new polyhydroxyalkanoate terpolymer-poly(3-hydroxybutyrate-co-3-hydroxyvalerate-co-3-hydroxyhexanoate) (PHBVHHx). We reported the first example of PHBVHHx nanoparticle loaded non-steroidal anti-inflammatory drug, ultimately being applied in systemic lupus erythematosus therapy. These nanoparticle are biodegradable, stable, and show improved pharmacokinetics, optimized biodistribution, low systemic toxicity

and excellent in vivo therapeutic efficacy in a MLR/lpr murine model of systemic lupus erythematosus. This delivery system may provide a new and general platform for the development of nanomedicines with enhanced therapeutic efficacy and reduced side effects.

## **MEDI 49**

### **Facial sebum levels and its relationship with the severity of acne vulgaris in African adolescents**

**Omotoyosi N. Ilesanmi**<sup>1,2,3</sup>, *ilesanmiomotoyosi@yahoo.com*. (1) Department of Medicine, University of Ilorin, Ilorin, Nigeria (2) Pharmacology and therapeutics, University of Ilorin, Ilorin, Kwara, Nigeria (3) Chemistry, University of Ilorin, Ilorin, Kwara, Nigeria

#### **Background**

Acne vulgaris is a disease of the pilosebaceous unit which usually develops in adolescence with associated scarring and adverse psychological effects. The relationship between seborrhea and development of acne is still being elucidated in this environment.

#### **Objectives**

To determine the pattern and severity of acne vulgaris, and assess the relationship between sebum levels and the severity of acne vulgaris in African adolescents.

#### **Methodology**

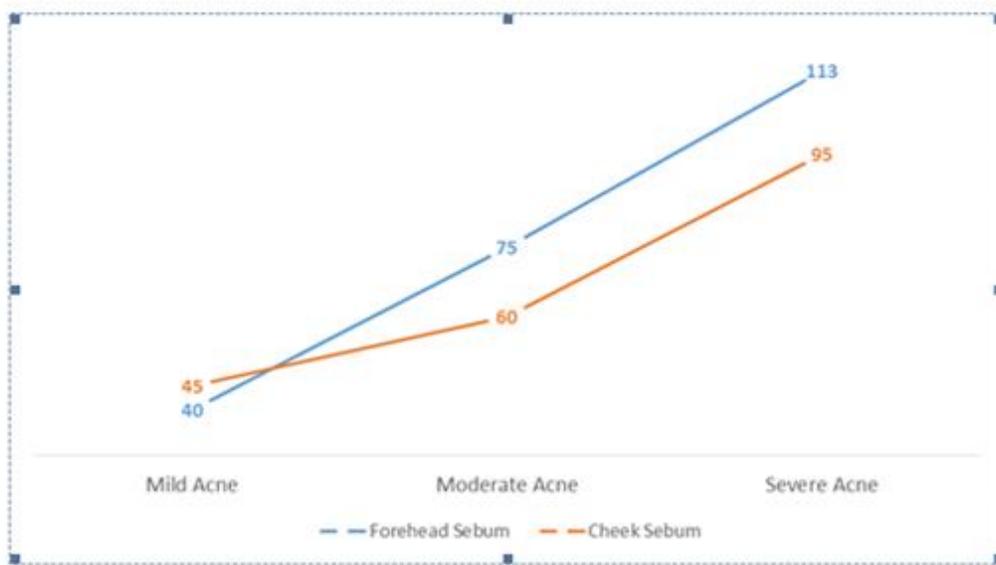
A total of 388 students, between ages 10 and 19 years were recruited for the cross-sectional study in Ibadan, Nigeria in 2013. A sebum analyzer (sebumeter) was used to measure sebum levels in all the subjects and the acne severity was graded, using the Combined Acne Severity Scale (CASS). Data was analyzed with the SPSS V.16

#### **Result**

The prevalence of acne was 81.9% and mild acne was the most prevalent, at 63.3%. The overall median causal sebum level was 50 (20-95) ug/cm<sup>2</sup>. Facial sebum levels were higher in adolescents with acne and there was a positive correlation between increasing sebum levels and the severity of acne vulgaris (p value 0.0012).

#### **Conclusion**

Facial sebum levels correlate directly with the severity of acne vulgaris from this study and reduction of seborrhea with newer and more efficacious sebum lowering drugs will reduce the severity and attendant complications of acne, including scarring and post-inflammatory hyperpigmentation.



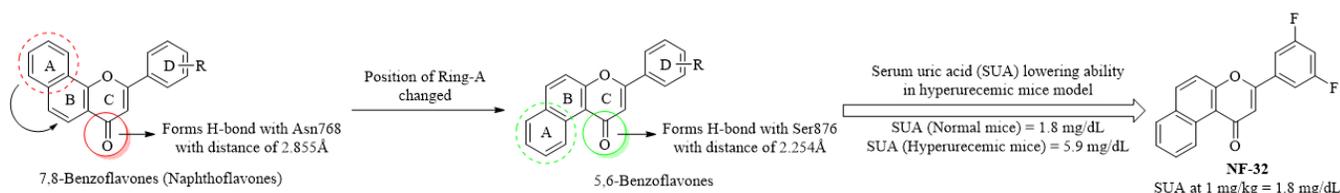
❖ Figure 1. Correlation between acne severity and sebum levels

## MEDI 50

### Benzoflavone derivatives as potent antihyperuricemic agents

**Harbinder Singh**, *singh.harbinder40@gmail.com*, **Jatinder Vir Singh**, **Amritpal Singh**, **Preet Mohinder Singh Bedi**. Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar, Punjab, India, 143005, Amritsar, Punjab, India

Xanthine oxidase (XO) is a molybdoflavoprotein that converts hypoxanthine to xanthine, which further generates uric acid within the human body. The potential increase in serum uric acid level (hyperuricemia) leads to deposition of sodium urate crystals in joints which results in inflammation and pain in joints. In this regard, xanthine oxidase is a selective target for sustaining broad-spectrum chemotherapy in hyperuricemic patients. Keeping in view the various biological attributes of flavones, two series of benzoflavone derivatives were rationally designed, synthesized and evaluated for their xanthine oxidase inhibitory potential. From both the series, eight compounds (**NF-2**, **NF-4**, **NF-9**, **NF-12**, **NF-16**, **NF-25**, **NF-28**, and **NF-32**) were found to exert significant XO inhibition with the  $IC_{50}$  values lower than 10  $\mu$ M. Enzyme kinetic studies revealed that the most potent benzoflavone derivatives (**NF-4** and **NF-28**) are mixed type inhibitors. Docking studies were also performed to investigate the binding interactions of potent molecules with the amino acid residues present in the active site of the enzyme, which confirmed that their favorable binding conformations in the active site of XO can completely block the catalytic activity of the enzyme. Benzoflavone derivatives exhibiting potent enzyme inhibition also showed promising results in hyperuricemic mice model, when tested *in vivo*.



## MEDI 51

### La-DOTA-melanocortin 1 receptor targeting ligand clearance route is controlled by linker polarity

**Hyun Joo Kil**<sup>1</sup>, [blackbeanjh@yahoo.com](mailto:blackbeanjh@yahoo.com), **Narges Tafreshi**<sup>2</sup>, **Darpan Pandya**<sup>3</sup>, **Michael Doligalski**<sup>4,2</sup>, **Chris Tichacek**<sup>5,6</sup>, **Mikalai Budzevich**<sup>7</sup>, **Eduardo Moros**<sup>5</sup>, **Thad Wadas**<sup>3</sup>, **David Morse**<sup>2</sup>, **Mark McLaughlin**<sup>1</sup>. (1) *Pharmaceutical Sciences, West Virginia University Health Science Center, Morgantown, West Virginia, United States* (2) *Cancer Physiology, Moffitt Cancer Center, Tampa, Florida, United States* (3) *Cancer Biology, Wake Forest University Health Science Center, Winston-Salem, North Carolina, United States* (4) *Chemistry, University of South Florida, Lutz, Florida, United States* (5) *Radiation Oncology, Moffitt Cancer Center, Tampa, Florida, United States* (6) *Physics, University of South Florida, Tampa, Florida, United States* (7) *Small Animal Imaging Laboratory, Moffitt Cancer Center, Tampa, Florida, United States*

New treatments for metastatic uveal melanoma are needed because it has a median overall survival of 6-10 months. In our previous studies, we have developed a targeted alpha-particle therapy (TAT) against metastatic uveal melanoma by conjugating <sup>225</sup>Ac-DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate) to MC1R-specific peptide ligand (MC1RL) and demonstrated significantly prolonged survival and decreased metastasis burden in *in vivo* studies. We also have observed <sup>225</sup>Ac-DOTA-MC1RL was cleared through the liver from *in vivo* studies. In order to potentially optimize pharmacokinetic properties of the targeted peptide ligand, we have synthesized a series of targeted ligands with diverse linkers such as glutamic acid (Glu) and lysine (Lys) and measured log D<sub>7.4</sub> of each targeted peptide ligand chelated with <sup>139</sup>La as a non-radioactive surrogate for <sup>225</sup>Ac. We also performed *in vivo* biodistribution (BD) studies of all the targeted peptide ligands with <sup>225</sup>Ac-DOTA to determine the clearance routes. The biodistribution (BD) data from *ex vivo* gamma spectroscopy of a range of tissues, including kidney and liver was compared to log D<sub>7.4</sub> data obtained from the shake-flask assay using LC-MS (liquid chromatography-mass spectrometry) with the <sup>139</sup>La chelate. We found the route of clearance of each conjugate correlated to their relative hydrophilicities, with lower LogD<sub>7.4</sub> values clearing primarily by the renal route and higher values by the hepatic route. This is important because essentially only the targeted tumor and clearance organs receive any significant radiation dose and linker selection can be adjusted to control predominant clearance radiation dosage.

**Table 1.** MC1RL peptides with different linkers

#	Compound	$K_d$ (nM)	Radiolabeling yield, purity (%)	Log $D_{7.4}$	Clearance route
1	DOTA-MC1RL	$0.08 \pm 0.03$	$\geq 95, \geq 99.2$	$-2.14 \pm 0.26$	predominant liver clearance
2	DOTA-Ahx-MC1RL	$0.2 \pm 0.2$	$\geq 97, \geq 99.8$	$-2.59 \pm 0.2$	predominant liver clearance
3	DOTA-di-D-Glu-MC1RL	$0.43 \pm 0.15$	$\geq 95, \geq 99$	$-3.4 \pm 0.27$	liver/renal clearance
4	DOTA-di-D-Lys-MC1RL	$0.06 \pm 0.03$	$\geq 98, \geq 99$	$-3.49 \pm 0.28$	predominant renal clearance
5	DOTA-D-Lys-D-Glu-MC1RL	$0.23 \pm 0.12$	$\geq 95, \geq 99.5$	$-3.88 \pm 0.17$	predominant renal clearance

## MEDI 52

### Purifying complex reaction mixtures via high-performance flash chromatography

**John R. Bickler**, *bob.bickler@biotage.com*. Biotage, LLC, Hampstead, North Carolina, United States

Synthetic chemistry is hard enough; purifying the reaction product can be even more challenging. If your reaction mixture shows you made your target but also many by-products, what do you do? You can resynthesize using different reaction conditions or you can purify using flash chromatography.

For many chemists, purification is the logical option, though it may be a challenge. In this poster, we show how using Thin-layer Chromatography (TLC) and the right flash chromatography tools can overcome the purification challenge.

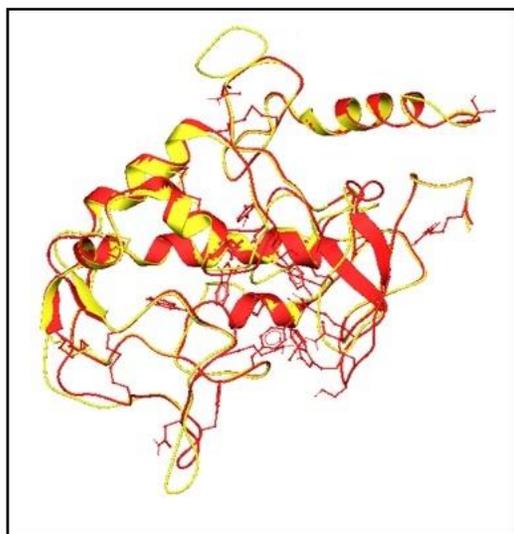
## MEDI 53

### Binding affinity of flavins to riboflavin binding protein using fluorescence spectrometry and isothermal titration calorimetry; and estimated binding energies using computational approaches

**A'Dryanna Jenkins**<sup>1</sup>, *auj475@psu.edu*, **Marquis McMillan**<sup>2</sup>, *mmm7378@psu.edu*, **Julie B. Ealy**<sup>3</sup>. (1) Biology, Penn State Lehigh Valley, Center Valley, Pennsylvania,

*United States (2) Engineering, Penn State Lehigh Valley, Center Valley, Pennsylvania,  
United States (3) Chemistry, Penn State Lehigh Valley, Nesquehoning, Pennsylvania,  
United States*

Modern drug development techniques are attempting to rely more on computational approaches to measure the estimated binding energy and subsequently calculate the binding affinity of ligand-protein interactions. However, computational programs do not always account for all the ligand-protein interactions that contribute to binding affinity and the specific protein crystal structure to perform the calculations may not be available. These difficulties can contribute to discrepancies between wet bench lab techniques and a computational approach. We assessed how ICM-Pro (computational software) performed in the determination of the estimated binding energy of the fluorescent molecules riboflavin, lumichrome, flavin mononucleotide (FMN), and flavin adenine dinucleotide (FAD) with human folate receptor alpha (4LRH.pdb), which is evolutionarily related to riboflavin binding protein (RBP). Structural analysis of RBP and human folate receptor alpha (HFRA) demonstrated a significant similarity between the two proteins thus indicating similar functions. Both RBP and HFRA have been implicated in cancer and researchers have been striving to develop new cancer drugs for these proteins. Two wet bench techniques, isothermal calorimetry titration (ITC) and fluorescence spectrometry were used to assess the binding affinity of the four flavins with RBP. A comparison of the binding affinities and estimated binding energy from the three methods is addressed.



HFRA (4LRH.pdb) in red superimposed on RBP in yellow.  
ICM-Pro was used to superimpose the two similar proteins.

## **MEDI 54**

**Discovery of (3S,4S)-3-methyl-3-(4-fluorophenyl)-4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxyprop-2-yl)phenyl)pyrrolidines as novel ROR $\gamma$ t inverse agonists**

**Bin Jiang**<sup>1</sup>, [bin.jiang@bms.com](mailto:bin.jiang@bms.com), *Jingwu Duan*<sup>1</sup>, *Carolyn A. Weigelt*<sup>1</sup>, *Sylwia M. Stachura*<sup>1</sup>, *Ananta Karmakar*<sup>2</sup>, *Hemalatha Hemagir*<sup>2</sup>, *Dhanya K. Raut*<sup>2</sup>, *Arun K. Gupta*<sup>2</sup>, *Javed Khan*<sup>1</sup>, *John S. Sack*<sup>1</sup>, *Dauh-Rung Wu*<sup>1</sup>, *Melissa Yarde*<sup>1</sup>, *Ding-Ren Shen*<sup>1</sup>, *Michael A. Galella*<sup>1</sup>, *Qihong Zhao*<sup>1</sup>, *Luisa M. Salter-Cid*<sup>1</sup>, *Percy H. Carter*<sup>1</sup>, *T. G. Murali Dhar*<sup>1</sup>. (1) *Research and Development, Bristol-Myers Squibb Company, Princeton, New Jersey, United States* (2) *Bristol-Myers Squibb-Biocon Research Center, Bangalore, India*

The nuclear receptor ROR $\gamma$ t plays a key role in the differentiation and proliferation of T helper 17 (Th17) cells, which are associated with the production of IL-17 and other pro-inflammatory cytokines. Antibodies of IL-17, such as Secukinumab, are approved for the treatment of psoriasis, ankylosing spondylitis, and psoriatic arthritis. Therefore, small molecule inverse agonists of ROR $\gamma$ t may be useful to treat the autoimmune diseases related to the IL-17 pathway. Based on the ROR $\gamma$ t binding mode of previously reported bicyclic sulfonamides from our team, a novel series of (3*S*,4*S*)-3-methyl-3-(4-fluorophenyl)-4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxyprop-2-yl)phenyl)pyrrolidines was designed, synthesized and evaluated as ROR $\gamma$ t inverse agonists. Structure-activity relationship of this series, as well as the X-ray co-crystal structure of a compound-bound ROR $\gamma$ t ligand binding domain, will be presented.

## **MEDI 55**

### **X-ray crystal structure determination of leukotriene A<sub>4</sub> hydrolase in complex with 4-methoxy-ARM1 and characterization of the aminopeptidase enzyme mechanism**

**Kyung Hyeon Lee**<sup>1,3</sup>, [kleep@masonlive.gmu.edu](mailto:kleep@masonlive.gmu.edu), *Greg Petruncio*<sup>1</sup>, *Y. Michael Shim*<sup>2</sup>, *Schroeder Noble*<sup>3</sup>, *Mikell Paige*<sup>1</sup>. (1) *Department of Chemistry and Biochemistry, George Mason University, Manassas, Virginia, United States* (2) *Division of Pulmonary & Critical Care Medicine, University of Virginia, Charlottesville, Virginia, United States* (3) *Bacterial Diseases Branch, Walter Reed Army Institute of Research, Silver Spring, Maryland, United States*

Activation of the aminopeptidase (AP) activity of the leukotriene A<sub>4</sub> hydrolase (LTA<sub>4</sub>H) enzyme with 4-methoxydiphenylmethane (4MDM) promoted resolution of neutrophil inflammation in several murine models of lung injury. 4-(4-benzylphenyl)thiazol-2-amine (ARM1) is a ligand for LTA<sub>4</sub>H AP activity with potential anti-inflammatory properties. Recently, ARM1 has been shown to preserve LTA<sub>4</sub>H AP activity while inhibiting LTA<sub>4</sub>H epoxy hydrolase (EH) activity. Since activation of the LTA<sub>4</sub>H AP activity with simultaneous inhibition of LTA<sub>4</sub>H EH activity is expected to be most desirable for targeting inflammation, a hybrid structure that include structural features from ARM1 and 4MDM was synthesized. Herein, we present the first X-ray crystal structure of the hybrid analogue 4-((2'-aminothiazolyl)phenyl)(4-anisoly)l)methane (4-methoxy-ARM1) in complex with LTA<sub>4</sub>H and the enzyme kinetic mechanisms for the LTA<sub>4</sub>H AP activity in the presence of 4MDM, ARM1, or 4-methoxy-ARM1 (hybrid).

## **MEDI 56**

## **Substrate-dependent hydrolysis by the leukotriene A<sub>4</sub> hydrolase in the presence of 4MDM**

**Kyung Hyeon Lee**<sup>1,3</sup>, *kleep@masonlive.gmu.edu*, **Y. Michael Shim**<sup>2</sup>, **Schroeder Noble**<sup>3</sup>, **Mikell Paige**<sup>1</sup>. (1) Department of Chemistry and Biochemistry, George Mason University, Manassas, Virginia, United States (2) Division of Pulmonary & Critical Care Medicine, University of Virginia, Charlottesville, Virginia, United States (3) Bacterial Diseases Branch, Walter Reed Army Institute of Research, Silver Spring, Maryland, United States

The aminopeptidase (AP) activity of LTA<sub>4</sub>H contributes to an anti-inflammatory phenotype in multiple murine models by catalyzing the hydrolysis of the tripeptide proline-glycine-proline (PGP). Previously, we reported that 4MDM activated LTA<sub>4</sub>H AP activity. Orning and co-workers showed that tripeptides with an arginine residue at the N-terminus were better substrates for LTA<sub>4</sub>H-mediated hydrolysis. Since alanine-pNA has been primarily used to assess LTA<sub>4</sub>H AP activity, we decided to investigate the kinetic mechanisms for LTA<sub>4</sub>H hydrolysis of other substrates such as Arg-pNA and Pro-pNA by LTA<sub>4</sub>H in the presence of 4MDM to determine substrate selectivity with respect to the amino acid residue. Our study demonstrated that 4MDM could either activate the hydrolysis of Pro-pNA by LTA<sub>4</sub>H with one mechanism or inhibit the hydrolysis of Arg-pNA with a different mechanism. Herein, we present distinctive mechanisms in which LTA<sub>4</sub>H enzymatic activity can be modulated by 4MDM depending on the substrate.

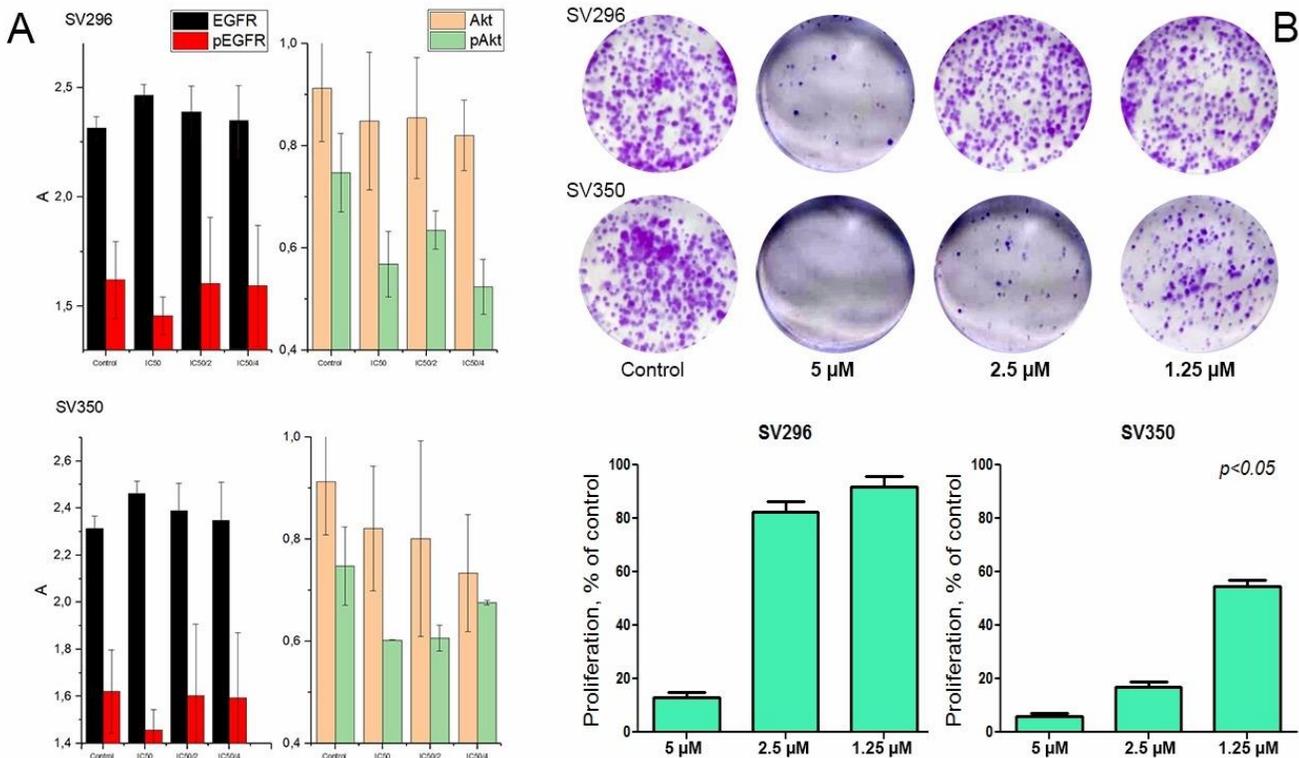
## **MEDI 57**

### **Novel 5-cyanopyrimidine derivatives induces inhibition EGFR signaling pathways in cancer cell lines**

**Dmitriy Khochenkov**<sup>1,2</sup>, *khochenkov@gmail.com*, **Yuliya Khochenkova**<sup>2</sup>, **Alexander S. Bunev**<sup>1</sup>, *a.s.bunev@gmail.com*. (1) Medicinal Chemistry Center, Togliatti State University, Togliatti, Samara Region, Russian Federation (2) Laboratory of biomarkers and tumor angiogenesis mechanisms, N.N. Blokhin National medical research center for oncology, Moscow, Russian Federation

To identify novel EGFR inhibitors with better biological function, a 5-cyanopyrimidine-based compound library containing 48 derivatives was synthesized and compared in the present study. The in vitro cytotoxic activity of all compounds was screened against 7 cancer cell lines (T47D, SK-BR-3, MCF-7, HaCaT, A375, A549, A431) by MTT cell viability assay. The results indicated that all compounds exhibited certain degree of inhibition to cancer cells in range ( $IC_{50}=0.485\text{--}49\ \mu\text{M}$ ), in which compounds SV296 and SV350 displayed excellent cellular activity. To investigate the effect of selected compounds on signal transduction mechanism, we performed In-Cell ELISA colometric assay of EGFR and its downstream signaling pathways: extracellular signal regulated kinase (ERK1/2) and Akt. As shown in Fig. 1A, A549 cells that express high EGFR were treated with  $IC_{50}$  concentrations of SV296 and SV350 and demonstrated a decrease in phosphorylation of EGFR and Akt, but not ERK1/2. Also, we study the effects of SV296 and SV350 on colony-forming potential of A549 and A431 cell line (Fig.1B). Both

compounds significantly inhibited the clonogenicity in A549 and A431 cells. Therefore, selected SV296 and SV350 derivatives may be promising for further development of novel EGFR inhibitors.



## MEDI 58

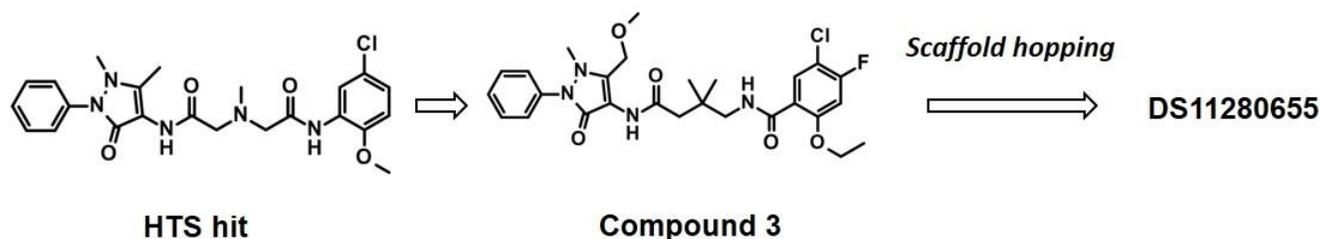
### Tip48/Tip49 inhibitors: Antipyrene derivatives with an oxadiazole ring as potential anticancer agents

**Tomoharu Tsukada**<sup>1</sup>, [tsukada.tomoharu.gz@daiichisankyo.co.jp](mailto:tsukada.tomoharu.gz@daiichisankyo.co.jp), Masayuki Ebisawa<sup>1</sup>, Yuuichi Sugimoto<sup>1</sup>, Toru Taniguchi<sup>1</sup>, Shimpei Hirano<sup>1</sup>, Fumihito Muro<sup>3</sup>, Takashi Suzuki<sup>1</sup>, TOMOAKI HAMADA<sup>1</sup>, Takeshi Murata<sup>1</sup>, Sho Takechi<sup>1</sup>, Rie Motoki<sup>1</sup>, Yoshiko Kagoshima<sup>1</sup>, Makoto Hirasawa<sup>1</sup>, Katsunobu Hagihara<sup>1</sup>, Yoshimine Fujii<sup>2</sup>, Koichi Hashimoto<sup>2</sup>, Takehiko Takata<sup>1</sup>, Ryo Murakami<sup>1</sup>, Koichi Iwanaga<sup>1</sup>, Noriyasu Haginoya<sup>1</sup>, Kouichi Uoto<sup>1</sup>. (1) Daiichi Sankyo Co., Ltd., Shinagawa-ku, Tokyo, Japan (2) Daiichi Sankyo RD Novare Co., Ltd., Edogawa-ku, Japan (3) Kitasato Daiichi Sankyo Vaccine Co., Ltd., Kitamoto-shi, Japan

Tip48 and Tip49 are two related and highly conserved eukaryotic AAA+ proteins (ATPases associated with various cellular activities) with an essential biological function and a critical role in major pathways that are closely linked to cancer. Small molecule inhibitors of Tip48/Tip49 are therefore considered attractive for anticancer treatment. Here we describe our efforts to discover DS11280655 including research background,

structure activity relationship (SAR) and *in vivo* evaluation of the compound. We had already obtained compound 3 through hit-to-lead optimization. Compound 3 showed potent inhibition of the ATPase activity of Tip48/Tip49 and potent growth inhibitory activity against Ramos cells (human Burkitt's lymphoma). However, compound 3 did not show *in vivo* pharmacological activity when dosed as a suspension in 0.5% methylcellulose solution (MC) because of its poor solubility.

To obtain good PK profiles by improvement of solubility, we tried a scaffold hopping approach to convert an amide moiety of the linker part of compound 3 into an oxadiazole ring. This resulted in the discovery of DS11280655, which showed potent *in vitro* activity and a good PK profile when dosed as a suspension in MC. Furthermore, oral dosing of DS11280655 in the suspension exhibited a robust tumor growth inhibition in subcutaneous models of Burkitt's lymphoma without significant body weight loss at tested dose levels.

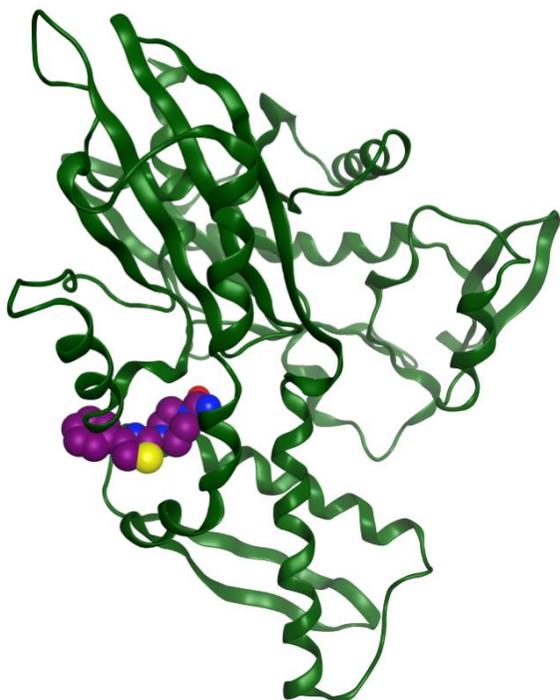


## MEDI 59

### Discovery and characterization of a novel allosteric binding site of HSP70 by fragment based screening

**Suzanne O'Connor**, [suzanne.oconnor@icr.ac.uk](mailto:suzanne.oconnor@icr.ac.uk), Yann-Vai Le Bihan, Rob van Montfort, Ian Collins. Cancer Therapeutics, Institute of Cancer Research, London, United Kingdom

HSP70 is a key molecular chaperone that is overexpressed in many cancers. It has proved difficult to develop clinical inhibitors of HSP70 by traditional drug discovery methods due to the flexible and hydrophilic nature of the ATP binding site and its high affinity for natural nucleotides. The aim of this work was to identify allosteric inhibitors of HSP70 using fragment based drug discovery. A fragment screen, designed to find allosteric inhibitors of HSP70, was carried out using Surface Plasmon Resonance to detect hits. The use of both wild type Tr-HSC70 and an ATP binding site mutant S275W allowed the identification of fragment hits outside of the ATP binding site. The x-ray crystal structure of a fragment hit was solved and found to bind to a previously undescribed allosteric site of HSP70, adjacent to the ATP binding site. Characterization of the binding site and analogues of the fragment hit was carried out using a variety of orthogonal techniques including SPR, CPMG and WaterLOGSY. This new ligand binding site of HSP70 may provide additional opportunities for future drug design.



## MEDI 60

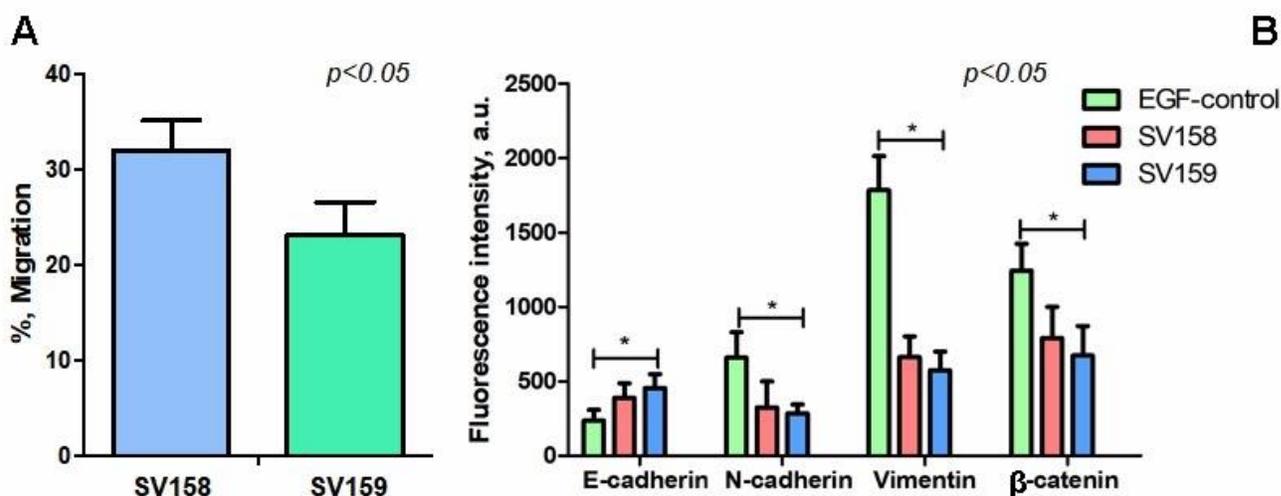
### 5-Cyanopyrimidine-based compounds inhibits migration in A549 lung cancer cells

*Viktoriya Dudanova*<sup>1</sup>, *brglab@gmail.com*, *Dmitriy Khochenkov*<sup>2,1</sup>, *Yuliya Khochenkova*<sup>2</sup>, *Alexander S. Bunev*<sup>1</sup>. (1) Medicinal Chemistry Center, Togliatti State University, Togliatti, Samara Region, Russian Federation (2) Laboratory of biomarkers and tumor angiogenesis mechanisms, N.N. Blokhin National medical research center for oncology, Moscow, Russian Federation

The ability of cancer cells to migration and invasion determine the possibility of malignancy to grow and metastasize. An important step in the metastasis of a tumor is the detachment from the primary tumor and the penetration of cells through the basement membrane. Migrating cells must undergo an epithelial-mesenchymal transition (EMT), resulting in cells losing polarity and cell-cell adhesion mediated by E-cadherin. EGFR-dependent signaling pathway can be involved in EMT via up-regulation of Twist gene expression.

We study novel 5-cyanopyrimidine derivatives SV158 and SV159 with better cytotoxic action on A549 lung cell line on the ability to inhibit the migration of tumor cells and the expression of EMT-related protein markers. To investigate the inhibition of A549 cell migration activity we performed the wound healing assay after 48 hours of cultivation with SV158 and SV159 derivatives (Fig.1A). Both compounds induce a severe inhibition

of cell migration compare to control group (32,1% and 23.2%, respectively). To assess whether inhibition of the migration activity of A549 cell line is associated with the expression of protein markers associated with the EMT, we performed an immunofluorescent analysis of A549 cells treated with SV158 and SV159 for 24 h (Fig.2A). SV158 and SV159 treatment upregulated E-cadherin expression, contrary to EGF-control and reduced N-cadherin, Vimentin and  $\beta$ -catenin in A549 lung cancer cells. Based on these results, it is evident that SV158 and SV159 is not only inhibiting cancer cell migration but affecting expression of EMT-related cell markers.



## MEDI 61

### Methylphenidate (Ritalin®) and synthetic cathinones (bath salts): Are they similar?

**Barkha J. Yadav**<sup>1</sup>, yadavb@vcu.edu, Jose Elti<sup>2</sup>, Richard A. Glennon<sup>1</sup>. (1) Department of Medicinal Chemistry, Virginia Commonwealth University, Richmond, Virginia, United States (2) Department of Physiology and Biophysics, Virginia Commonwealth University, Richmond, Virginia, United States

Synthetic cathinones are popular drugs of abuse that act at monoamine transporters as releasing agents or as reuptake inhibitors. The emergence of >150 new synthetic cathinones has attracted considerable attention from the medical and law enforcement community.  $\alpha$ -PVP (*flakka*), a second generation abused synthetic cathinone, is >50 times more potent than cocaine as a central stimulant and reuptake inhibitor at the dopamine transporter (DAT). Methylphenidate (MP), used for ADHD and narcolepsy, is also a DAT reuptake inhibitor. MP is structurally similar to the cathinones and has been well examined. Available MP literature (on >80 analogs) might help understand the actions of synthetic cathinones.

Our aim is to synthesize and examine MP-*flakka* hybrid molecules to determine if MP SAR can be applied to cathinone SAR. If so, this would reduce efforts to understand the SAR of new synthetic cathinones. Seven hybrid molecules were synthesized and

examined in competition assays at 10  $\mu\text{M}$  against APP+ at hDAT expressed in HEK cells. A complete dose-response study will be available soon. The Spearman rank-order correlation between the preliminary results and the literature-derived MP binding data was found to be 0.955 ( $n = 7$ ).

MP and hybrid molecules were docked at hDAT models derived from the dDAT crystal structure (PDB ID = 4XP4), and binding modes were identified which showed that MP and the hybrid molecules have a common binding pocket where the amine forms a hydrogen bond with Asp79. The carbonyl oxygen atom of the ester in MP also forms a hydrogen bond with Ser422 which is missing in the hybrid analogs.

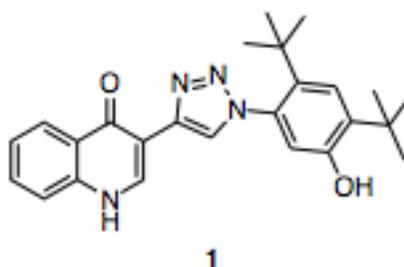
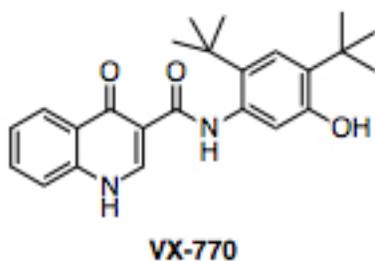
The results suggest that synthetic cathinones bind at DAT in a fashion similar to that of MP. The higher potency of MP relative to the synthetic cathinones might be due to an additional hydrogen bond that is absent in the latter.

## MEDI 62

### Pharmacological analysis of 1,2,3-triazoles as amide bioisosteres in potentiators of the cystic fibrosis transmembrane conductance regulator protein

*Jake Doiron<sup>1</sup>, Jake.Doiron@vikings.berry.edu, Gary W. Breton<sup>1</sup>, Liping Tang<sup>2</sup>, Wei Wang<sup>2</sup>, Steven M. Rowe<sup>2</sup>, Stephen G. Aller<sup>3</sup>, Mark L. Turlington<sup>1</sup>. (1) Chemistry, Berry College, Mount Berry, Georgia, United States (2) Gregory Fleming James Cystic Fibrosis Research Center, University of Alabama at Birmingham, Birmingham, Alabama, United States (3) Pharmacology and Toxicology, University of Alabama at Birmingham, Birmingham, Alabama, United States*

Cystic Fibrosis (CF) is a devastating lung disease resulting from mutations to the cystic fibrosis transmembrane conductance regulator (CFTR) gene that codes for the CFTR anion channel. Mutations to the CFTR gene cause deficits in protein folding, expression, and function. Ivacaftor (VX-770) is an FDA-approved drug that helps restore protein function by increasing the open probability ( $P_o$ ) of the CFTR channel. While VX-770 represents a landmark achievement in CF therapy, the development of improved drug therapies for CF remains a priority. Recently, the 1,2,3-triazole moiety has been successfully used as an amide bioisostere in many medicinal chemistry contexts. In many of these instances, use of the triazole improves drug potency and/or physiochemical properties, suggesting that the substitution of the amide in VX-770 with the 1,2,3-triazole could be beneficial. Here we describe the pharmacological analysis of VX-770 and its corresponding 1,2,3-triazole containing analog **1**. Surprisingly, Ussing chamber analysis across several mutant CFTR cell lines reveals that **1** is unable to improve CFTR function in the cellular assay. However, patch clamp analysis reveals that triazole **1** had similar potency (5nM) to VX-770 (1nM) when exposed directly to the CFTR channel. This finding suggests that triazole **1** is a potent potentiator of CFTR but is unable to reach the CFTR binding site in a cellular system. The loss of activity of triazole analog **1** in the cellular assay provides an important example of the less reported adverse impacts of the 1,2,3-triazole and suggests that caution should be used when considering the use of the triazole as an amide bioisostere.



## MEDI 63

### Development of potent GPR35 agonists with activity at human and rodent receptors

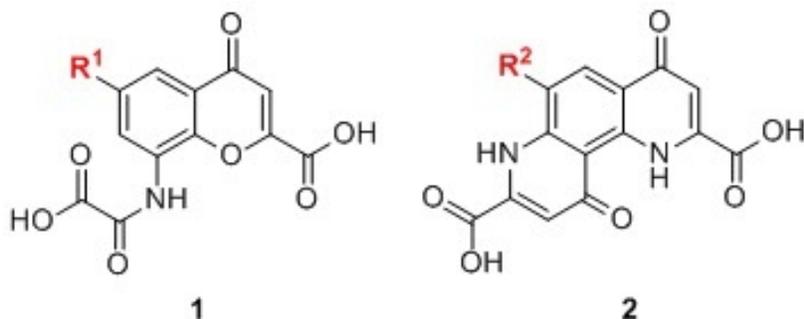
**Lukas L. Wendt**, [lwendt@uni-bonn.de](mailto:lwendt@uni-bonn.de), Dominik Thimm, Christa E. Muller. Pharmaceutical Chemistry, University of Bonn, Bonn, Germany

The G protein-coupled receptor (GPCR) GPR35 is expressed throughout the body, especially in gastrointestinal tissues and on immune cells. GPR35 agonists have potential for the treatment of inflammatory conditions, including inflammatory bowel disease and neuropathic pain, and may also be beneficial for treating hypertension and heart failure.

Several classes of potent agonists for the human GPR35 have been described, including 8-benzamidochromen-4-one-2-carboxylic acid derivatives developed by our group. However, large species differences are typically observed, and the compounds' potency is generally much lower at the rat and especially at the mouse as compared to the human receptor. This hampers target validation and exploration of the GPR35 agonists in animal models.

The present study was aimed at the development of novel GPR35 agonists with high potency at human, rat, and mouse receptors, combined with high selectivity versus related GPCRs.

Chromen-4-one-2-carboxylic acid derivatives (**1**) and related 1,7-phenanthroline-2,8-dicarboxylic acid derivatives (**2**) were synthesized and characterized in GPR35-dependent *beta*-arrestin recruitment assays. Careful analysis of structure-activity relationships served as a basis for optimization to obtain agonists with similar, nanomolar potencies in all three targeted species. The best compounds of the present series showed EC<sub>50</sub> values in the low nanomolar range. All of the compounds were found to be highly selective versus closely related GPCRs including GPR55, determined in the same test system.



## MEDI 64

### Library of covalent, bifunctional small-molecule probes for the targeting of cysteine residues

*Eva Altmann*<sup>1</sup>, [eva.altmann@novartis.com](mailto:eva.altmann@novartis.com), *Shin Numao*<sup>2</sup>, *Peter Ertl*<sup>1</sup>, *Lynn McGregor*<sup>2</sup>, *Steffen Renner*<sup>2</sup>. (1) Global Discovery Chemistry, Novartis, Basel, Switzerland (2) CBT, Novartis, Basel, Switzerland

Selective, covalent probes are of widespread interest in chemoproteomics research, as they have proven to be invaluable tools in studies of protein function. In this contribution, we describe the design and synthesis of a library of new bifunctional tool compounds for chemoproteomic studies and we report initial results from cellular screens with this library.

The compounds contained in this library are composed of a covalent irreversible warhead, a small scaffold and a flexible linker moiety terminating in an alkyne tag. The terminal alkyne moiety enables the rapid conversion of hits to labelling- or pull down agents via click chemistry. As a key benefit, the screening with alkyne labelled compounds circumvents the synthesis of an alkyne labelled probe post hit identification. Accordingly, the primary use of this bifunctional probe library is not in the identification of starting points for further development but in the discovery of tool compounds, which could be used immediately for target identification and validation, target characterization, the development of new assays (e.g. a target-engagement assay) or the construction of imaging probes.

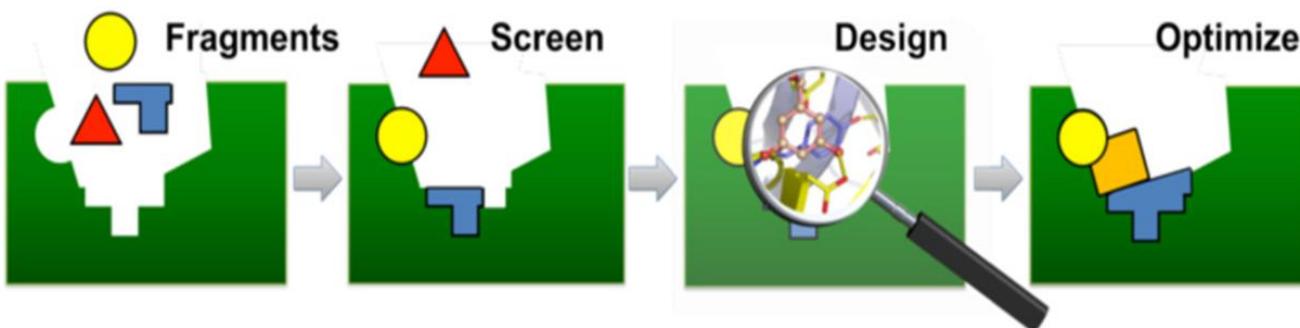
Library design entailed the selection of a diverse set of scaffolds that allowed for easy attachment of an electrophile as well as the incorporation of a linker moiety with an alkyne tag. In addition, scaffold selection was based on the calculated properties of the final probes, such that they were predicted to exhibit a high likelihood for cell permeability. Finally, the preparation of target compounds had to be amenable to parallel synthesis, in order to provide a 384-well plate ready for screening. Initial results from the profiling and screening of this library will be presented.

## MEDI 65

## FRAGNET: A European consortium to advance fragment-based drug discovery and educate its future advocates

**Maikel Wijtmans**, [wijtmans@few.vu.nl](mailto:wijtmans@few.vu.nl), *Jacqueline van Muijlwijk-Koezen, Iwan de Esch. Department of Chemistry and Pharmaceutical Sciences, Vrije Universiteit Amsterdam, Amsterdam, Netherlands*

The European Marie Skłodowska-Curie Innovative Training Network (ITN) FRAGNET has been set up to train a new generation of Early Stage Researchers (ESRs) in the much needed holistic understanding of the many aspects of Fragment-Based Drug Discovery (FBDD) thereby enabling them to use the different methods and technologies to develop the next generation of medicines. In the last ten years, FBDD has proven to be an effective approach towards the discovery of small-molecule compounds (ligands) that can bind to biological target molecules such as proteins and nucleic acids. FBDD projects begin with screening low molecular weight compounds (so-called fragments) against a biological target (most often a protein). This requires a fragment library and an experimental method to detect binding. Once hits have been identified, the structure of hit fragments binding to the target is determined by X-ray crystallography, NMR methods or molecular modelling approaches. The fragments are then evolved to compounds with higher affinity and activity by structure-based design and synthetic chemistry. The resulting compounds can be used as pharmacological tool compounds and starting points for drug discovery. Within FRAGNET, all of these different aspects and steps of FBDD are studied by fifteen ESRs. This poster will give an overview of the consortium setup, the different ESR projects and cross-fertilization strategies.



## MEDI 66

### Aurora-A inhibitor alisertib potentiates VEGFR inhibitors in glioblastoma cell lines

**Kendall Smith**<sup>1,2</sup>, [smithk20@hanover.edu](mailto:smithk20@hanover.edu), *Caroline Mifsud<sup>2</sup>, Cory Zumber<sup>2</sup>, Norman Lehman<sup>2</sup>. (1) Hanover College, Hanover, Indiana, United States (2) University of Louisville, Louisville, Kentucky, United States*

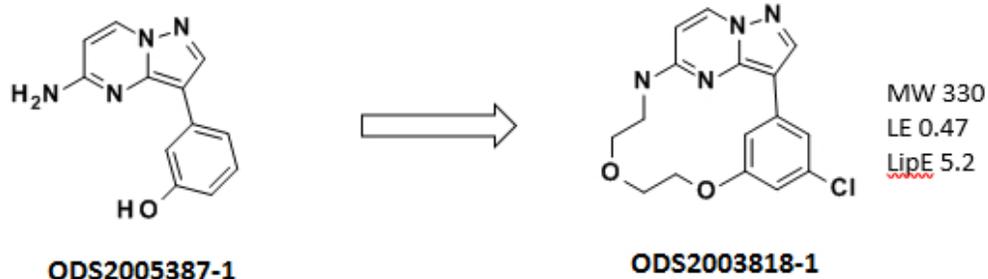
Glioblastoma is the most common primary malignant brain tumor in adults and has a very poor prognosis due to a lack of effective treatment options. Aurora-A (AURKA) is a serine-threonine kinase critical for mitotic progression through its role in centrosome maturation and mitotic spindle assembly. Vascular endothelial growth factor (VEGF) is a regulator of tumor angiogenesis and vasculogenesis. Both AURKA and VEGF are commonly overexpressed in glioblastoma. The AURKA inhibitor alisertib and inhibitors of VEGF have been shown to inhibit glioblastoma cell proliferation *in vitro* and *in vivo*, and both have been used in clinical trials for glioblastoma. Here we tested the ability of alisertib to potentiate the effects of the VEGF receptor (VEGFR) inhibitors cabozantinib and vandetanib using colony formation assays in U1242 and U87 glioblastoma cell lines. Chou-Talalay and Bliss independence models confirmed that this growth inhibition was synergistic in some cases. Annexin V binding assays were performed to examine the extent to which apoptosis could account for the inhibitory effects of these drug combinations in U87 cells. A concentration of alisertib that caused no apoptosis as a single agent was found to increase the induction of apoptosis caused by cabozantinib. These results support further *in vitro* and *in vivo* studies of the combined use of alisertib and VEGFR inhibitors, including possible future clinical trials.

## **MEDI 67**

### **Nanokinib: A cyclic library of hinge binder and chemocentric approach for the discovery of selective kinases inhibitor**

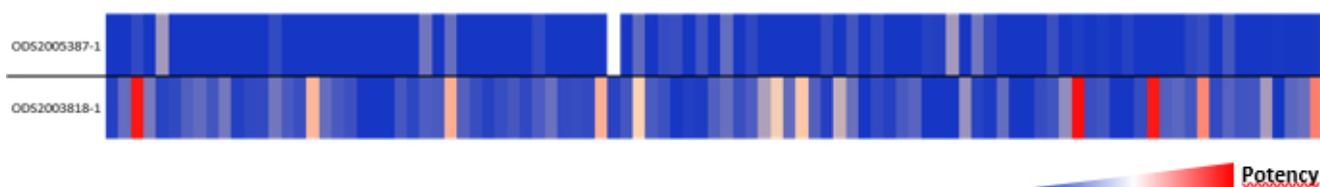
**Nicolas George**, *nicolas.george@oncodesign.com*, Pascal Benderitter, Petra Blom, Marie-Hélène Fouchet, Alexis Denis, Jan Hoflack. Oncodesign, Villebon-sur-Yvette, France

Nanokinib, is a kinase focused library of small macrocyclic hinge binder, designed in a chemocentric approach to identify attractive and selective kinases inhibitors across the kinome. All the compounds are in the drug-like properties space and hit compounds display nM potencies and good selectivity against a small number of kinases. Nanokinib design is based on the macrocyclisation paradigm of known hinge binder scaffolds resulting in tighter binding site recognition, potency and selectivity towards the ATP site. Exploring different lengths and functionalities of the cyclic linker allow populating the conformational space of every template and to identify an optimal match between the size and mobility of the binding site and the macrocyclic ligand. Potent and selective inhibitors of therapeutic kinases such as LRRK2, RIPK2 and ALK1 have been identified by this approach and their optimization to advanced lead will be briefly described.



ALK2	LRRK2	RIP2	SIK2	TGFBR2	IC <sub>50</sub> (nM)	ALK2	LRRK2	RIP2	SIK2	TGFBR2
2465	3001	710	1846	2817		3	152	5	6	87

96 k panel @ 100nM:



“Signature” of first generation compound ODS2003818 (386 kinases panel) shows high potency with selectivity for small subset of kinases

## MEDI 68

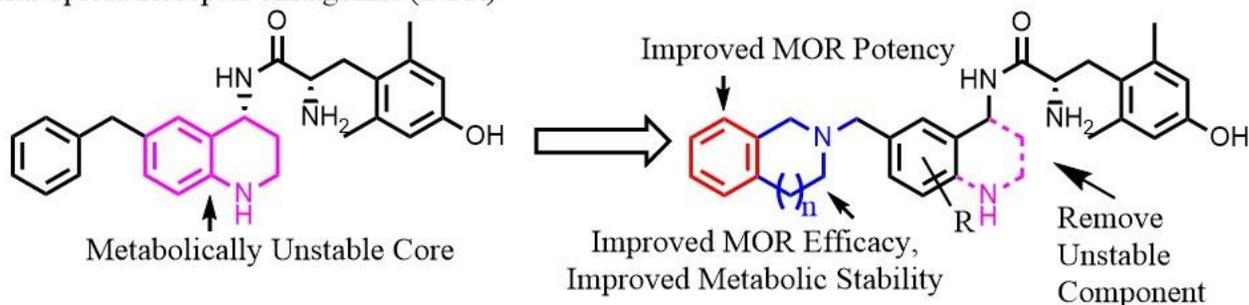
### Structural evolution of novel opioid peptidomimetics with reduced abuse liabilities

**Sean Henry<sup>1</sup>**, seanph@med.umich.edu, **Nicholas Griggs<sup>2</sup>**, **Jessica P. Anand<sup>2</sup>**, **Bryan Sears<sup>2</sup>**, **John R. Traynor<sup>2</sup>**, **Emily Jutkiewicz<sup>2</sup>**, **Katarzyna Sobczyk-Kojiro<sup>1</sup>**, **Henry I. Mosberg<sup>1</sup>**. (1) Medicinal Chemistry, University of Michigan, Ann Arbor, Michigan, United States (2) Pharmacology, University of Michigan, Ann Arbor, Michigan, United States

Opioid analgesics are the gold standard for treating chronic and severe pain. However, they are plagued with negative side effects, including tolerance, dependence, addiction, constipation, and death through respiratory depression. Millions of Americans are given prescription opioids to manage their pain, creating the need for strong opioid analgesics that are devoid of these side effects. A growing body of evidence suggests that agonism at the  $\mu$ -opioid receptor (MOR) with concomitant antagonism at the  $\delta$ -opioid receptor (DOR) can induce opioid mediated analgesia with reduced or abolished side effects. To this end, our lab has developed a bifunctional peptidomimetic series with the aforementioned profile that induces antinociception *in vivo* without tolerance, dependence, or drug-seeking behavior. However, these ligands express poor metabolic stability in mouse liver microsome assays. As such, we have opted to pursue an SAR campaign aimed at improving their pharmacokinetic profile. This SAR campaign has

produced novel structures that are highly potent and efficacious MOR ligands, do not stimulate DOR, are stable in mouse liver microsomes, and show antinociception *in vivo*.

Mu-opioid Receptor Agonist (MOR),  
Delta-opioid Receptor Antagonist (DOR)



## MEDI 69

### Regioselective alkylation, arylation, and heteroarylation of 3-substituted pyrazoles

**Ally Bao**, sbao@wellesley.edu, Adrian Huang. Chemistry, Wellesley College, Wellesley, Massachusetts, United States

Pyrazoles are heterocyclic compounds with two adjacent nitrogen atoms and constitute the core of some leading non-steroidal anti-inflammatory drugs (NSAIDs) such as celecoxib. The common method of preparing pyrazole derivatives involves condensation reactions of monosubstituted hydrazines and 1,3-dielectrophiles. Unfortunately, such an approach can limit the diversity of the N-substitutions on the pyrazole ring as it requires early installation of the N-substituents and often leads to an unpredictable distribution of the N1 and N2 regioisomers. The two regioisomers generally have different bioavailabilities and therefore must be separated through a costly and time-consuming process of chromatography. As a result of these shortcomings, we believe that the N-substitution reaction of 1*H*-pyrazoles would be a more efficient and regioselective route to preparing pyrazole derivatives. Using a variety of 3-substituted pyrazoles and electrophiles of different electronic and stereochemical properties, we have conducted a series of N-alkylation, -arylation, and -heteroarylation experiments. <sup>1</sup>H NMRs, <sup>13</sup>C NMRs, NOESY and X-ray crystallography were used to confirm the structure of the final products. DFT calculations were carried out to help explain the results of the observed regioselectivity. A simple and regioselective reaction protocol has been established to functionalize the pyrazole rings at the N1 position in good to excellent yields. The resulting functionalized pyrazoles are valuable precursors to various 3-substituted pyrazoles through established reactions, which can then be employed to prepare the analogues of drugs such as lonazolac and celecoxib.

## MEDI 70

## **Novel imidazobenzodiazepine GABA<sub>A</sub> receptor $\alpha$ 2/ $\alpha$ 3 selective PAM for the treatment of refractory/resistance epilepsy**

*Lalit K. Golani, golani@uwm.edu, Jeffrey M. Witkin, James M. Cook. Department of Chemistry & Biochemistry, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin, United States*

Benzodiazepines (BDZs) act on the gamma-amino-butyric acid A (GABA<sub>A</sub>) receptor and potentiate the influx of chloride ions via ion channels, imparting a hyperpolarized state to the neuron. The pharmacological action exerted by a BZD is dependent on the discrete subunits of the receptor complex. Convergent evidence from transgenic animals and molecules with selectivity for the proteins required for ligand-gating has suggested that  $\alpha$ 1 comprised GABA<sub>A</sub> receptors mediate tolerance and sedative/ataxic effects of drugs whereas  $\alpha$ 2 and  $\alpha$ 3 comprised GABA<sub>A</sub> receptors mediate anticonvulsant effects of drugs distinct from sedative/ataxic effects. A compelling clinical opportunity exists in the development of  $\alpha$ 1-sparing subtype-selective GABA<sub>A</sub> receptor ligands. These ligands are expected to result in superior treatments for seizures and anxiety without causing amnesia and ataxia, or the propensity for addiction/dependence.

The ligand HZ-166 is an  $\alpha$ 2/ $\alpha$ 3- subtype selective imidazobenzodiazepine that has been reported to effect anticonvulsant activity at non-motor-impairing doses in both mice (maximal electroshock, and PTZ) and rats (maximal electroshock, PTZ, and hippocampal kindling). However the ester functionality of HZ-166 is metabolically labile and results in low bioavailability in the CNS. In an effort to improve metabolic stability, the ester function was replaced with the more stable oxazole bioisostere (KRM-II-81). In the present study, we evaluated the anticonvulsant effects KRM-II-81 across several rodent models of convulsions. KRM-II-81 suppressed hyper-excitation in a network of cultured cortical neurons without affecting the basal neuronal activity. KRM-II-81 was active against electroshock-induced convulsions in mice, pentylenetetrazole (PTZ)-induced convulsions in rats, elevations in PTZ-seizure thresholds, and amygdala-kindled seizures in rats with efficacies greater than that of diazepam. KRM-II-81 was also active in the 6 Hz seizure model in mice. We further evaluated KRM-II-81 in human cortical epileptic tissue where it was found to significantly-attenuate picrotoxin- and AP-4-induced increases in firing rate spikes across an electrode array.

Ester bioisosteres of HZ-166 are thus presented as novel agents for the potential treatment of epilepsy, acting via selective positive allosteric amplification of GABA<sub>A</sub> signaling via  $\alpha$ 2/ $\alpha$ 3-containing GABA<sub>A</sub> receptors.

### **MEDI 71**

**Structure of membrane bound pyrophosphatase from *Thermotoga maritima* in complex with imidodiphosphate and *N*-[(2-aminobenzo[*d*]thiazol-6-yl)methyl]-1*H*-indole-2-carboxamide**

Keni Vidilaseris<sup>4</sup>, Alexandros Kiriazis<sup>1</sup>, Ainoleena Turku<sup>1</sup>, Ayman Khattab<sup>2</sup>, **Niklas G. Johansson**<sup>1</sup>, niklas.johansson@helsinki.fi, Teppo O. Leino<sup>1</sup>, Paula S. Kiuru<sup>1</sup>, Gustav Boije af Gennäs<sup>1</sup>, Seppo Meri<sup>2</sup>, Jari T. Yli-Kauhaluoma<sup>1</sup>, Henri Xhaard<sup>1</sup>, Adrian Goldman<sup>3,4</sup>. (1) Drug Research Program, Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, Helsinki, Finland (2) Malaria Research Laboratory, Immunobiology Research Program, Department of Bacteriology and Immunology, Haartman Institute, University of Helsinki, Helsinki, Finland (3) School of Biomedical Sciences and Astbury Centre for Structural Molecular Biology, University of Leeds, Leeds, United Kingdom (4) Research Program in Molecular and Integrative Biosciences, University of Helsinki, Helsinki, Finland

Membrane-bound pyrophosphatases (mPPases) are large homodimeric integral membrane proteins found in archaea, bacteria, plants and protist parasites. These enzymes couple the hydrolysis of pyrophosphate (PP<sub>i</sub>) to the pumping of H<sup>+</sup> or Na<sup>+</sup> ions, generating an electrochemical potential across a membrane. They are essential for many organisms since PP<sub>i</sub> is a by-product from many biosynthetic pathways and too high concentrations may disturb physiological reactions. Although mPPases can be found in many pathogenic parasites, such as *Leishmania spp.*

(leishmaniasis), *Toxoplasma gondii* (toxoplasmosis), *Trypanosoma spp.* (trypanosomiasis) and *Plasmodium spp.* (malaria), there are no homologous proteins in humans, thereby making them promising drug targets. In addition the structures of the Na<sup>+</sup>-pumping *Thermotoga maritima* mPPase (TmPPase) and H<sup>+</sup>-pumping *Vigna radiata* mPPase were recently solved.

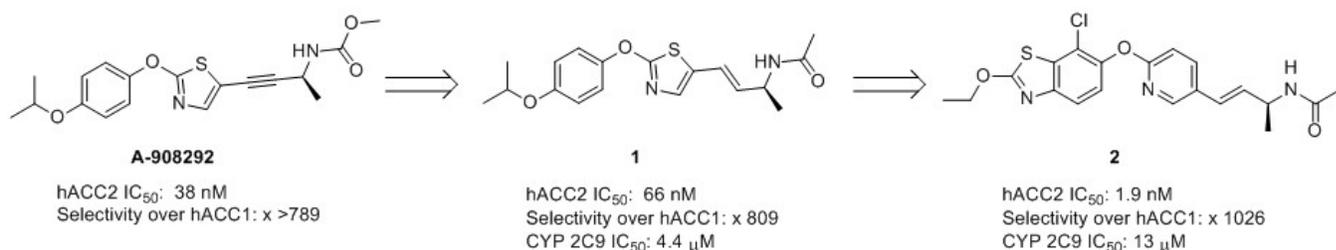
Our aim is to develop novel protozoan mPPase inhibitors capable of disrupting the essential electrochemical potential of the pathogenic parasites in order to decrease their viability. So far only phosphorus-containing inhibitors of mPPases have been reported, limiting their therapeutic utility. Through sequential screening efforts we found novel organic inhibitors of the *Thermotoga maritima* PPase and our best hit compound inhibited the enzyme activity uncompetitively with an IC<sub>50</sub> of 1.7 μM. The binding mode was solved by X-ray crystallography at 3.7 Å resolution together with the substrate analogue imidodiphosphate. As the hit compound binds to the protein monomer near the exit channel, it forms a hydrophobic clamp that locks the enzyme conformation in the closed state thus preventing hydrolysis and sodium pumping activity.

## **MEDI 72**

### **Discovery of a novel olefin derivative as a highly potent and selective acetyl-CoA carboxylase 2 inhibitor**

**Yuji Nishiura**<sup>1</sup>, yuji.nishiura@shionogi.co.jp, Akira Matsumura<sup>2</sup>, Naotake Kobayashi<sup>1</sup>, Atsuyuki Shimazaki<sup>1</sup>, Shingo Sakamoto<sup>1</sup>, Naohisa Kitade<sup>1</sup>, Yutaka Tonomura<sup>1</sup>, Akira Ino<sup>1</sup>, Takayuki Okuno<sup>1</sup>. (1) Shionogi & Co., Ltd, Osaka, Japan (2) Shionogi TechnoAdvance Research Co., Ltd., Osaka, Japan

Acetyl-CoA carboxylase (ACC) is an enzyme which catalyzes the carboxylation of acetyl-CoA to malonyl-CoA, and is considered as a key regulator of fatty acid metabolism. The inhibition of ACC is expected to reduce malonyl-CoA, resulting in decreased production of fatty acid, accelerated oxidation of fatty acid, and improvement of insulin sensitivity. Therefore, ACC is expected as an attractive target for the treatment of metabolic syndrome. There are two characterized isoforms of ACC known as ACC1 and ACC2. Genetic studies have demonstrated that the ACC1 knockout mice show embryonic lethality. In contrast, the ACC2 knockout mice are a normal and healthy phenotype, and have a higher fatty oxidation rate and lower body fat mass than wild-type mice. Therefore, ACC2 selective inhibition may offer a safe therapeutic potential for metabolic syndrome. In our research, novel ACC2 selective inhibitors were identified by the conversion of the alkyne unit of A-908292 to the olefin linker. Modification of the center and the left part on the lead compound **1** improved the inhibitory activity of ACC2 and CYP450 inhibition profile, and afforded a highly selective ACC2 inhibitor **2** which showed potent *in vivo* efficacy in C57BL/6 mice.



## MEDI 73

### New organic photo CORM and the PCBA polymer nanoparticle incorporating it

**Adnan Elgattar**<sup>1</sup>, [aelgattar2012@my.fit.edu](mailto:aelgattar2012@my.fit.edu), **Almutasim Alwagdani**<sup>1</sup>, [aalwagdani2017@my.fit.edu](mailto:aalwagdani2017@my.fit.edu), **thaaer khalil**<sup>1</sup>, [tkhalil2013@my.fit.edu](mailto:tkhalil2013@my.fit.edu), **Hemant Pal**<sup>1</sup>, [hpal2014@my.fit.edu](mailto:hpal2014@my.fit.edu), **Yi Liao**<sup>2</sup>, [yiliao@fit.edu](mailto:yiliao@fit.edu). (1) Biomedical and Chemical Engineering and Sciences Department, Florida Institute of Technology, Palm Bay, Florida, United States (2) Chemistry Dept, Florida Institute of Technology, Melbourne, Florida, United States

Carbon monoxide (CO), although is notorious for its toxicity, is naturally produced gasotransmitter, which plays important roles in regulating cell functions and has shown therapeutic effects in clinic studies. A new organic photo carbon monoxide releasing molecule (CORM), 2,6-di-tert-butyl-4a,9,9a,10-tetrahydro-9,10-[1,2]epicyclobutaanthracene-13,14-dione (DK4), was designed and synthesized features. Previous works showed that the diketone (DK) type CORMs are capable of releasing two molecules of CO under visible-light. However, DKs can be hydrated in aqueous condition and need to be protected by a hydrophobic environment, e.g, micelles. DK4 has two bulky hydrophobic t-butyl groups in its structure, which protect it in from hydration. In addition, DK4 is easier to synthesize comparing to the previously developed hydrophobic DK3. DK4 was loaded to poly(n-butyl cyanoacrylate) (PCBA)

nanoparticle. The release of CO under 470 nm irradiation was confirmed by UV-Vis spectroscopy. Dynamic scattering light (DSL) has determined that the nanoparticle has an average size of 243 nm with PDI of 0.44 D A zeta potential of -42 mv indicated a high stability.

#### **MEDI 74**

##### **First-generation structure-activity relationship studies of 2,3,4,9-tetrahydro-1H-carbazol-1-amines as CpxRA modulators**

*Yangxiong Li<sup>1</sup>, Jessi J. Gardner<sup>1</sup>, jessica.j.gardner-1@ou.edu, Katherine R. Fortney<sup>2</sup>, Stanley Spinola<sup>2</sup>, Adam S. Duerfeldt<sup>1</sup>. (1) Chemistry & Biochemistry, University of Oklahoma, Norman, Oklahoma, United States (2) Microbiology and Immunology, Indiana University School of Medicine, Indianapolis, Indiana, United States*

The urgent need to develop new antibacterials is indisputable, especially for infections resulting from multi- and extensively-drug resistant Gram-negative pathogens. The current arsenal of antibacterials target a limited number of essential enzymes and processes and resistance evolution now outpaces our ability to derivatize known chemotypes and advance the new entities through clinical evaluation. Despite great effort, very few new targets have been identified for Gram-negative bacteria in the last 50 years. In contrast to the dogma that only compounds that completely inhibit cell growth will find clinical utility, one strategy gaining significant traction is to render organisms vulnerable to host immune clearance by targeting virulence determinants or processes that control the expression of pathogenicity. In this context, bacterial two-component signal transduction systems (2CSTS) represent promising targets.

Bacterial 2CSTS are conserved across many drug-resistant Gram-negative pathogens, and are known to regulate gene transcription involved in cell growth, envelope integrity, quorum sensing, and expression of virulence factors. As such, modulation of these systems represents a promising antibacterial strategy and is expected to exhibit complementarity to existing approaches. CpxRA is a 2CSTS found in many drug-resistant Gram-negative pathogens and genetic activation of CpxRA abolishes the virulence of a number of pathogens in murine models. Recently, small molecule 2,3,4,9-tetrahydro-1H-carbazol-1-amines were shown to activate the CpxRA system by inhibiting the phosphatase activity of CpxA. This poster will present our recent progress towards advancing this chemotype to provide chemical probes poised for utilization in advancing the understanding of the biological significance and therapeutic potential of CpxRA and 2CSTS in general. Results will include a discussion of the stereochemical requirements of this chemotype and the features that drive potency.

#### **MEDI 75**

##### **Targeting glioma progression: Human heparanase inhibition by a novel class of non-anticoagulant heparinoids**

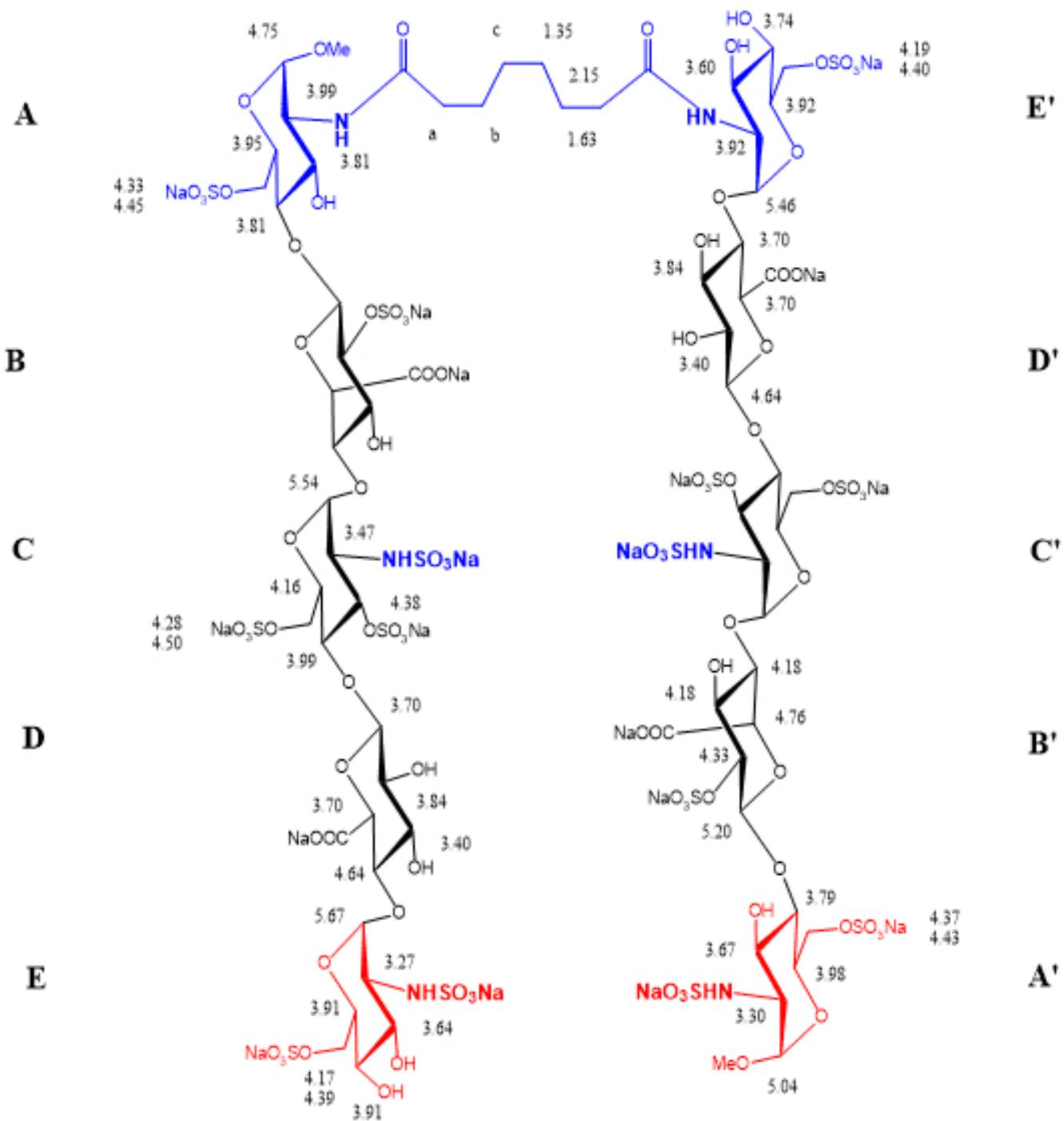
**Sourena Nadji**, *snadji@pharmaren.com*, Raj K. Dhar. Drug Discovery, PharmaRen LLC, Saint Louis, Missouri, United States

Glioblastoma (GBM) is the most common primary malignant brain tumor of adults and confers a poor prognosis. Their high aggressiveness is primarily determined by the active invasion of the growing tumor into surrounding normal brain tissue. The progression depends on both the invasive potential of the tumor cells and the structure of extracellular matrix (ECM). One of key component of ECM and cell surface of almost all mammalian tissues is Heparan Sulfate (HS), which comprises long linear polysaccharide chains with a high negative charge and extremely heterogeneous structure.

In GBM, the expression of HS glycosaminoglycans and the enzymes that regulate their function are altered. The disorganization of the HS biosynthetic system might be potential molecular mechanism for the changes of HS structure and content in tumor microenvironments, thus, contributing to the invasion of glioma cell and the development of the disease.

Human Heparanase (HPSE) that breaks down sugar chains on the cell surfaces in the extracellular space have been shown to confers a growth advantage on glioblastoma cells both *in vitro* and *in vivo*, and therefore suggests that It could be clinically relevant to target HPSE in glioma. Currently, we are developing new class of synthetic heparinoids as potential anticancer agents for the treatment of GBM. To be a drug candidate, these molecules must have HPSE inhibition potency, exhibit much reduced anticoagulant characteristics, and more importantly, to reach the central nervous system (CNS).

In this poster, we are demonstrating data for the preparation and the inhibition of HPSE by one of the members of this class of heparinoids as depicted below.



MEDI 76

Azulene-based compounds targeting orexin receptors

Teppo O. Leino<sup>1</sup>, teppo.leino@gmail.com, Ainoleena Turku<sup>1,2</sup>, Jari T. Yli-Kauhaluoma<sup>1</sup>, Jyrki P. Kukkonen<sup>2,3</sup>, Henri Xhaard<sup>1</sup>, Erik Wallen<sup>1</sup>. (1) Division of Pharmaceutical

*Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, Helsinki, Finland (2) Department of Veterinary Biosciences, Faculty of Veterinary Medicine, University of Helsinki, Helsinki, Finland (3) Department of Physiology, Faculty of Medicine, University of Helsinki, Helsinki, Finland*

The orexin system consists of two G protein-coupled orexin receptors, OX<sub>1</sub>R and OX<sub>2</sub>R, and their activating orexin peptides, orexin-A and orexin-B. The system is essential in sleep-wake regulation, and therefore the orexin receptors provide a promising clinical target to treat insomnia and narcolepsy by antagonism and agonism, respectively. In recent years, the research has focused on the successful development of orexin receptor antagonists. However, at the same time agonists have gained only scant attention. The existing agonists are mostly peptides, which are generally known to be unsuitable therapeutic molecules. Only one series of effective non-peptide orexin receptor agonists has been published to date. Thus, there is an urgent need for the development of orexin receptor activating ligands.

To discover novel ligands for orexin receptors, we first developed efficient synthetic routes to access diverse 1,3,6-trisubstituted azulenes. Next we designed a virtual library consisting of 70 000 azulene-based compounds with substituents in the 1-, 3- and 6-position, which were accessible with our synthetic methods. After docking the database to the three-dimensional structure of OX<sub>2</sub> receptor and visual examination of the top-scoring compounds, we synthesized a series of di- and trisubstituted azulenes. We were able to identify new orexin receptor ligands: antagonists with  $K_i$  values in the low micromolar range, as well as weak agonists. We also discovered compounds potentiating the orexin-A response to OX<sub>1</sub> receptors two-fold at 10  $\mu$ M. Our results offer an interesting starting point for further development of antagonists, agonists and potentiators for orexin receptors.

## **MEDI 77**

### **PPE51-mutation effect the sensitivity of *Tubercle bacilli* to selected thio-sugars**

**Zbigniew J. Witczak**<sup>1</sup>, [zbigniew.witczak@wilkes.edu](mailto:zbigniew.witczak@wilkes.edu), *Malgorzata Korycka-Machala*<sup>2</sup>, *Anna Brzostek*<sup>2</sup>, *Paulina Borowka*<sup>2</sup>, *Dominik Strapagiel*<sup>3</sup>, *Jaroslaw Dziadek*<sup>2</sup>. (1) Dept of Pharm SCI Sch of Phar, Wilkes Univ, Wilkes Barre, Pennsylvania, United States (2) Institute of Medical Biology, Polish Academy of Science, Lodz, 93-232, Poland (3) Department of Molecular Biophysics, Biobank Lab, Lodz, 93232, Poland

In our previous study we have evaluated the bactericidal activity of thio-functionalized carbohydrate derivatives (1-3). A few of the investigated compounds presented a potent activity against tubercle bacilli (*Mtb*), the causative agent of tuberculosis. The compounds affecting the growth of mycobacteria were either thiodisaccharides or thioglycosides. All of these compounds were able to inhibit the growth of *Mtb* deposited within human macrophages.

Here, we have selected spontaneous mutants displaying resistance against investigated thiosugars. The resistant-mutants selected in three independent experiments were

subjected to the genome analysis using next generation sequencing (NGS, MiSeq Illumina). Five of six analyzed mutants, resistant to high concentrations of the tested chemicals, carried nonsynonymous mutations in the *ppe51* gene (named after their N-terminal Pro-Pro-Glu (PPE) motifs). Next, the *Mtb ppe51* mutants were transformed with plasmid DNA carrying a wild type copy of *ppE51* resulting in the reversal of the resistant phenotype to the wild type level.

The effect of PPE51 protein depletion, the uptake of thiosugars by wild type and *ppe51 Mtb* mutants, as well as, the interaction of PPE51 and the investigated compounds were also evaluated in this work.

## **MEDI 78**

### **Progress towards orally bioavailable, potent, and selective small-molecule inhibitors of CD73 for immunooncology**

*Rhiannon Thomas-Tran*<sup>1</sup>, *Erick Lindsey*<sup>1</sup>, *Kenneth Lawson*<sup>1</sup>, ***Joel Beatty***<sup>1</sup>, *jbeatty@arcusbio.com*, *Jenna Jeffrey*<sup>1</sup>, *Jeremy Fournier*<sup>1</sup>, *Debashis Mandal*<sup>1</sup>, *Xuelei Yan*<sup>1</sup>, *Samuel Drew*<sup>1</sup>, *Nigel Walker*<sup>1</sup>, *Susanne Moschütz*<sup>2</sup>, *Norbert Sträter*<sup>2</sup>, *Ada Chen*<sup>1</sup>, *Manmohan Reddy Leleti*<sup>1</sup>, *Jay Powers*<sup>1</sup>. (1) Arcus Biosciences, HAYWARD, California, United States (2) Leipzig University, Leipzig, Germany

Extracellular adenosine (ADO) is present in high concentrations within the tumor microenvironment (TME). ADO is a potent inhibitor of T cell and NK cell activation, resulting in suppression of immune function. The generation of ADO is dependent upon the ectonucleotidases CD39 (transforms ATP to AMP) and CD73 (transforms AMP to ADO). Inhibition of CD73 represents a promising therapeutic approach for preventing ADO-mediated immunosuppression in the TME. Here we present the discovery of a novel class of small molecules that are capable of inhibiting CD73, starting from a high throughput screening hit. Several potent small-molecule CD73 inhibitors have been co-crystallized with recombinant human CD73. They have been found to bind to the closed form of CD73 and to occupy the adenosine binding pocket, maintaining the same  $\pi$ - $\pi$  stacking interaction observed with the CD73 inhibitor AMPCP. This class of molecules also demonstrates a key hydrogen bond with CD73 residue ASP506 to provide a drastic improvement in CD73 inhibition. Compounds exhibit potent CD73 inhibition in multiple biochemical and cell-based assays, providing IC<sub>50</sub> values of less than 20 nM against both soluble and membrane-bound CD73. Inhibitors have also been screened against various NTPDases as well as the adenosine receptors and were found to be highly selective for CD73. Select molecules do not show significant inhibition of the major CYP450 isoforms. Pharmacokinetic properties in rodents indicate the potential for oral bioavailability with low to moderate clearance. Structure-activity relationships, X-ray co-crystal structural characterization, and preclinical pharmacokinetic parameters for this series of inhibitors will be presented.

## **MEDI 79**

## **Discovery and characterization of potent and selective small-molecule inhibitors of ecto-nucleotidase CD73 for cancer immunotherapy**

**Ehesan U. Sharif**<sup>1</sup>, *esharif@arcusbio.com*, **Kenneth Lawson**<sup>1</sup>, **Jarek Kalisiak**<sup>1</sup>, **Erick Lindsey**<sup>1</sup>, **Eric Newcomb**<sup>1</sup>, **Brandon Rosen**<sup>1</sup>, **Nigel Walker**<sup>1</sup>, **Lixia Jin**<sup>1</sup>, **Emma R. Scaletti**<sup>2</sup>, **Norbert Sträter**<sup>2</sup>, **Ada Chen**<sup>1</sup>, **Manmohan Reddy Leleti**<sup>1</sup>, **Jay Powers**<sup>1</sup>. (1) *Arcus Biosciences, Inc., Hayward, California, United States* (2) *Leipzig University, Leipzig, Germany*

Adenosine (ADO) is a potent inhibitor of T cell and NK cell activation and is present in high concentrations in the tumor micro-environment (TME), resulting in an immunosuppressed phenotype. In the TME, generation of ADO relies on the sequential hydrolysis of ATP by two ecto-nucleotidases, CD39 (ATP→AMP) and CD73 (AMP→ADO). Inhibition of CD73 eliminates a major pathway of ADO production and can reverse ADO-mediated immune suppression. We have developed a novel series of potent and selective CD73 inhibitors via interrogation of structure activity relationships (SAR) and structure-based drug design. Key molecular interactions were identified from high resolution X-ray structure data of select inhibitors bound to human CD73. These inhibitors were found to occupy the adenosine pocket and form an array of hydrogen bonds with CD73 residues D506, R354, and N390. Furthermore, a strong hydrophobic  $\pi$ -stacking interaction between two phenylalanine residues (F417 and F500) and coordination of the di-zinc catalytic center was integral to retain high potency. A001202, a representative member of this series, potently inhibits soluble and membrane-bound CD73 ( $IC_{50}$  = 0.86 and 2.6 nM, respectively). Similar potency was measured in cell lines ( $IC_{50}$  = 0.55 nM, SKOV-3). A001202 exhibits a favorable preclinical profile. A001202 is >10,000-fold selective against related ecto-nucleotidases (NTPDase 2,3,8 and CD39), does not inhibit the major CYP450 isoforms, and its pharmacokinetic properties in rodents are characterized by low clearance and a long half-life. These efforts have expanded the understanding of the structural underpinnings of small-molecule CD73 inhibition.

### **MEDI 80**

## **Discovery of SAM competitive and non-nucleoside derivative PRMT5 inhibitors with potent antitumor activity**

**Xiaozhi Yang**<sup>1</sup>, *moon.xyang@gmail.com*, **Wei Zhou**<sup>2</sup>, **Chenglong Li**<sup>1</sup>. (1) *Medicinal Chemistry, University of Florida, Gainesville, Florida, United States* (2) *UNIVERSITY OF FLORIDA, Gainesville, Florida, United States*

Protein arginine methyltransferase 5 (PRMT5), the major type II arginine methyltransferase, has been reported to have a series of bioactive functions during multiple cellular processes including tumorigenesis. Although the mechanism of PRMT5 related to tumorigenesis is still unclear, S-adenosylmethionine (SAM), as the co-factor of PRMT5, plays essential roles in the processes of methylating a variety of cytoplasmic and nuclear substrates that are involved in tumorigenesis. Typically, there are two types

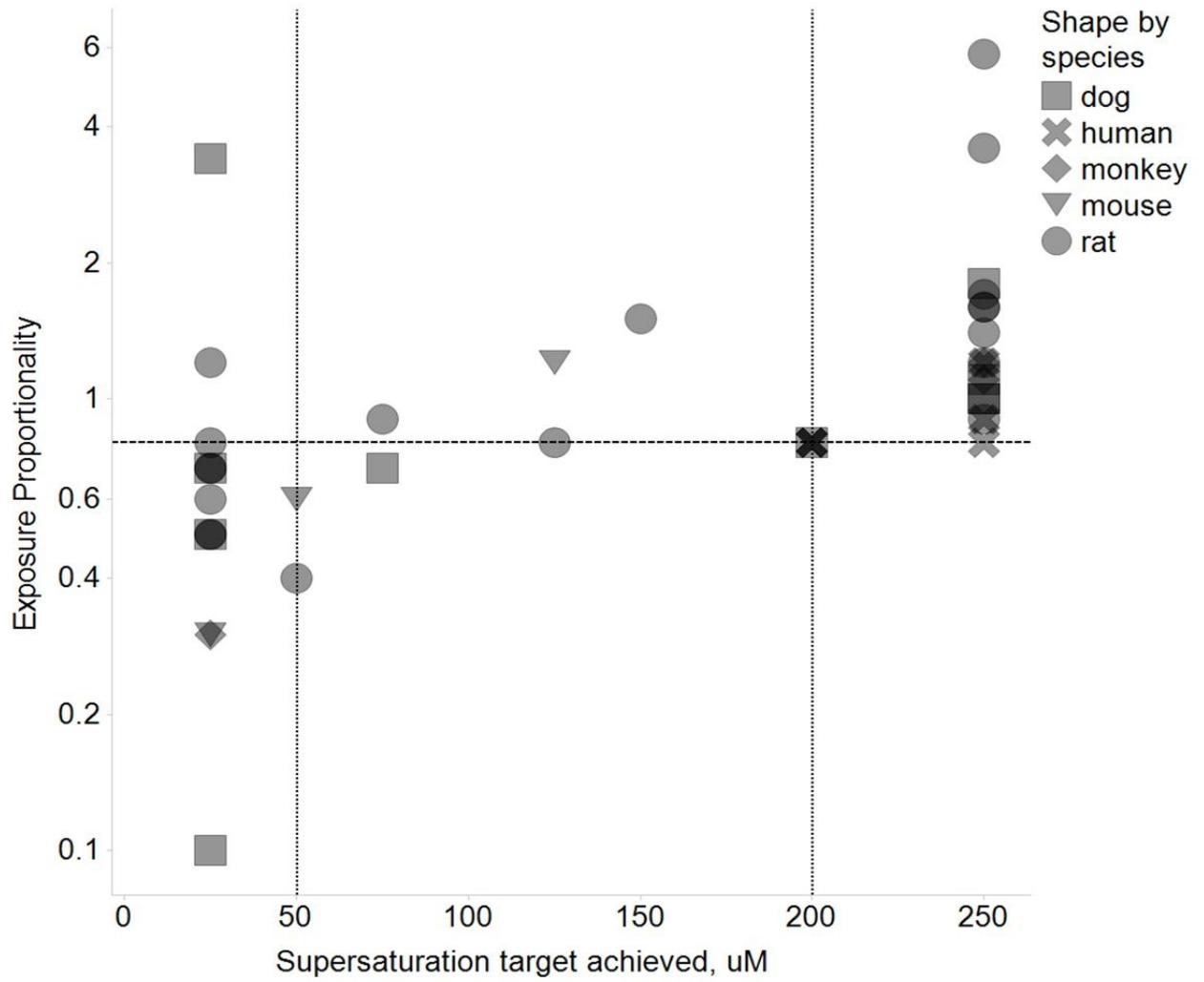
of PRMT 5 inhibitors according to their binding sites. One targets the enzyme substrate site, whose binding is dependent of SAM or SAM analogues' binding, such as EPZ015666; the other targets co-factor site, such as LLY-283, which binds directly to SAM pocket and the majority of inhibitors in this type are nucleoside based. Here we describe a series of indole-based compounds optimized from the lead compound (CMP5). The binding affinity and efficacy have been increased by 25 folds and 40 folds respectively. Furthermore, the binding and enzymatic assays show that our compounds are SAM competitive PRMT5 inhibitors.

## **MEDI 81**

### **Impact of automated supersaturation stability assay to differentiate poorly soluble compounds in Novartis drug discovery and development**

**Suzanne Skolnik**<sup>1</sup>, [suzanne.skolnik@novartis.com](mailto:suzanne.skolnik@novartis.com), **Stephanie Dodd**<sup>2</sup>, **Gina Geraci**<sup>1</sup>. (1) *Global Discovery Chemistry, Novartis Institutes for Biomedical Research, Cambridge, Massachusetts, United States* (2) *Chemical and Pharmaceutical Profiling, Novartis Institutes for Biomedical Research, Cambridge, Massachusetts, United States*

*In vitro* assays that evaluate a compound's supersaturation propensity are increasingly helpful for compound characterization and formulation assessment throughout the drug discovery and development process. We previously published an approach to determine supersaturation stability by solvent-shift after 16 minutes in FaSSIF. Initially, we demonstrated *in vivo* relevance of *in vitro* supersaturation by comparing target concentration achieved and the percentage of area under the curve (AUC) dose-proportionality in 42 preclinical and clinical studies. Eighty-one percent of low supersaturation stability compounds (target concentrations  $\leq 50 \mu\text{M}$ ) had proportionality  $< 0.8$ , while 100% of high supersaturation stability compounds (target concentrations  $\geq 200 \mu\text{M}$ ) demonstrated proportionality  $\geq 0.8$ . Since development of this assay, we have employed it within Novartis projects to differentiate compounds with otherwise attractive properties for pharmacokinetic studies. We have also projected exposure using physiologically based pharmacokinetic (GastroPlus™ PBPK modeling platform) simulation using supersaturation stability values as solubility inputs. We will share this prospective use of the assay, our successes and learnings.



Target Achieved, uM: Classification	Exposure Proportionality		Total Studies
	≥0.8	<0.8	
≤50: Low	3 (19%)	13 (81%)	16
75-150: Borderline	4 (80%)	1 (20%)	5
≥200: High	21 (100%)	0	21

Distribution of achieved supersaturation targets and exposure proportionality in all dose

escalation studies. When targets met were  $\leq 50 \mu\text{M}$ , 81% of studies (13/16) had an  $\text{EP} < 0.8$  and thus were classified as low supersaturation stability. When targets met were  $\geq 200 \mu\text{M}$ , 100% (21/21) were associated with  $\text{EP} \geq 0.8$  and subsequently classified as high supersaturation stability.

## **MEDI 82**

### **Phytochemical screening and antioxidant activities of *Irvingia gabonensis* and its effect on alloxan-induced diabetes rats**

**Oluwasayo E. Ogunjinmi**, *oluwasayoesther@yahoo.com*, Ibrahim A. Salaudeen, Mubarak O. Abdulganeey. *Chemistry, The Polytechnic, Ibadan, Oyo State, Nigeria, Ibadan, Oyo State, Nigeria*

Natural products, especially those derived from plants, have been used to help sustain mankind health. Glucose is an indispensable fuel for the brain and other tissues, chronic amounts of circulating glucose causes toxic effects on the structure and function of organs, including pancreatic islets. Therefore, there is need to regulate glucose in the body. This study determines antioxidant activities of *Irvingia gabonensis* fruit and leaves crude extracts and its effect on alloxan induced diabetes rats. Phytochemical screening and antioxidant capacities of *Irvingia gabonensis* crude extracts were determined using DPPH and Total antioxidant methods and its effect on diabetes induced alloxan rats were also investigated. Phytochemical screening results showed that *Irvingia gabonensis* fruits possessed alkaloids, flavonoids, saponins, tannins and glucosides. *Irvingia gabonensis* leaves revealed highest antioxidant capacity when compared with the fruits. The DPPH scavenging assay of *Irvingia gabonensis* leaves shows the % scavenging of 97.1, 97.3, 97.6, 98.3, 98.7 and 98.8. The leaves extract was effective on induced diabetes rats when compared with the standard drugs and could be used as alternative naturally occurring antioxidants.

## **MEDI 83**

### ***In-situ* single-step electrochemical detection of DL-methionine in human serum sample**

**Abdel N. Kawde**, *akawde@kfupm.edu.sa*. *Chemistry Department, King Fahd University of Petroleum Minerals, Dhahran, Saudi Arabia*

A proficient and cost-effective electrochemical method for the determination of DL-methionine (DLM) has been successfully developed. The *in-situ* single-step AgO modification of the graphite pencil electrode (GPE) was characterized by Field Emission Scanning Electron Microscope (FE-SEM), Energy Dispersed X-ray (EDX), X-ray Photoelectron Spectroscopy (XPS), and cyclic voltammetry. The electrocatalytic activity of the silver ions in 0.10 M NaOH ( $\text{pH } 13.70 \pm 0.20$ ) initiated the oxidation reaction of DLM on the GPE surface via  $\text{Ag}^{2+}$  metal-induced reaction of hydroxyl radical ( $\text{OH}\cdot$ ). Electrode linearity dependence obtained is given as for a linear range concentration of

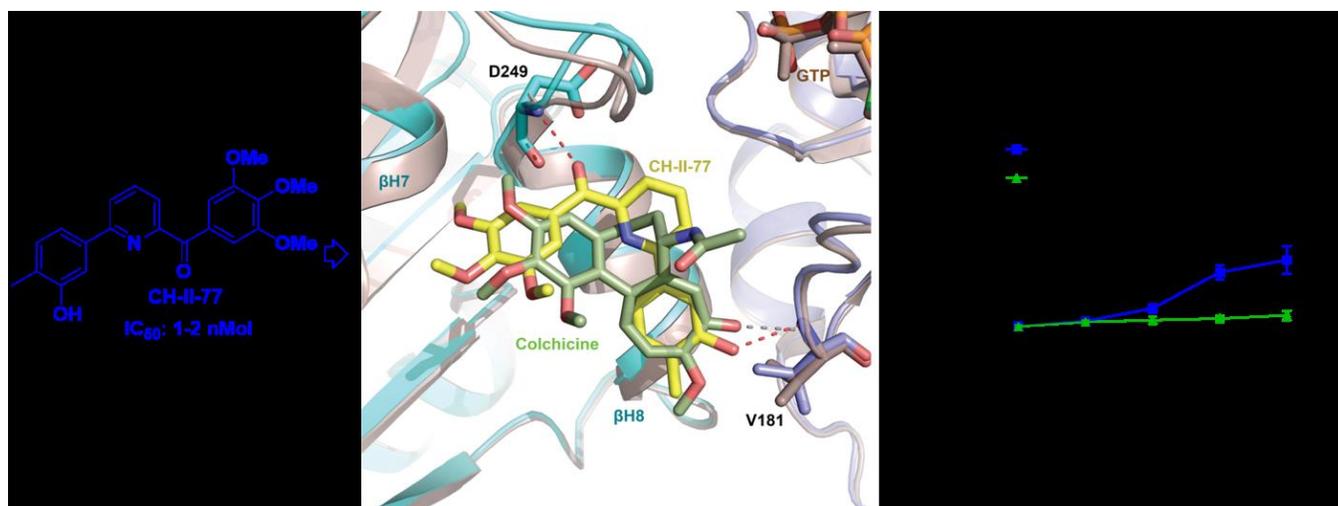
60  $\mu\text{M}$  - 500  $\mu\text{M}$  with a correlation coefficient ( $R^2$ ) of 0.986 and limit of detection of 0.42  $\mu\text{M}$ . Effects of potential interferences such as ascorbic acid (AA), L-alanine (Aln) and cysteine was found to be insignificant. The developed detection method was found to be suitable for both voltammetric and amperometric techniques for the development of non enzymatic sensor of DLM, and its real life application in human serum sample by standard addition method with a correlation coefficient ( $R^2$ ) of 0.999.

## **MEDI 84**

### **Discovery of novel 6-aryl-2-benzoyl-pyridines as tubulin polymerization inhibitor with potent antiproliferative properties**

**Hao Chen**<sup>1</sup>, *hchen55@uthsc.edu*, **Shanshan Deng**<sup>1</sup>, **Najah Albadari**<sup>1</sup>, **Duane D. Miller**<sup>2</sup>, **Wei Li**<sup>3</sup>. (1) Department of Pharmaceutical Sciences, university of Tennessee, Cordova, Tennessee, United States (2) Department Pharmaceutical Sciences, College of Pharmacy, Memphis, Tennessee, United States (3) University of Tennessee HSC, Memphis, Tennessee, United States

A novel series of structurally related pyridine analogues based on our previously reported lead compound (2-(p-tolyl)-1H-imidazol-4-yl)(3,4,5-trimethoxyphenyl)methanone (ABI-274), was designed and synthesized in an effort to find a molecule with improved cytotoxic potency. Most of these pyridine compounds exhibited potent cytotoxicity when tested in a panel of melanoma and breast cancer cell lines, with  $\text{IC}_{50}$  values in the low nanomolar range. Among them, CH-II-77 represented the most potent compound with  $\text{IC}_{50}$  value of 1–2 nM against these cancer cell lines, including several drug-resistant cancer cell lines. The high-resolution X-ray crystal structure of CH-II-77 in complex with tubulin confirmed its direct binding to the colchicine-binding site and mechanism of action studies revealed that CH-II-77 maintained its mode of action by inhibition of tubulin polymerization. It induced G2/M phase arrest and apoptosis in triple-negative breast cancer (TNBC) cells. Additionally, compound CH-II-77 exhibited strong anticancer activity on tumor growth in a human melanoma xenograft model and orthotopic TNBC model, and CH-II-77 was able to induce tumor necrosis, inhibit angiogenesis and lead to cancer cell apoptosis *in vivo*. Collectively, these studies suggest that CH-II-77 is a promising new generation of tubulin inhibitor.

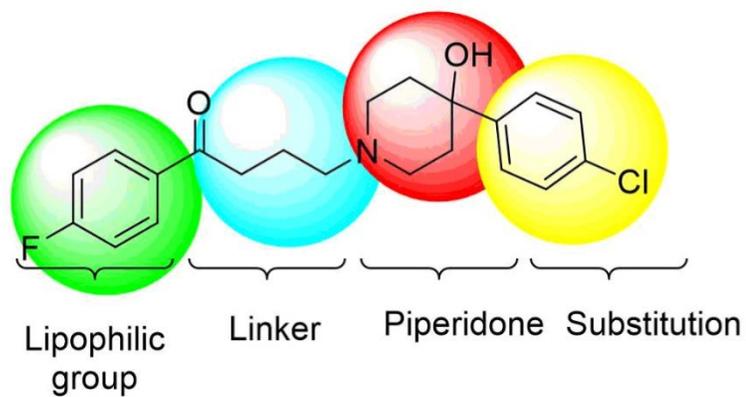


## MEDI 85

### Design and development of novel selective D<sub>4</sub>-receptor ligands as CNS-therapeutics

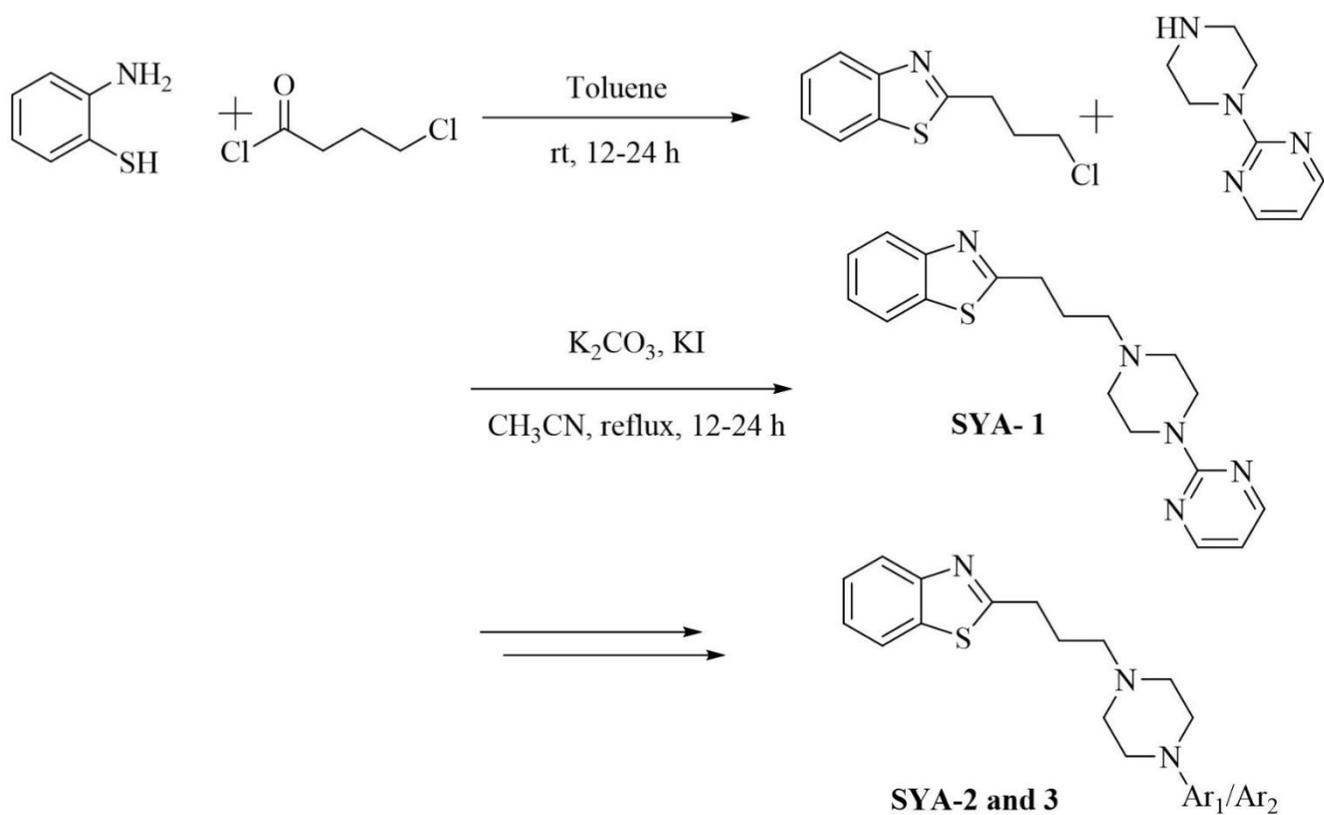
*Uma Maheshwar Gonela, uma.gonela@fam.u.edu, Seth Y. Ablordeppey. Basic Pharmaceutical Sciences, Florida A&M University, Tallahassee, Florida, United States*

The dopamine D<sub>4</sub> receptor has been shown to play key roles in certain CNS pathologies including substance use disorders, reversing cognitive deficits in schizophrenia, L-DOPA-induced dyskinesias, Parkinson's disease and treating erectile dysfunction. Thus, selective D<sub>4</sub> ligands could be helpful in treating some of these disorders. In our laboratory, previous studies have indicated that the piperazine analog of haloperidol, when compared to its piperidine analog, exhibits increased and selective affinity to the DRD<sub>4</sub>-subtype. This led us to further explore the piperazine analogs to develop the novel DRD<sub>4</sub> selective agents. In our study, we found that the SYA-2 ( $KiD_4 = 0.84$  nM) was the most potent of the compounds tested, with moderate selectivity for the DRD<sub>4</sub>. SYA-1 and 3 ( $KiD_4 = 3.9$  and 2 nM) were more discriminatory for the D<sub>4</sub> receptor subtype with little or no binding affinity to any of the other four DA receptor subtypes. SYA-1 and 3 were potentially useful D<sub>4</sub>-selective ligands for probing disease treatments involving the D<sub>4</sub> receptor.



**Scheme:**

**Haloperidol**



Scheme 1: General strategy and synthesis

Compd	D <sub>2</sub>	D <sub>3</sub>	D <sub>4</sub>	D <sub>2</sub> /D <sub>4</sub>	D <sub>3</sub> /D <sub>4</sub>
Clozapine	130	240	54.0	2.4	4.4
SYA-1	MT	MT	3.9	>2564	>2564
SYA-2	26.5 ± 4.5	100 (7.0 ± 0.1)	0.84 ± 0.09	31.5	119
SYA-3	1142.19	335.71	2.00	571.0	167.8

Table 1: Binding Affinity (K<sub>i</sub> nM) Data of compounds at relevant dopamine receptors

## MEDI 86

### Antioxidant activity of eugenol derivatives

**Ellie Siech**, *emsiech@gmail.com*, **Victoria Thurman**, *toria\_leigh1@hotmail.com*, **Anuradha Vummenthala**, *Maryville University of St. Louis, St. Louis, Missouri, United States*

2-methoxy-4-prop-2-enylphenol, commonly known as Eugenol, is a major chemical constituent of cloves. It is known to possess excellent antioxidant, antimicrobial and anesthetic activities. If consumed in excess, it forms a toxic quinone methide intermediate. Its toxicity is due to the oxidant and electrophilic behavior which causes oxidative stress and damages biological systems in the human body (Monks, T J, and D C Jones *et al.*). The objective of this study is to identify an alternate ester derivative of eugenol that possibly can not form quinone methide, while maintaining its beneficial properties. We synthesized various ester derivatives of eugenol using Fisher esterification method and tested their antioxidant activity using DPPH scavenging method. Fluorinated ester derivatives of eugenol showed comparable antioxidant activity properties to that of Eugenol.

Dose dependent studies of one of the Fluorinated compounds showed higher antioxidant activity than that of Eugenol at 0.001M concentration.

## MEDI 87

### Discovery of a novel second-site corrector for delF508 CFTR mutations

**Philip Lam**<sup>1</sup>, *philip.lam.14@gmail.com*, **Kelly D. Boss**<sup>1</sup>, **Atwood K. Cheung**<sup>1</sup>, **Robert Epple**<sup>2</sup>, **Sheryll Espinola**<sup>2</sup>, **Ayako Honda**<sup>1</sup>, **Cecilia Lay**<sup>2</sup>, **Wei L**<sup>2</sup>, **Hasnain A. Malik**<sup>1</sup>, **Lewis Whitehead**<sup>1</sup>, **Baogen Wu**<sup>2</sup>, **William G. Barnes**<sup>2</sup>, **Sejal J. Patel**<sup>1</sup>. (1) *Global Discovery Chemistry, Novartis Institutes for BioMedical Research, Somerville, Massachusetts, United States* (2) *Genomics Institute of the Novartis Research Foundation, San Diego, California, United States*

Cystic fibrosis (CF) is the most common lethal genetic disease in the Caucasian population and is caused by the loss-of-function in the CF transmembrane conductance regulator (CFTR) chloride channel. Recent clinical trials have demonstrated the efficacy of combinations of a CFTR-potentiator with one or more CFTR-correctors. We will present the hit to lead story of a pyrazole series of compounds that are structurally distinct from current correctors. This novel CFTR-corrector has demonstrated additive potency and efficacy on top of standard of care in an *in-vitro* setting, ideal physicochemical properties, favorable *in-vivo* exposure, and displays a clean off-target profile.

## **MEDI 88**

### **Discovery and SAR studies of novel 2-anilinopyrimidine-based selective inhibitors against triple-negative breast cancer cell line**

*Jeyun Jo, jju02160@gmail.com, Sou Hyun Kim, Heegyu Kim, Myeonggyo Jeong, Young-Suk Jung, Hwayoung Yun. College of Pharmacy, Pusan National University, Busan, Korea (the Republic of)*

Triple-negative breast cancers (TNBCs) are an invasive subtype of breast cancers that phenotypically defined by the absence of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). TNBCs account for about 15%-20% of all diagnosed breast cancer cases and are highly intractable due to its unique molecular profile and distinct metastatic patterns. Although TNBCs can be treated with chemotherapy, but approximately 20% of TNBC patients responds to standard chemotherapy. Recently, the overexpression of epidermal growth factor receptor (EGFR) has been investigated as a substantial target for anti-TNBC agents, however, TNBCs frequently show resistance to EGFR tyrosine kinase inhibitors. In connection with development of novel EGFR-overexpressing TNBC selective inhibitors, an in-house chemical library was initially screened in TNBC cell line MDA-MB-468 and luminal type breast cancer cell line MCF-7 using a dose dependent MTT assay. A hit compound possessing a 2-anilinopyrimidine structure was identified that exhibited selective cytotoxic activity against MDA-MB-468 cell line. Based on this screening result, we designed and synthesized a novel series of 2-anilinopyrimidine derivatives. An intensive SAR study of synthesized compounds was conducted and the influence of lipophilicity on cytotoxicity was evaluated. In addition, the selectivity of the analogs on the TNBC cell line was confirmed by selectivity index (SI).

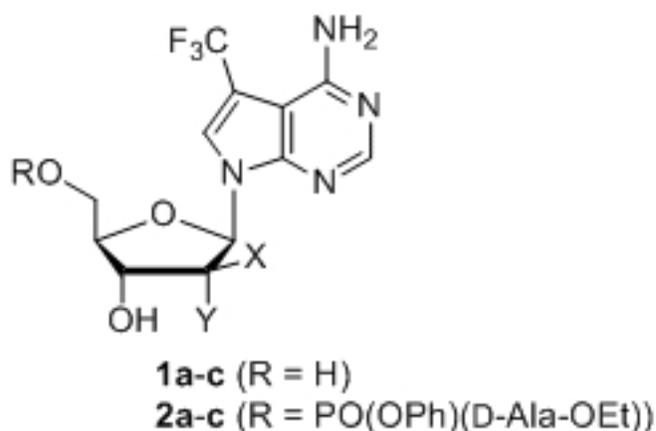
## **MEDI 89**

### **Efficient synthetic methods of 7-trifluoromethyl-7-deazapurine ribonucleoside analogs and their phosphoramidate prodrugs**

*JONG HYUN CHO<sup>2,1</sup>, jhcho1@dau.ac.kr, Se Myeong Choi<sup>1</sup>, Ji Su Kim<sup>1</sup>, Franck Amblard<sup>2</sup>, Lead C. Bassit<sup>2</sup>, Raymond F. Schinaz<sup>2</sup>. (1) Medicinal Biotechnology, Dong-A*

University, Busan, Korea (the Republic of) (2) LOBP, Pediatrics, Emory University, Atlanta, Georgia, United States

New 7-trifluoromethyl-7-deazapurine ribonucleoside analogs (**1a-c**) and their prodrugs (**2a-c**) were successfully synthesized from riborlactol and 1-*a*-bromo-ribose derivatives using Silyl-Hilbert-Johnson or nucleobase-anion substitution reaction and then aromatic trifluoromethyl substitution as key step reactions. The *b*-selective glycosylation reaction of the benzyloxonium ribose, or 1-*a*-bromo-ribose intermediates with persilylated 6-chloro-7-iodo-7-deazapurine, or anionized compound, followed by the aromatic trifluoromethylation reaction with MFSDA and CuI and then treatment with ammonia afforded 7-trifluoromethyl-7-deazapurine ribonucleosides (**1a-c**) in excellent yield, which were converted into their phosphoramidate prodrugs (**2a-c**) employing chlorophosphoramidate derivative. Unfortunately, none of them showed any marked anti-HCV, anti-Zika and anti-Ebola activities.



## MEDI 90

### ***In silico* discovery of new small-molecule immune checkpoint inhibitors as an innovative approach to treat cancer**

**Salvatore Ferla**<sup>1</sup>, [ferlas1@cardiff.ac.uk](mailto:ferlas1@cardiff.ac.uk), **Simone Lanfredin**<sup>2</sup>, **Girish Patel**<sup>2</sup>, **Andrea Brancale**<sup>1</sup>. (1) Medicinal Chemistry, Cardiff, Cardiff, United Kingdom (2) European Cancer Stem Cell Research Institute, Cardiff University, Cardiff, United Kingdom

Immune responses are strongly regulated by different co-stimulatory and co-inhibitory molecules, which allow the immune system to distinguish between physiological cells and malignant cells, recognised as “foreign”. A hallmark of cancer cells is to avoid detection by the immune system, and tumours evade immune responses by exploiting immune checkpoint pathways.

In recent years, a growing understanding of the biology of immune checkpoints and tumour immune evasion mechanisms has led to the development of immune checkpoint inhibitors in the form of monoclonal antibodies, designed to target co-stimulatory and

co-inhibitory molecules in order to re-engage the immune system and restore anti-tumour immune responses. Despite this advance, many cancers still escape the immune system detection and fail to respond to the immune therapy. On top of this, as all immune checkpoint inhibitors explored so far fall in the category of monoclonal antibodies, therapy with these agents is associated with very high costs, longer response times in comparison with standard chemotherapy and several systemic side-effects.

Immune checkpoint therapy has dramatically changed the efficacy of anti-cancer treatment and the exploration of novel immunological targets, along with the design of new small-molecule modulators of these pathways, constitutes a global research priority and an innovative research field.

Searching for new immune checkpoint modulators, we are focussing our efforts on three different immune checkpoint proteins and their ligands: **CTLA-4:B7-1/B7-2, PD-1:PD-L1 and CD200:CD220R**. Using molecular modelling techniques, we have performed a series of virtual screenings of different libraries of commercial compounds (~3 millions), in order to identify novel small-molecules able to block these immune checkpoint proteins by disrupting their interactions with the ligands. The molecules selected *in silico* have been evaluated for their ability to block immune checkpoint protein-ligand interactions, to re-engage the immune system and restore anti-tumour immune responses using different biochemical and cell-based assays.

## **MEDI 91**

### **Delivering glutathione persulfide by an esterase-sensitive donor**

**Zhengen Yuan**<sup>1</sup>, [zyuan3@student.gsu.edu](mailto:zyuan3@student.gsu.edu), **Yueqin Zheng**<sup>1</sup>, **Bingchen Yu**<sup>1</sup>, **Siming Wang**<sup>1</sup>, **Xiaoxiao Yang**<sup>1</sup>, **Binghe Wang**<sup>2</sup>. (1) Chemistry, Georgia State University, Atlanta, Georgia, United States (2) Dept of Chem, Georgia State University, Atlanta, Georgia, United States

Sulfur signaling is widely accepted as a critical process in mammalian physiology. However, whether it is the sulfide or persulfide species that is the “active” component is a debatable subject. The lack of chemical tools to afford “pure” persulfide hinders studies in this area. Among all the reactive sulfur species (RSS), glutathione persulfide (GSSH) is the most abundant species. However, because of its unstable nature, the detail chemical and biological functions of GSSH are still unclear. Although others and we have developed some persulfide delivery systems, no existing methods can deliver unprotected GSSH. In this work, we describe a new strategy of delivering a “pure” GSSH through the use of an esterase-sensitive prodrug. The release profile was studied by direct trapping of GSSH with 1-fluoro-2,4-dinitrobenzene (DNFB) and monitoring the formation of a side product. The donor was examined for its inhibitory effect toward glyceraldehyde 3-phosphate dehydrogenase (GAPDH). Under highly oxidative conditions, the donor also show cytoprotective effects in H9c2 cardiomyocytes.

## **MEDI 92**

## **Highly advanced intermediate towards a macrocyclic ketone mimic of zampanolide**

**Ziran Jiang**, *ZiranJiang@mail.fresnostate.edu*, **Guanglin Chen**, **Qiaohong Chen**. *Chemistry, California State University, Fresno, Fresno, California, United States*

(-)-Zampanolide is a naturally occurring macrolide that was isolated from two species of marine sponge. It has been established as a very attractive anticancer lead compound due to its unique covalent-binding with tubulin and low nanomolar antiproliferative potency even against multi-drug resistant cancer cell lines. In addition to the limited supply, we envision that the lactone moiety is not drug-like enough due to the metabolically instability. This study thus aims to synthesize a stabilized and simplified zampanolide mimic by replacing the lactone core structure in zampanolide with a macrocyclic ketone, as well as by removing the tetrahydropyran ring.

To this end, a highly advanced intermediate towards the zampanolide mimic has been successfully achieved through a Horner-Wadsworth-Emmons reaction of Fragment C13-C18 branched with C17-CH<sub>2</sub>-C1-C2 and Fragment C3-C8. The Fragment C3-C8 was built up from commercially available 2-butyne-1-ol via a seven-step transformation. Fragment C13-C18 branched with C17-CH<sub>2</sub>-C1-C2 has been successfully constructed via a twelve-step sequence. Most importantly, the critical C17-CH<sub>2</sub>-C1=C2 bond for the macrocyclic ketone mimic of zampanolide has been constructed by a cross-coupling alkylation mediated by CuI/TMEDA/LiOMe. All synthesized intermediates have been characterized by interpreting the <sup>1</sup>H and <sup>13</sup>C NMR spectra.

## **MEDI 93**

### **Development of a platform for resveratrol delivery: Functionalization of resveratrol-loaded nanoparticles and hypertrophy modulation in cardiac cells**

**Paola Garcia**, *pao.la.95@hotmail.com*. *Tecnológico de Monterrey, Monterrey, Nuevo Leon, Mexico*

Cardiovascular diseases (CVDs) are the clinical syndromes responsible for the highest death rate worldwide. Amongst them, heart failure is an ending stage of CVD, where blood pumping by the myocardium is severely reduced due in part to heart remodeling expressed as cardiac myocyte hypertrophy and cardiac fibrosis. It has been shown that Resveratrol, a polyphenol, can reduce hypertrophy in the cardiac myocytes. However, its therapeutic use is limited by low bioavailability and high metabolization rate. To this end, the use of polymeric nanoparticles (NPs) promotes a protected drug transport, avoiding such disadvantages, while offering a controlled and sustained release.

The purpose of this work is to understand the new possible interactions between the use of a NPs to deliver Resveratrol into cardiac cells, and assess whether this route offers a better way to treat cardiac hypertrophy. Resveratrol was encapsulated by poly (D, L-lactic-co-glycolic acid). These NPs were functionalized with either chitosan (CS) or polyethylene glycol (PEG) to improve cell internalization and blood flow circulation time,

respectively. The NPs were characterized and presented a mean diameter of  $147.9 \pm 59.68$  and  $191.5 \pm 28.03$  nm, and zeta potential of  $6.32 \pm 0.78$  mV and  $-4.74 \pm 1.43$  mV for CS and PEG, respectively. The resveratrol entrapment efficiency was 61.35%. The FTIR spectrum were consistent with the structure of functionalized nanoparticles by covalent binding showing and amide band at  $1646 \text{ cm}^{-1}$ . Functionalized NPs show no cytotoxicity at high NP cell doses (100 g/mL). Preliminary results show that PLGA-Resveratrol NPs can modulate hypertrophy the cardiac cells line H9c2.

## **MEDI 94**

### **Chromatography and fractionation of *Schinus terebinthifolius* extracts which inhibit breast cancer cell migration *in vitro***

**Maria Pina**, *mpina@stu.edu*, **Jonathan M. Brown**, *jbrown4@stu.edu*, **Alexis Tapanes-Castillo**. *St. Thomas University, Miami Gardens, Florida, United States*

Medicinal plants continue to attract increasing attention because of their potential benefits in the field of medicine and pharmacology. The present study was prompted by claims that the Brazilian pepper tree (*Schinus terebinthifolius*) is traditionally used in regions of South America to alternatively treat many conditions, including certain types of cancer. Recently, the study of antioxidant levels in plants has received a great deal of attention because it is widely believed that increased oxidative stress and free radical levels in the body lead to the progression of diseases. A 50:50 v/v ethanolic/aqueous extract prepared from the bark of the Brazilian pepper tree exhibited high levels of antioxidant activity in DPPH (2,2-diphenyl-1-picrylhydrazyl), Total Phenolic Content TPC, and Ferric Reducing Antioxidant Power FRAP assays. Furthermore, the same bark extract inhibited breast cancer cell migration *in vitro*. Scratch migration assays, performed on invasive BT549 triple-negative breast tumor cells, demonstrated that the average migration velocity of cells treated with bark extract was significantly decreased compared to untreated control cells. In order to study and identify the bioactive molecules contributing to this effect, the extract was fractionated via column chromatography, and the fractions were tested in migration assays. Fractions that retained anti-migratory activity and crude bark extracts were analyzed by GC-Mass Spectrometry. The results of these experiments will be presented.

## **MEDI 95**

### **Computational designed new inhibitors of xanthine oxidase for treatment of gout**

**Chao Dong**, *dongc0613@gmail.com*, **Victor Usanga**. *Physical Sciences, University of Texas of Permian Basin, Odessa, Texas, United States*

Gout is a chronic, inflammatory condition due to slow urate metabolism. The xanthine oxidase inhibitors, such as allopurinol and febuxostat, are recommended to reduce the uric acid level and prevent gout to attack in adult patients. The emerging new generation of xanthine inhibitor, FYX051, displays a high cost effectiveness compared

with febuxostat therapy in chronic gout patients. However, the metabolites of N-oxides from FYX-051 (Topiroxostat) could potentially have adverse effect on patients with severe renal impairment if they have been taking an oral injection for a long period of time as shown in the report on the deliberation results for evaluation of FYX051 (Topiroxostat). Therefore, it is desirable to design new inhibitors without 1,2,4-triazole C=N components.

Here, we computationally designed several modified inhibitors with 1,2,4-triazole ring being replaced by furan, thiophene, pyrrole, selenophene. The computational results indicate that the binding energy of new inhibitors with xanthine oxidase active site is slightly smaller than that from FYX051. In addition, the new designed inhibitors will also help to probe the protonation state of glutamate 832, which is proposed to contribute the energy stabilization of inhibitors by hydrogen bonding.

## **MEDI 96**

### **Structure Activity Relationship (SAR) studies of a nucleotide reverse transcriptase inhibitors (NRTI) AZT (Zidovudine) analogs using Gaussian computational techniques**

*Saraswathi Narayan, snarayan@stevenson.edu, Kendel Quirk, Karleigh Baldwin. Chemistry, Stevenson University, Owings Mills, Maryland, United States*

Quantum mechanical calculations for several AZT (Zidovudine) a nucleoside reverse transcriptase (NRTI) derivatives are presented in this investigation using Gaussian 09W- Density Functional Theory (DFT) and Hartree–Fock (HF) methods using several basis sets. Structure Activity Relationship studies involved several isosteres on sugar moiety as well as the thymidine moiety in the lead AZT molecule. In the thymidine moiety the thymidine was replaced with 5-fluorouracil (a pyrimidine analog) with the hope of added effect of 5-Fluorouracil that is known to have both anti-tumor as well as anti-viral properties. The theoretical modeling calculations were all carried out on the molecules with optimized geometry. Several molecular properties like dipole moment data, polarizabilities and total energy were calculated.  $\Delta G$  solvation in water and n-Octanol were also calculated using Self-Consistent Reaction Field (SCRF) method that performs Polarizable Continuum Models (PCM) calculations.. The calculations were compared to the calculations performed on the lead compound (AZT). The dipole moment calculated for various analogs of AZT derivatives showed similar trends for various basis sets. Total energies calculated for various substituents were interpreted in terms of molecular interactions during drug development, a primary tool in drug design.  $\Delta G$  solvation energies in n-octanol and water calculated, were interpreted in terms of Partition Coefficients that is related to drug absorption in the body. Gaussian calculations along with future molecular docking using MOE will be used to determine the suitability of these drugs as a possible alternative to AZT option for a more effective treatment of HIV.

## **MEDI 97**

## **Time-on-target: Easy method development for reverse phase preparative chromatography**

*Jack E. Silver, jacksilver86@gmail.com, Chester Bailey, Deen Johnson, Ronald Lewis. Teledyne ISCO, Lincoln, Nebraska, United States*

A technique was developed to easily create optimized both preparative HPLC and flash chromatography reverse phase methods from analytical HPLC/UHPLC runs. Preparative chromatography methods for normal phase chromatography are easily created from thin-layer chromatography (TLC) plates. Reverse phase methods are more difficult to create because TLC plates require a significantly longer time to run. Using HPLC/UHPLC for method development often requires complex scale-up calculations to determine gradient segment lengths to effect the same resolution.

Time-on-Target uses a model compound to set a desired retention time on the preparative HPLC or flash chromatography system. The determined solvent composition from the preparative system is then used to calibrate the scouting gradient used on the analytical LC system. Compounds to be purified are run using the same scouting gradient as that used for the initial analytical calibration. Their retention time is adjusted by the calibrated scouting gradient to calculate a solvent composition which centers on an efficient focused gradient. The determined gradient is fast, saving solvent and reducing waste. Once calibrated, reverse-phase method development for reverse phase chromatography is faster than that using TLC for normal phase.

### **MEDI 98**

#### **Searching for sensitizers of bacteria toward existing antibiotics**

*Manjusha Roy Choudhury, mroychoudhury1@student.gsu.edu, Bingchen Yu, Arvind Kumar, Mengyuan Zhu, David W. Boykin, Binghe Wang. Dept of Chem, Georgia State University, Atlanta, Georgia, United States*

The rapid emergence of antibiotic-resistant bacterial strains is an urgent public health concern worldwide. In the USA alone, the death toll has risen to 23000 per year as a result of such infections. Given the plethora of existing antibiotics, one practical way to overcome this challenge is to sensitize bacteria to existing antibiotics and thus help overcome drug resistance and subsequently lower the rate at which bacteria develop resistance. Our group has screened a series of compounds and found some initial leads, which can sensitize both Gram-positive and Gram-negative bacteria toward existing antibiotics by 20-200 fold. This poster will focus on the results of our screening effort and discuss structural optimization approaches.

### **MEDI 99**

#### **On-column dilution: A method to improve loading and resolution in chromatography**

**Jack E. Silver**, *jacksilver86@gmail.com*, Chester Bailey, Deen Johnson, Ronald Lewis. Teledyne ISCO, Lincoln, Nebraska, United States

Compounds should be dissolved in the mobile phase for best results during purification. Using mobile phase as the dissolution solvent avoids disturbing equilibration of the column and maximizes resolution between peaks. Unfortunately, complex mixtures contain compounds that may not be soluble in the mobile phase. Dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) are often used in reverse phase chromatography because they dissolve a wide variety of compounds and are “weaker” solvents compared to the “strong” solvent in the mobile phase, which causes the compounds to elute. These solvents are still stronger eluting solvents than water, causing limited sample loading. On-column dilution is a method that allows the use of DMSO and DMF while preserving peak shape and loading capacity. The use of On-Column Dilution allows 2 to 3 fold improvement in purification throughput.

## **MEDI 100**

### **Optimization of structural features of the 4-anilinoquin(az)oline scaffold for chordoma utilizing an innovative toxicology profiling assay panel**

**Christopher R. Asquith**<sup>1,2</sup>, *chris.asquith@unc.edu*, Andrew A. Bieberich<sup>3</sup>, Kaitlyn Maffuid<sup>4</sup>, Raymond Fatig<sup>3</sup>, Graham J. Tizzard<sup>5</sup>, Tuomo Laitinen<sup>6</sup>, Michael P. East<sup>1</sup>, Chad D. Torrice<sup>4</sup>, David Drewry<sup>2</sup>, Gary J. Johnson<sup>1</sup>, Daniel J. Crona<sup>4,7</sup>, Brad Calvin<sup>3</sup>, David C. Morris<sup>8</sup>, William J. Zuercher<sup>2,7</sup>. (1) Department of Pharmacology, School of Medicine, 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) AsedaSciences Inc., 1281 Win Hentschel Boulevard, West Lafayette, Indiana, United States (4) Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States (5) UK National Crystallography Service, School of Chemistry, University of Southampton, Southampton, Hampshire, United Kingdom (6) School of Pharmacy, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland (7) Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States (8) UNC Catalyst for Rare Diseases, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States

The 4-anilinoquin(az)oline is a well known kinase inhibitor scaffold underlying clinical inhibitors gefitinib, erlotinib, afatinib, and lapatinib that have all previously demonstrated activity against chordoma cell lines *in vitro*. We screened a focused array of compounds based on the 4-anilino-quinoline/quinazoline/3-cyanoquinoline scaffold on both U-CH1 and the EGFR-inhibitor-resistant U-CH2. In order to prioritize the hit compounds for further development, we screened the compound set in an 8-component predictive SYSTEMETRIC® cell health toxicity assay. The de-risked compounds were then screened against a number of patient derived cell lines and showed low micromolar

efficacy in cells. We also investigated the properties that gave rise to the toxophore markers, including the structural and electronic features, using both modelling and small molecule crystal structures. Utilizing the Multiplexed Inhibitor Beads (MIBs) kinome profiling platform to assist in target identification, we identified the most prevalent hit as epidermal growth factor receptor (EGFR). However, a number of other kinases were identified that may contribute to observed efficacy. These de-risked leads present a potential new therapeutic avenue for treatment of chordomas.

## **MEDI 101**

### **Biphenyl acid derivatives as APJ receptor agonists**

**Shun Su**, *sushunss@gmail.com*, Adam Clarke, Ying Han, Hannguang Chao, Jeffrey Bostwick, William Schumacher, Tao Wang, Mujing Yang, Mei-Yin Hsu, Eric Simmons, Yi Hsiao, Emily E. Luk, Marta Dabros, Michael A. Galella, Joelle Onorato, David Gordon, Ruth R. Wexler, Peter S. Gargalovic, Michael Lawrence. Bristol Myers Squibb, Wallingford, Connecticut, United States

The APJ receptor (APJ-R) is a class A GPCR that is widely expressed in various tissues, especially in the cardiovascular system including the heart, blood vessels and kidney. Activation of APJ-R by its endogenous ligand (pyr<sup>1</sup>)apelin-13 demonstrated cardiovascular protective effects in preclinical rodent models. Furthermore, infusion of (pyr<sup>1</sup>)apelin-13 over 6 hours into healthy volunteers and to patients with heart failure increased ejection fraction and improved cardiac output without significantly affecting blood pressure or heart rate. Since (pyr<sup>1</sup>)apelin-13 and related peptides exhibit a short half-life in circulation, activation of APJ-R has been limited by continuous infusion delivery. Activation by small molecule agonists with improved exposure profiles is an attractive therapeutic prospect for the chronic treatment of heart failure. The identification and optimization of a series of biphenyl acid based small molecule APJ agonists will be disclosed. The lead molecule in the series compared favorably with the endogenous ligand (pyr<sup>1</sup>) Apelin-13 in terms of *in vitro* potency, activation of APJ signaling pathways, and acute *in vivo* hemodynamic response in rodents.

## **MEDI 102**

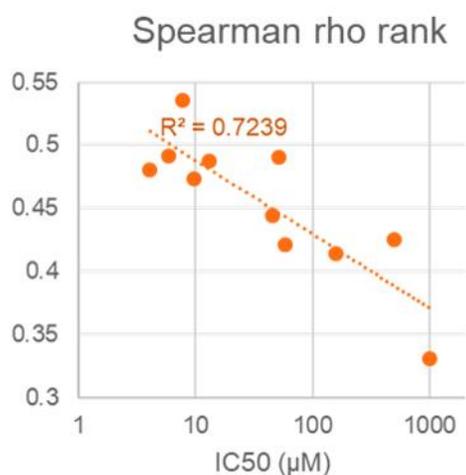
### **Using electrostatic complementarity to design compounds: A new approach to visualize and predict activity**

**Tim Cheeseright**, *tim@cresset-bmd.com*, Sylvie Sciammetta, Matthias Bauer, Mark D. Mackey. Cresset, Cambridgeshire, United Kingdom

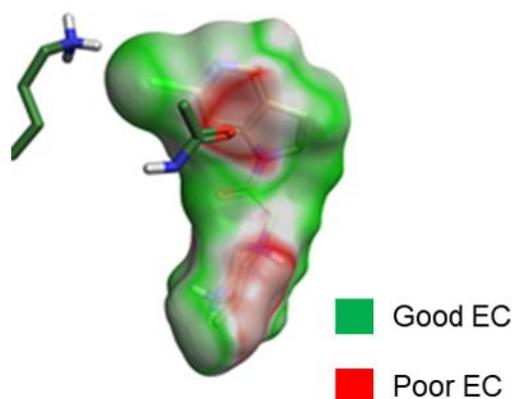
Electrostatic interactions between small molecules and their respective receptors are a key contributor to the free energy of binding. Understanding the Electrostatic Complementarity™ (EC) between ligands and binding pockets holds great promise for the optimisation of ligand binding and feedback into molecular design.

The polarizable XED force field is an excellent base for calculating electrostatic properties due to its description of anisotropic atomic charge distributions and relatively modest computational costs. By computing electrostatic potentials for both ligand and protein with XED, the EC of complexes can be calculated and translated into both a simple coloring scheme on the ligand and protein surface and an overall score for the match.

We present the theoretical background of our EC calculations and discuss their application to mGluR5, XIAP, and other selected targets. We demonstrate the use of EC surfaces to visualize and guide the design of new molecules on a one-by-one basis and the use of EC scores as a generalised predictor of activity.



Electrostatic Complementarity versus observed activity for a set of XIAP ligands.



Visual feedback of complementarity.

## MEDI 103

### Cruentaren A analogs and their biological activities

**Bhargav Patel**, *bpatel1@nd.edu*, Michael Topinka, Brian S. Blagg. Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana, United States

F1FO-ATP synthase is involved in the regulation of cellular ATP production and maintenance of the mitochondrial membrane potential. Cruentaren A, a macrolactone obtained from myxobacterium *Byssovorax cruenta*, is a highly selective inhibitor of F1FO-ATP synthase and is also a highly cytotoxic agent against select cancer cell lines. Hsp90, the most abundant heat shock protein, plays a vital role in the maturation of client proteins via the assistance of co-chaperones and partner proteins, such as F1FO ATP synthase. We have previously shown that cruentaren A selectively binds F1FO ATP synthase and disrupts the Hsp90-F1FO ATP synthase interaction resulting in client protein degradation without concomitant induction of the heat shock response (HSR).

Previous SAR studies on Cruentaren A identified structural features leading to a more potent analog, which manifested an IC<sub>50</sub> of 0.7 nM against the L-929 mouse fibroblast cell line. In this study, the structure of cruentaren A was simplified to identify the pharmacophore necessary for anticancer activity and inhibition of F1FO-ATP synthase.

## **MEDI 104**

### **Potential correlation between chlorine-treated drinking water and cancer incidences**

*Alexandra Avalos, alexaval@msmu.edu, Stephany Rodriguez. Mount Saint Mary's University, Chino, California, United States*

The importance of clean water is a universal matter because water is utilized on a daily basis and is necessary for survival. Whether it's for drinking, cooking, or more, safe water is a concern for many. In instances where individuals don't have access to clean water, they opt for at home techniques, often without guidelines. While conducting a health survey in Peru, the interviewees were asked about the cleanness of water and the significance it held to them. Concerns about clean water were found to be of high importance for this Peruvians felt it was necessary to treat their water. One of the techniques mentioned included the use of chlorine to disinfect the water. Out of the people surveyed, it was found that about 20% of families routinely resort to chlorine to treat their water. These findings are alarming due to the effects that residual chlorine could be playing in the overall health of individuals. In addition to vital risks from the chlorine itself, there are also a series of other issues that arise from chlorination byproducts, formed from reactions between disinfectants and naturally occurring organic matter and anthropogenic contaminants. One of these byproducts is trihalomethane, a compound fairly similar to chloroform. Exposure to chlorination byproducts is known to increase the rate for certain cancers. Such findings should be of concern considering that some of the effects mentioned above result from consumption of professionally treated water; therefore, the effects resulting from water treated by homemakers can be amplified and even more detrimental. Overall, at home treatments of water utilized by many Peruvians may be unsafe and could generate increasing carcinogens consumption, potentially leading to cell damage and a higher risk of cancer. Currently, chlorinated water at varying concentrations is being tested on HeLa cells to observe cytotoxicity and cell viability.

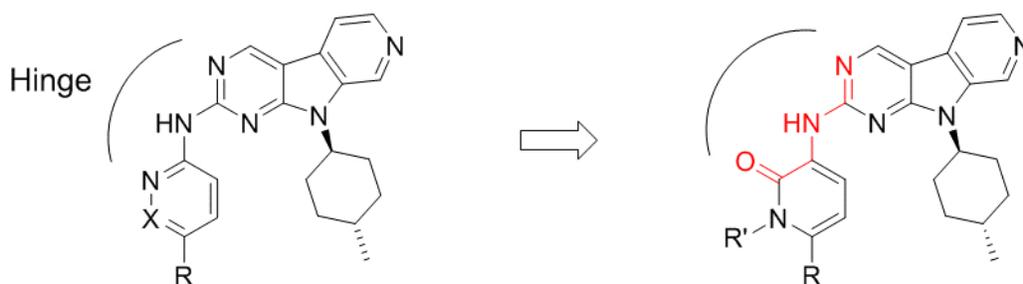
## **MEDI 105**

### **Design and optimization of CDK4/6 and FLT3 dual inhibitors with a novel hinge binder**

*Kexue Li, kexuel@yahoo.com, Lawrence R. McGee, John E. Eksterowicz, Derek Piper, Zhulun Wang, Grace Alba, Mark Ragains, Rachel Ngo, Mei-Chu Lo, Ji Ma, Kathleen Keegan, Cong Li, Lingming Liang, Kang Dai. Amgen, Inc., Thousand Oaks, California, United States*

The cyclin D-cyclin-dependent kinases 4 and 6 (CDK4/6)-retinoblastoma (Rb) pathway controls cell cycle progression by regulating the G1-S checkpoint. Multiple CDK4/6 inhibitors have received approval for the treatment of ER+ breast cancer, with additional clinical studies ongoing. FLT3 is a type III receptor tyrosine kinase, the mutation of which is the most frequent genetic alteration in acute myeloid leukemia (AML). Mutational resistance has been a serious clinical challenge for FLT3 inhibitors. It has been demonstrated in preclinical studies that the combined inhibition of FLT3 and CDK4 reduces occurrence of FLT3 resistance mutations, and thereby may prolong clinical responses.

A series of potent, highly selective and efficacious CDK4/6 and FLT3 dual inhibitors will be disclosed featuring a novel hinge binder, 3-(pyrimidin-2-ylamino)pyridin-2(1H)-one. The design and optimization of this series will be presented including physicochemical properties, PK/PD/xenograft efficacies, and kinase panel selectivity.



## MEDI 106

### Transporter informatics: Predicting substrates for transmembrane transporters

**Gerhard F. Ecker**, [gerhard.f.ecker@univie.ac.at](mailto:gerhard.f.ecker@univie.ac.at), **Stefan M. Kohlbacher**, Dept. Pharmaceutical Chemistry, University of Vienna, Wien, Austria

Transmembrane transporters of the ABC- and SLC-family play a major role in drug pharmacokinetics and are key for maintaining concentration gradients across membranes. Predicting substrate profiles of small molecules towards transporters may help medicinal chemists to prioritize compounds in an early phase of the drug development process. However, with the exception of very few transporters, available data sets are far too small to allow the development of decent machine learning models for predicting substrate properties. In order to overcome this problem, we analysed the NCI60 screening set and compiled datasets for classification of ABC- and SLC-transporter substrates.

For model building, descriptors and fingerprints were computed in RDKit, and models were implemented in scikit-learn. Applicability domain assessment follows a distance to model approach based on the 5 nearest neighbors. Models with acceptable quality have been implemented as a web-service, which allows to compute probabilities for a compound to be a substrate of a considerable number of ABC- and SLC-transporters.

## **MEDI 107**

### **Discovery of a pan-mGluR PAM for the treatment of CNS disorders**

**Stanislas Mayer**, *smayer@domaintherapeutics.com*. DOMAIN THERAPEUTICS SA, Illkirch, France

Glutamate which is the main neurotransmitter in the brain is at the center of several different neurological and psychiatric diseases. Therefore, glutamate receptors (GluRs) are key therapeutic targets in the treatment of conditions associated with altered glutamatergic signaling and conditions which can be affected by alteration of glutamate level or signaling. Among these receptors, it has been shown that the positive modulation the metabotropic glutamate receptors (mGluRs) of group III (mGluR4, 6, 7 and 8) results in neuroprotection and pro-motor effects that can be beneficial in the treatment of several neurological disorders including Parkinson disease, Alzheimer's disease, schizophrenia or autism. This poster will disclose *in vitro* and *in vivo* data of brain-penetrant compound, a potent pan-mGluR group III positive allosteric modulator. In particular, this compound shows anti-cataleptic effects in mice, at surprisingly low *per os* doses.

## **MEDI 108**

### **Fisetin derivatives as anti-prostate cancer agents**

**Kevin W. Muthima**<sup>1</sup>, *muthima@mail.fresnostate.edu*, **Qiaohong Chen**<sup>2</sup>, **Guanglin Chen**<sup>1</sup>, **Maizie Lee**<sup>3</sup>. (1) Chemistry, California State University Fresno, Fresno, California, United States (2) Chemistry, California State University, Fresno, Fresno, California, United States (3) Chemistry, Emory University, Atlanta, Georgia, United States

The most common cancer among men worldwide is prostate cancer. Early stage prostate cancer is treatable with hormone therapies, unfortunately, there is yet an effective treatment available for metastatic, advanced prostate cancer. Fisetin, a bioactive phenolic flavonol found in fruits, exhibits potential in treating prostate cancer according to *in vitro* and *in vivo* studies. The limitations of fisetin are moderate potency and low bioavailability. This study aims to alleviate, at least partially, the drawbacks of fisetin as an anti-prostate cancer agent through appropriate chemical modifications. To this end, four 7-O-aminopropyl-3,3',4'-O-trimethylfisetins, and one bifisetin derivative have been successfully synthesized. All synthesized fisetin derivatives have been characterized by their NMR data. Our WST-1 cell proliferation assay data indicate that methylation of 3,3',4'-trihydroxyl groups only led to slightly increased potency in suppressing cell proliferation towards three human prostate cancer cell models. Incorporation of an amine group through a three-carbon linker to 7-hydroxyl group of fisetin can significantly increase the anti-proliferative potency.

## **MEDI 109**

## **Immuno-oncology (IO) drug conjugate concentrates at cells and tumors and enhances survival**

**Sridhar Reddy Kaulagari**<sup>1,4</sup>, [sridharreddy.kaulagari@hsc.wvu.edu](mailto:sridharreddy.kaulagari@hsc.wvu.edu), Michael Doligalski<sup>2,3</sup>, Allison S. Cohen<sup>3</sup>, Hong Zheng<sup>5</sup>, Veronica Estrella<sup>3</sup>, Amer Beg<sup>5</sup>, David Morse<sup>3</sup>, Mark McLaughlin<sup>1,4</sup>. (1) Department of Pharmaceutical Sciences, West Virginia University, Morgantown, West Virginia, United States (2) Department of Chemistry, University of South Florida, Tampa, Florida, United States (3) Department of Cancer Imaging and Metabolism, Moffitt Cancer Center, Tampa, Florida, United States (4) Modulation Therapeutics Inc, Morgantown, West Virginia, United States (5) Department of Immunology, Moffitt Cancer Center, Tampa, Florida, United States

Targeted cancer therapy is gaining significant importance due to in part with the rapid improvement in understanding of the human immune system. Anti-CTLA4<sup>1</sup>, anti-PD1, and anti-PDL1 are immuno-oncology breakthrough drugs in the cancer treatment. Metastatic cutaneous melanoma has been the disease that has provided overwhelmingly positive early evidence of IO therapy safety and efficacy, but it is becoming clear that this drug class is effective against many other cancers<sup>2,3</sup>. In 2016, there were >250 ongoing clinical trials involving IO drug and drug candidate combinations<sup>3</sup>. These IO drug and clinical candidates unblock or directly activate the secondary signals that T cells require to stay fully activated in the tumor microenvironment. Unfortunately, not all cancer patients respond and most patients experience mild to moderate adverse immune events during or following the treatment<sup>4,5</sup>. Here we show that adding multiple copies of a targeting ligand for lung cancer to murine anti-PD1 enables the conjugate to specifically bind cells and concentrate at syngeneic murine tumors that express the targeted lung cancer-specific receptor. The tumor targeting allows for the use of safer doses of targeting ligand-anti-PD1 conjugate that reduced lung tumor burden and significantly extended survival after a single dose. The proof of concept studies with lung cancer targeting of murine anti-PD1 can be expanded to a fully humanized version and other IO agents can be lung cancer targeted using the same approach. Other cancer-specific targeting ligands may also be used to design tumor-specific IO agents for those respective cancers<sup>6,7</sup>.

## **MEDI 110**

### **Discovery and characterization of peptide inhibitors of RsmC function**

**Davidhan D. To**, [dto@kent.edu](mailto:dto@kent.edu), Keshav GC, Sanjaya Abeyirigunawardena. Chemistry and Biochemistry, Kent State University, Akron, Ohio, United States

The World Health Organization (WHO) has announced that antibiotic resistance in bacteria has become a global health crisis. Multidrug-resistant *Mycobacterium tuberculosis* has caused more than 250,000 deaths in 2015. According to the Center for Disease Control and Prevention (CDC), patients in the United States have been prescribed more than 250 million antibiotic doses each year, yet approximately 23,000

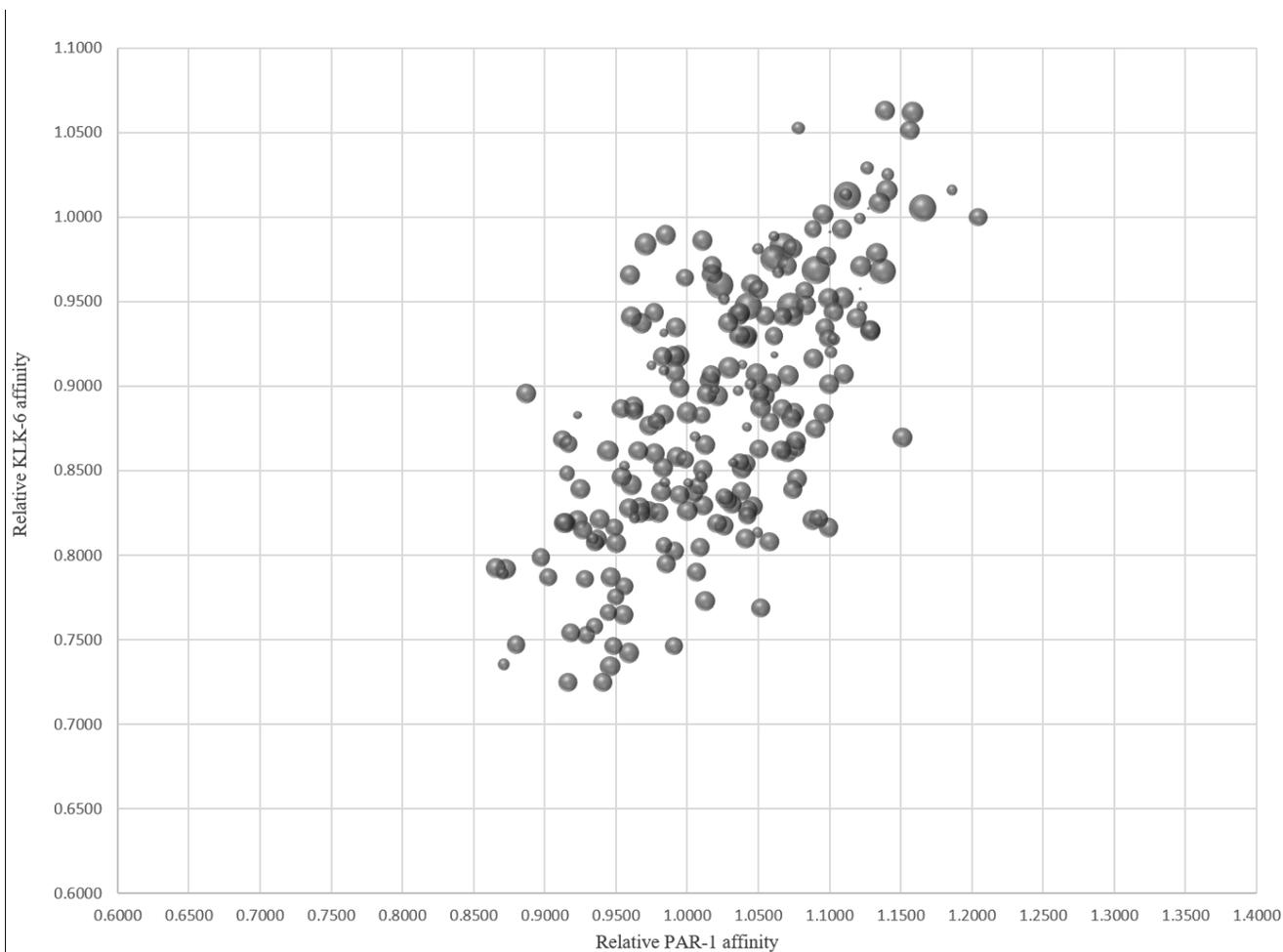
annual deaths in the US are caused by multi drug-resistant bacterial infections. Thus, development of novel antibiotics has become a necessity. The goal of our research is to disrupt ribosomal assembly mechanisms by inhibiting ribosomal modification enzymes. Our research is focused on protein RsmC (ribosomal RNA small subunit methyltransferase C), which binds to the 3' helix 34 (3'-h34) of the 16S 3'-major domain rRNA and methylates a guanine at position 1207 (G1207; *E. coli* numbering). Transverse mutations at position 1207 resulted in a lethal phenotype, perhaps due to the formation of a nonfunctioning ribosome. We have discovered a 7-mer peptide that binds tightly to 3'-h34 RNA using phage display. Tryptophan quenching experiments confirmed the binding of the peptide to 3'-h34. Furthermore, FRET inhibition assays showed that the peptide inhibits binding of RsmC to its target. This peptide will be further characterized to improve its delivery to bacterial cells as well as its binding affinity to the target RNA.

## **MEDI 111**

### **Implementation of vector analysis for the identification of potential KLK-6/PAR-1 dual inhibitors for the treatment of multiple sclerosis through molecular docking, molecular dynamics and chemoinformatic studies**

*Juan Fco. S. Tejeda, jfco\_sanchez@yahoo.com.mx, Marco A. Loza-Mejia, Samuel Fuentes-Villegas, Mario D. Salinas-Parra, Velia Villegas-Gonzalez. Chemical Sciences School, Universidad La Salle Mexico, Nezahualcoyotl, Mexico*

Multiple Sclerosis is a neurodegenerative disease associated to the demyelination of axons that currently has no cure. KLK-6 and PAR-1 are proteins that have been considered as potential targets for its treatment. Starting from the structure of known ligands of KLK-6 and PAR-1 and applying modification strategies like isosterism and scaffold-hopping, we designed a library of 211 compounds. The theoretical affinity to PAR-1 and KLK-6 was calculated using molecular docking and an *in silico* ADME/Tox profile was predicted, which we used to construct a chemoinformatic score (CIS). We applied a vector analysis, using as coordinates the CIS, and the docking score for PAR-1 and KLK-6. We interpreted the norm of the vector, G, as a parameter which summarized the evaluated properties; the ligands with largest values correspond to the most desirable in terms of dual binding and ADME/Tox properties. Molecular dynamics simulations helped us to understand the potential interaction of the best ligands to PAR-1 and KLK-6, allowing us to identify 2-benzoyl-2,3-dihydrobenzofuran as a potential dual scaffold. From this experience, vector analysis was found to be a helpful form of visualizing and analyzing results, particularly in the identification potential dual or multitarget ligands.



Graphic 1. Distribution of relative affinity of the ligands to both proteins; the chemoinformatic score is represented in the width of the circle.

Distribution of relative affinity of the ligands to both proteins; the chemoinformatic score is represented in the width of the circle.

## MEDI 112

### Molecular docking of torreyunlignans in phosphodiesterases 9A, 4B, and 8A: Computational analysis of torreyunlignan inhibition

***Eucolona M. Bonett***, *eucolona.bonett.15@cnu.edu*, Margaret McEwan, Kathryn E. Cole, Jeffrey M. Carney. *Molecular Biology and Chemistry, Christopher Newport University, Newport News, Virginia, United States*

Torreyunlignans (TA-D) are natural products isolated from the Yunnan Nutmeg Yew, *Torreya yunnanensis*. These compounds are the first reported naturally occurring inhibitors of phosphodiesterase 9A (PDE9A), a high-affinity cGMP-specific enzyme. Previous research has indicated that PDE9A inhibitors are of therapeutic utility for the

treatment of Alzheimer's Disease and diabetes mellitus. The active site of PDE9A contains key residues Y424, F56, F441, and the conserved Q453, as well as a hydrophobic clamp composed of F441, V417, L421, and A452. Previous studies have shown that interactions with these residues and exploitation of the hydrophobic clamp are the most common among known PDE9A inhibitors, as well as its substrate. It was proposed that interactions with Y424 may be a basis for PDE9A selectivity since all PDE families, with the exception of 8 and 9, contain phenylalanine in place of Y424. Additionally, selectivity for PDE9A may be accomplished by increasing  $\pi$ -stacking interactions with F441, which is an isoleucine in other PDE families. Thus, PDE9A inhibitor binding and selectivity are likely to be maximized if interactions with all key residues are present. The structure-activity relationships of TA-D are not currently known. Additionally, their inhibitory action against other PDEs has not been fully explored. Modeling of TA-D in other PDEs is a valuable approach towards understanding the structure-activity relationships of TA-D, as well as active site ligand interactions in general. TA-D were modeled in PDE9A, as well as PDE4B and PDE8A, using Autodock Vina. TA-D had the lowest binding energies, thus highest affinity, when complexed with PDE9A as compared to the binding energies of TA-D in PDE8A and PDE4B. Additionally, TA-D displayed interactions with Y424 and either sandwich or parallel offset  $\pi$ -stacking with F441. This research ultimately seeks to aid the development of structural analogs with increased specificity and inhibitory action towards PDE9A by elucidating structure-activity relationships and providing insight into PDE9A selectivity.

## **MEDI 113**

### **Molecular docking and lead optimization of torreyunlignans, phosphodiesterase 9A inhibitors**

***Eucolona M. Bonett***, *eucolona.bonett.15@cnu.edu*, Kathryn E. Cole, Jeffrey M. Carney. *Molecular Biology and Chemistry, Christopher Newport University, Newport News, Virginia, United States*

Torreyunlignans (TA-D) are natural products isolated from the Yunnan Nutmeg Yew, *Torreya yunnanensis*. These compounds are the first reported naturally-occurring inhibitors of phosphodiesterase 9A (PDE9A), a high-affinity cGMP-specific enzyme. Previous research has indicated that PDE9A inhibitors are of therapeutic utility for the treatment of Alzheimer's Disease and Diabetes mellitus. The active site of PDE9A contains key residues Y424, F56, F441, and the conserved Q453, as well as a hydrophobic clamp composed of the F441, V417, L421, and A452. Previous studies have shown that interactions with these residues and exploitation of the hydrophobic clamp are the most common among known PDE9A inhibitors, as well as its substrate. The potential therapeutic properties of TA-D make them a candidate for molecular docking and lead optimization studies. TA-D were modeled in PDE9A using AutoDock Vina and structural analogs of TA-D were developed. Computational predictions of absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties were also calculated to determine the drug candidate potential of TA-D and their structural

analogs. Known inhibitors were also modeled in order to validate the computational analysis. Each showed the same active site orientation as their crystal structure, providing evidence that the AutoDock Vina modeling displayed an accurate representation of active site orientation. TA-D had higher affinity than the known inhibitors, which was improved in the structural analogs. Additionally, TA-D displayed interactions with all key residues aside from Q453. Of the high-affinity analogs (A), only A52 displayed Q453 interactions. Further work regarding the lead optimization of TA-D will be conducted to synthesize high-affinity analogs with drug-like pharmacokinetic attributes.

## **MEDI 114**

### **Cytosine-based TET enzyme inhibitors**

*Haoyu Sun<sup>1</sup>, hsun@bates.edu, Nathanael Kuzio<sup>1</sup>, Michael J. Bennett<sup>1</sup>, Gabriella Chua<sup>1</sup>, Kelly L. Wassarman<sup>1</sup>, Joseph A. Alp<sup>1</sup>, Emma I. Jarczyk<sup>1</sup>, Beth G. Malachowsky<sup>1</sup>, Andrew Kennedy<sup>2</sup>. (1) Bates College, Lewiston, Maine, United States (2) Chemistry and Biochemistry, Bates College, North Garden, Virginia, United States*

The stabilization of long-term memory requires the activity of DNA methyltransferases (DNMTs), which methylate plasticity-regulatory genes. Reducing DNA methylation through the inhibition of DNMT, is sufficient to impair long term memory. These methyl groups on the DNA can be removed through the activity of the ten-eleven translocation (TET) family of enzymes. The genetic deletion of TET enzymes in mice has been shown to increase DNA methylation and improve memory, both associative and spatial. Here, an approach is being taken to design, synthesize, and evaluate therapeutic compounds that increase the fidelity of DNA methylation by inhibiting TET enzymes. A library of first generation inhibitors was synthesized, of which some demonstrated inhibitory activity at low micromolar concentrations. Following these results, computational modeling using Molecular Operating Environment (MOE) software was used to identify specific molecular interactions within the TET enzyme binding site, based of the crystal structure of TET2 bound to methylated DNA and homology models of the other TET enzymes. The data collected by this *in silico* analysis, as well as the activity of first generation compound Bobcat339, have led to the development of second generation inhibitors. Paralleling this research, *in vitro* testing was conducted in order to determine the efficacy of this library in mouse hippocampal neuronal cell culture. Ultimately, producing a successful TET inhibitor could result in wide-ranging therapeutic applications for diseases and disorders associated with epigenetic dysregulation, including disorders of memory function.

## **MEDI 115**

**Comparison of native ribose and conformationally-constrained (N)-methanocarba nucleosides for A<sub>1</sub> adenosine receptor agonists: Design and *in vivo* characterization**

**Dilip Tosh**<sup>1</sup>, [toshd@mail.nih.gov](mailto:toshd@mail.nih.gov), Harsha Rao<sup>1</sup>, Amelia Bitant<sup>3</sup>, Veronica Salmaso<sup>1</sup>, Philip Mannes<sup>1</sup>, David I. Lieberman<sup>1</sup>, John A. Auchampach<sup>3</sup>, Antonella Ciancetta<sup>4</sup>, Naili Liu<sup>2</sup>, Zhenzhong Cu<sup>2</sup>, Zhan-Guo Gao<sup>1</sup>, Marc L. Reitman<sup>2</sup>, Oksana Gavrilova<sup>2</sup>, Kenneth A. Jacobson<sup>1</sup>. (1) Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Disease, National Institutes of Health, Bethesda, Maryland, United States (2) Endocrinology, and Obesity Branch, National Institute of Diabetes and Digestive and Kidney Disease, National Institutes of Health, Bethesda, Maryland, United States (3) Department of Pharmacology, Medical College of Wisconsin, Milwaukee, Wisconsin, United States (4) School of Pharmacy, Queen's University Belfast, Belfast, United Kingdom

(N)-Methanocarba ([3.1.0]bicyclohexyl) adenosines and corresponding ribosides were synthesized to identify novel A1 adenosine receptor (A1AR) agonists for CNS or peripheral applications. Human and mouse AR binding was determined to assess the A1AR compatibility of the constrained ring system in adenosine analogues in combination with N<sup>6</sup>, C2 and C5' substitution. An N<sup>6</sup>-dicycloalkyl ribose agonist (MRS7469) was >2000-fold selective for A1AR in two species and drug-like, based on in vitro and in vivo ADME-tox testing. The pure N<sup>6</sup>-(S)-endo-norbornyl diastereoisomer of known riboside CI-ENBA displayed high hA1AR selectivity. Methanocarba modification reduced A1AR selectivity of N<sup>6</sup>-dicycloalkylmethyl and endo-norbornyl adenosines, but when applied to the antiviral drug ribavirin increased A1AR selectivity compared to the riboside. Thus, alternative nucleobases can be considered in the design of A1AR agonists. Most analogues tested (ip.) were inactive or weak in inducing mouse hypothermia, despite mA1AR full agonism and variable mA3AR efficacy, but strong hypothermia by MRS7469 depended on A1AR with peripheral A3AR participating (determined using A1AR or A3AR null mice). The interaction of the nucleosides with the hA1AR was modeled using the recently determined cryo-EM structure of an active state hA1AR. Conserved H-bonds were preserved in modeling of MRS7469 and methanocarba equivalent MRS7587. Thus, we identified, and characterized in vivo and computationally, novel ribose and methanocarba-modified nucleosides that potently activate A1AR.

## **MEDI 116**

### **Curcumin-metal complexes as inhibitors of beta-amyloid aggregation**

**Matilda Dervisevic**, [matildadervisevic4@gmail.com](mailto:matildadervisevic4@gmail.com), Anuradha Vummenthala, **Josh Brabant**, [jbrabant1@live.maryville.edu](mailto:jbrabant1@live.maryville.edu). Maryville, St. Louis, Missouri, United States

Alzheimer's disease is a type of dementia in which patients are found to have beta-amyloid aggregations that form into plaques and further degrade the patient's brain function. Curcumin, a compound commonly found in turmeric, has been found to decrease beta-amyloid plaque formation. One of the drawbacks of Curcumin is its poor bioavailability. Literature results suggested that conversion of Curcumin to a metal complex not only addressed the poor bioavailability but also showed increasing anti-cancer and anti-oxidant activities. This experiment primarily focused on enhancing the

effect of Curcumin on beta-amyloid aggregation by converting it into Curcumin-Metal complex. The metals chosen were Aluminum and some d-block elements such as Zinc, Copper, Cobalt, and Gallium that have been previously shown to augment the properties observed in Curcumin. These metal complexes showed promising results in delaying the kinematics of the beta-amyloid aggregation.

## **MEDI 117**

### **Biochemical analysis of *Syzygium aromaticum* as potential agent in the treatment of diabetes**

**Grecia W. Garcia**, *grecia.garcia03@utrgv.edu*, Arnulfo Mar, Helia M. Morales. Chemistry, University of Rio Grande Valley, Brownsville, Texas, United States

Our research involves the biochemical study of plants that are used as folk remedies in the treatment of diabetes. *Syzygium aromaticum*, also known as clove bud, is native to the Maluku Islands in Indonesia and has been found to possess medicinal properties. The ingestion of this spice infusions has been claimed to regulate blood sugar levels and to alleviate the symptoms associated with this illness. In these studies, we analyzed aqueous extracts from the clove buds for amino acids, proteins and carbohydrates. Amino acid analysis was done by means of Ninhydrin reagent, protein content was performed by means of the Biuret reagent with detection at 540 nm. Sugar content determination was done qualitatively using the Benedict Reagent and quantitatively using the sulfuric acid-phenol method. Total phenols were detected using Folin-Ciocalteu reagent. The Total anti-oxidant capacity (TAOC) is determined using the FRAP (Ferric reducing antioxidant power) assay. The determination of ascorbic acid is done by using meta-phosphoric acid and 2, 4 dinitrophenylhydrazine. Our results show no evidence for the presence of amino acids or proteins in the extracts. Reducing sugars were detected in the extracts and the concentrations were determined. Future work involves the analysis of plant extracts by using SDS electrophoresis and thin layer chromatography. Preparative column chromatography and RP-HPLC will be done to investigate the presence of quercetin, gallic and ferulic acids in *Syzygium aromaticum* since these phenols have been previously proven to regulate clotting patterns and to decrease cellular oxidative stress.

## **MEDI 118**

### **Structure-function studies of a novel allosteric site of the dopamine transporter as a target for alternative therapeutics against cocaine use disorder**

**Shaili Aggarwal**<sup>3</sup>, *shaili.x.aggarwal@gmail.com*, Xiaonan Liu<sup>3</sup>, Caitlyn Rice<sup>3</sup>, Sandhya Kortagere<sup>1</sup>, Joseph Salvino<sup>2</sup>, Ole Mortensen<sup>3</sup>. (1) Department of Microbiology and Immunology, Drexel University College of Medicine, Philadelphia, Pennsylvania, United States (2) Molecular Screening and Protein Expression Facility, The Wistar Institute, Philadelphia, Pennsylvania, United States (3) Department of Pharmacology and

*Physiology, Drexel University College of Medicine, Philadelphia, Pennsylvania, United States*

The dopamine transporter (DAT) serves a pivotal role in controlling dopamine (DA)-mediated neurotransmission by clearing DA from synaptic and perisynaptic spaces, and controlling its action at postsynaptic DA receptors. Major drugs of abuse such as amphetamine and cocaine interact with DAT to mediate their effects by enhancing extracellular DA concentrations. Thus, DAT is a viable target for the treatment of psychostimulant abuse and addiction. We have recently identified a novel allosteric site that lies outside the central substrate and inhibitor binding pocket of DAT. This allosteric site was identified using information derived from comparative modeling of human and parasite *Schistosoma mansoni* monoamine transporters. Site-directed mutagenesis has validated the functional significance of this allosteric site. In addition, the hybrid structure-based (HSB) method has identified conformation-specific molecules that can potentially stabilize the transporter in certain beneficial conformations that may alter its interaction with cocaine and amphetamine without affecting uptake activity of DA. Interestingly, KM822, one of the ligands identified in a virtual screening experiment, was found to decrease the affinity of cocaine for DAT by 3-folds in an *in vitro* cell-based assay. In addition, KM822 also reduced the potency of cocaine towards DAT-mediated DA reuptake inhibition in an *ex vivo* model of striatal synaptosome preparations. The preliminary *in vivo* effects of KM822 on cocaine potency were tested on psychostimulant-associated behaviors in a planarian model where KM822 specifically inhibited the locomotion elicited by DAT-interacting stimulants amphetamine and cocaine. We have further identified the structural determinants of KM822 allosteric binding site by employing substituted cysteine scanning accessibility methods (SCAM) and biotinylation experiments. Additional studies are being employed to directly determine the point of interaction of KM822 within the allosteric pocket by using affinity-based labeling and biorthogonal click chemistry techniques. In addition, we have also performed a SAR evaluation of several KM822 analogs to find more potent and efficient DAT modulators. Overall, KM822 provides a unique opportunity as a molecular probe to identify novel mechanistic aspects of DAT function and can lead to the development of more unique compounds with promising mechanism of action.

## **MEDI 119**

### **Cyclization-centered structure-activity relationship of a noncovalent inhibitor of the KEAP1-NRF2 interaction**

**Kenneth M. Booker**<sup>1</sup>, [kennethmbooker@gmail.com](mailto:kennethmbooker@gmail.com), **Terry W. Moore**<sup>2</sup>, **Brian David**<sup>3</sup>. (1) *Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Chicago, Illinois, United States* (2) *Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Chicago, Illinois, United States* (3) *Medicinal Chemistry, University of Illinois at Chicago, Chicago, Illinois, United States*

The adaptive stress response is a physiological mechanism that protects the body against electrophilic or oxidative stress by producing antioxidant enzymes. This

response is controlled by the protein-protein interaction between the transcription factor **NRF2** and its negative regulator **KEAP1**. Normal interaction of KEAP1 with NRF2 promotes NRF2's degradation. Some electrophiles can disrupt this interaction by binding KEAP1, thus freeing, or "activating," NRF2 so that it can transcriptionally upregulate detoxifying enzymes like heme oxygenase 1 and glutathione S-transferases. Because chronic oxidative stress is implicated in many diseases, including multiple sclerosis and diabetic wound healing, NRF2 activation has become an attractive pharmacological strategy. Many drug candidates are electrophiles that exhibit off-target activity. In contrast, our lab develops non-electrophilic NRF2 activators. Our starting point has been a non-electrophilic 1,4-diaminonaphthalene scaffold known to bind competitively to KEAP1's Kelch domain, a crucial site for normal KEAP1-NRF2 interaction. Suggestive co-crystal structures have led us to develop a structure-activity relationship focused on cyclization of this scaffold. We hypothesize that constraining these molecules into their Kelch-bound conformation will enhance their binding affinities and membrane permeabilities. Two types of cyclic molecules were synthesized using hydrocarbon linkers in one of two ring substitution patterns. The linkers are stabilized at their terminal ends by either 1) amide bonds, or 2.) ether bonds. Preliminary data from *in vitro* binding assays suggest that amide-based linkages in *meta*-substituted bis-anilines are tolerated, especially when carboxymethyls are incorporated into the structure. This work identifies cyclization as a potentially useful strategy for studying the pharmacology of diaminonaphthalenes and similar scaffolds.

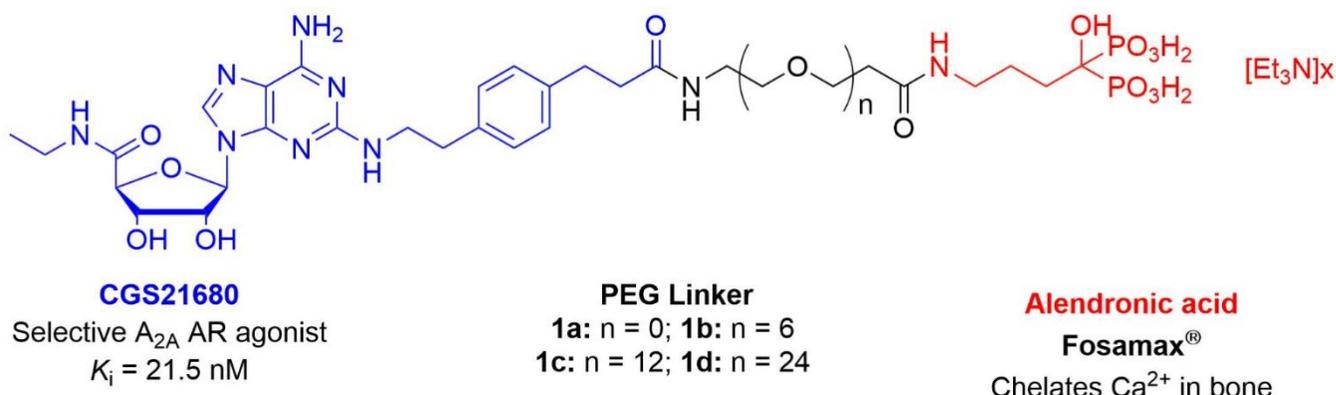
## **MEDI 120**

### ***In vivo* effect of PEG-tethered A<sub>2A</sub> adenosine receptor agonist-alendronic acid conjugates on induced bone degeneration**

**Kiran S. Toti**<sup>1</sup>, [kiran.toti@nih.gov](mailto:kiran.toti@nih.gov), Ane Larrañaga-Vera<sup>2</sup>, Alexandra Gadiano<sup>1</sup>, Eugene Warnick<sup>1</sup>, Harsha Rao<sup>1</sup>, Zhan-Guo Gao<sup>1</sup>, Bruce N. Cronstein<sup>2</sup>, Kenneth A. Jacobson<sup>1</sup>. (1) Molecular Recognition Section, LBC, NIDDK, National Institutes of Health, Bethesda, Maryland, United States (2) Division of Translational Medicine, Department of Medicine, NYU Langone Health, New York, New York, United States

Many prosthetic surgeries result in local inflammation and bone degradation, which eventually lead to implant failure. Bisphosphonate drugs (e.g. alendronic acid) prevent bone loss in osteoporosis patients by chelating to calcium in the bone surface and by other mechanisms. The recent finding by the co-authors Cronstein et al. (Sci. Transl. Med. 2012, 4, 135ra65) suggests that selective A<sub>2A</sub> adenosine receptor (AR) agonists decrease osteolysis and promote osteoblast differentiation. In an *in vivo* (murine) ultrahigh-molecular weight-polypropylene wear particle-induced bone degeneration model, administration of A<sub>2A</sub>AR agonist CGS21680 reduced bone loss and associated inflammation. We envisaged combining the effects of both bisphosphonate and A<sub>2A</sub>AR agonist by linking the small molecules via PEG conjugation. Co-administration of compound **1b** (hA<sub>2A</sub>AR, radioligand binding  $K_i = 69.2$  nM) with wear particles resulted in bone regeneration with a considerable reduction in bone loss and associated

inflammation. Synthetic routes to prepare the novel conjugates, *in vitro* binding studies and *in vivo* findings will be presented



## MEDI 121

### Treatment of sensorimotor gating deficits in neuropsychiatric disorders using deuterated $\alpha 6$ -GABA<sub>A</sub>R subtype selective ligands

**Daniel E. Knutson**<sup>1</sup>, knutsond@uwm.edu, Revathi Kodali<sup>1</sup>, Marco Trever<sup>2</sup>, Branka Divovic<sup>3</sup>, Hsin-Jung Lee<sup>4</sup>, Jui-Feng Chou<sup>4</sup>, Hon-Lie Chen<sup>4</sup>, Lih-Chu Chiou<sup>4</sup>, Margot Ernst<sup>2</sup>, Marko D. Mihovilovic<sup>5</sup>, Miroslav M. Savić<sup>3</sup>, Werner Sieghart<sup>2</sup>, James M. Cook<sup>1</sup>. (1) Department of Chemistry & Biochemistry, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin, United States (2) Center for Brain Research, Department of Molecular Neurosciences, Medical University of Vienna, Vienna, Austria (3) Department of Pharmacology, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia (4) Graduate Institute of Pharmacology, National Taiwan University, Taipei, Taiwan (5) TU Wien—Institute of Applied Synthetic Chemistry, Vienna, Austria

GABA<sub>A</sub> receptors (GABA<sub>A</sub>Rs) containing the  $\alpha 6$  subunit are primarily found in the granule cells of the cerebellum. Attenuation of granule cell activity by positive allosteric modulation of cerebellar  $\alpha 6$ -GABA<sub>A</sub>Rs has recently been shown to rescue disrupted prepulse inhibition of the startle response (PPI). Thus, we hypothesized that enhancing the activity of  $\alpha 6$ -GABA<sub>A</sub>Rs in the cerebellum may be effective in the treatment of neuropsychiatric disorders with sensorimotor gating deficits such as but not limited to schizophrenia, Tourette's syndrome, obsessive compulsive disorder, and attention deficit disorders. Herein, the results of electrophysiological, pharmacokinetic and PPI studies of three deuterated, structurally similar pyrazoloquinolinones (**DK-I-56-1**, **DK-I-58-1** and **DK-I-59-1**) are reported. All three functionally selective ligands act at the  $\alpha 6 + \beta 3$ - interface (PQ Site) of  $\alpha 6$ -GABA<sub>A</sub>Rs as positive allosteric modulators (PAMs). Deuteration of the methoxy groups of these ligands improves their metabolic stability and enhances their bioavailability. Results obtained indicate that PAM action at cerebellar  $\alpha 6$ -GABA<sub>A</sub>Rs significantly rescues the effect of methamphetamine induced

PPI disruption in mice. Additionally, the  $\alpha 6$ -selective ligands have been shown to be non-toxic to liver or kidney cells and devoid of the classical benzodiazepine-type side effects such as sedation, motor-impairment and ataxia. Therefore, these ligands which selectively modulate  $\alpha 6$ -GABA<sub>A</sub>Rs are novel candidates to treat neuropsychiatric disorders with sensorimotor gating deficits.

## **MEDI 122**

### **Anti-glycation effect and advanced glycation end-products protein cross-links breaking ability of *Psidium guajava* leaf extracts**

**Oluwaseyefunmi I. Adeniran**<sup>1</sup>, *seyefunmiadeniran@gmail.com*, Alfred Mogale<sup>1</sup>, L. J. Sha<sup>2</sup>. (1) Biochemistry, Sefako Makgatho Health Sciences University, Pretoria, Gauteng, South Africa (2) Biomedical Sciences, Tshwane University of Technology, Pretoria, GAUTENG, South Africa

Advanced glycation end-products (AGEs) are implicated in the pathogenesis of diabetes and age-related diseases such as Alzheimer's disease. There is no clinically approved anti-glycation agent yet. The objectives of the study were to investigate and compare the anti-glycation effect of *Psidium guajava* leaf extracts (PGLETs) with that of aminoguanidine (AG) and to assess the PGLETs' AGE-cross-link breaking ability. Bovine serum albumin (BSA) was incubated with glucose in the presence of hexane, ethyl acetate, methanol and water PGLETs at 37°C for 40 days. Total immunogenic AGEs (TIAGEs), carboxymethyllysine (CML), carboxyethyllysine (CEL) and fluorescent AGEs (FAGEs) formed were measured using ELISA and spectrophotofluorometry and the percentage anti-glycation activity of each plant extract was calculated. The ability of PGLETs to break BSA-AGE-collagen cross-links was also investigated by means of ELISA. After 40 days incubation, hexane, ethyl acetate and methanol PGLETs demonstrated higher anti-glycation activity against TIAGEs while hexane and the polar extracts (methanol and water) demonstrated higher anti-glycation effect than AG against CEL. Only the methanol and water PGLETs demonstrated higher anti-glycation activity than AG against CML and FAGEs. With regard to the ability of PGLETs to breakdown AGEs-protein cross-links, hexane and ethyl acetate PGLETs demonstrated higher ability to break AGE-protein cross-links than methanol and water PGLETs. Crude PGLETs have the ability to inhibit the formation of AGEs and to breakdown AGE-protein cross-links. Work is underway in our laboratory to isolate bioactive compounds from PGLETs.

## **MEDI 123**

### **Renoprotective effects of hypoxylonol derivatives isolated from *Hypoxylon truncatum* against cisplatin-induced cytotoxicity**

**Jungyeob Ham**<sup>4,5</sup>, *ham0606@kist.re.kr*, Ki Sung Kang<sup>3</sup>, Buyng Su Hwang<sup>2</sup>, Dahae Lee<sup>3</sup>, Pilju Choi<sup>1,3</sup>, Taejung Kim<sup>1</sup>, Young-Tae Park<sup>1</sup>, Seon-Jun Choi<sup>1</sup>, Bong Geun Song<sup>1</sup>, Kiu-Hyung Cho<sup>6</sup>. (1) Natural Products Research Institute, Korea Institute of Science and

Technology, Gangneung, Korea (the Republic of) (2) Bioresources Industrialization Research Division, Nakdonggang National Institute of Biological Resources, Sangju, Korea (the Republic of) (3) College of Korean Medicine, Gachon University, Sunghnam, Korea (the Republic of) (4) Natural Products Research Institute, Korea University of Science and Technology, Gangneung, Korea (the Republic of) (5) Division of Bio-Medical Science and Technology, University of Science and Technology, Daejeon, Korea (the Republic of) (6) Research Division, Gyeongbuk Institute for Bio Industry, Andong, Korea (the Republic of)

Although cisplatin is the standard platinum-based anticancer drug used to treat various solid tumors, it can cause damage in normal kidney cells. Protective strategies against cisplatin-induced nephrotoxicity are therefore clinically important and urgently required. To address this challenge, we investigated the renoprotective effects of *Hypoxyylon truncatum* collected in Yeongok-myeon, Gangneung city, Korea. Chemical investigation of the active fraction from the methanol extract of *H. truncatum* resulted in the isolation and identification of the renoprotective compounds, hypoxylylonol C and F, which ameliorated cisplatin-induced nephrotoxicity to approximately 80% of the control value at 5  $\mu$ M. The mechanism of this effect was further investigated using hypoxylylonol F, which showed a protective effect at the lowest concentration. Upregulated phosphorylation of p38, extracellular signal-regulated kinases, and c-Jun N-terminal kinases following cisplatin treatment were markedly decreased after pre-treatment with hypoxylylonol F. In addition, the protein expression level of cleaved caspase-3 was significantly reduced after co-treatment with hypoxylylonol F. These results show that blocking the mitogen-activated protein kinase signaling cascade plays a critical role in mediating the renoprotective effect of hypoxylylonol F isolated from *H. truncatum* fruiting bodies.

## MEDI 124

### **Incarvillateine produces antinociceptive and motor suppressive effects via adenosine receptor activation**

**Jinwoo Kim**<sup>1</sup>, jinwookim031@gmail.com, Diane M. Bogdan<sup>2</sup>, Matthew W. Elmes<sup>3</sup>, Monaf Awwa<sup>1</sup>, Su Yan<sup>1</sup>, Joyce Che<sup>3</sup>, Garam Lee<sup>3</sup>, Dale G. Deutsch<sup>3</sup>, Robert C. Rizzo<sup>4</sup>, Martin Kaczocha<sup>3</sup>, Iwao Ojima<sup>5</sup>. (1) Chemistry, Stony Brook University, Port Jefferson, New York, United States (2) Anesthesiology, Stony Brook University, Stony Brook, New York, United States (3) Biochemistry and Cell biology, Stony Brook University, Stony Brook, New York, United States (4) Applied Mathematics and Statistics, Stony Brook University, Stony Brook, New York, United States (5) Chem Dept/ICBDD, Stony Brook University, Stony Brook, New York, United States

(-)-Incarvillateine (INCA) is a monoterpene alkaloid produced by *Incarvillea sinensis* that has been used as a pain reliever in China for a long time. Previous work by our group has identified truxillic acid monoesters (TAMEs) as a new class of inhibitors targeting fatty acid binding protein 5 (FABP5) and showing both antinociceptive and anti-inflammatory effects in mouse models. Due to the structural similarity between INCA

and TAMEs, we hypothesized that INCA could exert its antinociceptive effects via FABP inhibition. Our findings show that INCA does not bind to four human FABP isoforms (FABP3, FABP4, FABP5 and FABP7) *in vitro* and the putative monoester metabolite of INCA, INCA-TAME, which closely resembles TAMEs also lacked affinity for FABPs. Further investigation in mouse studies showed that INCA exerts not only potent antinociceptive but also motor suppressive effects at equivalent doses while INCA-TAME was ineffective. This result implies that the observed antinociceptive effects of INCA should be interpreted with caution.

## **MEDI 125**

### **Study of the biochemistry of lemon grass: A widely used diabetes remedy**

*nalley trejo, nallely.trejo01@utrgv.edu. university of texas rio grande valley, Brownsville, Texas, United States*

The research involves the biochemical study of home-grown plants, along the Texas-Mexico border that people use for the treatment of diabetes. Cymbopogon better known as lemon grass is easy found in Austria, Africa and Asia and it is used a medicinal plant along the Texas-Mexico border for the treatment of diabetes and other problems relate with this illness. In these studies, we have analyzed aqueous extracts from the plant for amino acids, proteins and carbohydrates. Among the techniques used are: UV-visible spectrophotometry, pH measurement, sugar content determination using the Benedict Reagent and the sulfuric acid-phenol method, amino acid analysis by means of ninhydrin, and protein tests using the Biuret reagent. Preliminary results show evidence of the presence of amino acids and proteins in the extracts. No reducing sugars were detected in our experiments. Analysis of plant extracts by using SDS electrophoresis and protein separation by means of preparative column chromatography has been done presently we are developing methods for the analysis of plant extracts using RP-HPLC. Further work involves the determination of total phenol content in the aqueous extracts.

## **MEDI 126**

### **Investigation of effects of rigidity on kinase inhibitor selectivity**

*Caiqun Yu<sup>1</sup>, caiqunyu@usc.edu, Amir Assadieskandar<sup>2</sup>, Chao Zhang<sup>3</sup>. (1) Chemistry, University of Southern California, Los Angeles, California, United States (2) University of Southern California, Los Angeles, California, United States (3) Department of Chemistry, University of Southern California, Los Angeles, California, United States*

Protein kinases control various cellular processes such as cell division, proliferation, and differentiation. Small-molecule kinase inhibitors are useful tools for dissecting the functions of protein kinases in cells as they can acutely turn off the catalytic activity of kinases. Because dysregulation of the kinase activity in the cell signaling pathways can drive cancer growth, many protein kinases are pursued as therapeutic targets. While small-molecule kinase inhibitors have been developed as therapeutics for the treatment

of cancer, the majority of them suffer from poor target selectivity because of the high homology in the catalytic domain among the hundreds of human kinases. Here we report a new strategy of rigidifying the inhibitors to achieve selective kinase inhibition. Specifically, we applied the ring closure strategy to a pyrazolo[3,4-*d*]pyrimidine-based inhibitor which afforded dramatic improvement in selectivity for RAF kinases. The optimized rigidified inhibitor potently blocked the activity of BRAF<sup>V600E</sup> and the proliferation of cancer cells. More importantly, the optimized molecule selectively suppressed the cell proliferation in cancer cells harboring BRAF<sup>V600E</sup> in a panel of 60 cancer cell lines. The crystal structures of optimized inhibitors bound to BRAF were solved to confirm the binding mode and further explain the improved selectivity.

## **MEDI 127**

### **Androgen receptor degraders and transactivation domain inhibitors targeting castration-resistant prostate cancer**

**D. Elshan N. G. Ralalage**<sup>1</sup>, [elshan@chem.ucla.edu](mailto:elshan@chem.ucla.edu), Jiabin An<sup>2</sup>, Michael E. Jung<sup>1</sup>, Matthew B. Rettig<sup>2,3</sup>. (1) Department of Chemistry and Biochemistry, University of California - Los Angeles, Los Angeles, California, United States (2) Division of Hematology/Oncology, VA Greater Los Angeles Healthcare System West LA, Los Angeles, California, United States (3) Departments of Medicine and Urology, David Geffen School of Medicine, University of California - Los Angeles, Los Angeles, California, United States

Prostate cancer (PCa) is the second leading cause of cancer-related mortality in men in the United States. Androgen deprivation therapy (ADT) through surgical or chemical castration is the mainstay of therapy for patients with metastatic PCa. The androgen receptor (AR) plays a central role in the progression of this disease. The AR has three distinct regions in its structure; a *N*-terminal transactivation domain (TAD), a DNA binding domain (DBD), and a ligand binding domain (LBD). ADT and all current AR antagonists function by directly or indirectly targeting the AR–LBD which inhibits PCa progression. Patients eventually develop resistance to these current therapies, leading to the lethal form of PCa termed metastatic castration-resistant prostate cancer (mCRPC). Primary resistance mechanisms involve but are not limited to 1) LBD mutations and 2) the evolution of constitutively active AR splice variants that lack a functional LBD. Given that the primary resistance mechanisms are centered upon the AR–LBD, there is an unmet need to develop therapies that target the other functional domains on the AR. Here, we show the targeting of CRPC through a novel class of AR inhibitors that target the AR–TAD and also enhance the degradation of AR protein. These compounds have shown excellent *in vitro* and *in vivo* characteristics in inhibiting AR-driven CRPC tumor growth. Given the promising ability to inhibit the AR signaling axis even in the presence of constitutively active AR splice variants, these compounds are currently being further-developed as potential therapeutics for the treatment of CRPC.

## **MEDI 128**

## **Discovery and SAR studies of novel non-toxic azacyclic derivatives for the treatment of type 2 diabetes mellitus**

**Hyeonjin Choi**<sup>1</sup>, s071130@gmail.com, Yeong Hye Park<sup>1</sup>, Jinsook Kwak<sup>1</sup>, Eun-Bee Jung<sup>2</sup>, Min-Kyu Yang<sup>2</sup>, Ki Sung Kang<sup>3</sup>, Hwayoung Yun<sup>1</sup>. (1) College of Pharmacy, Pusan National University, Busan, Korea (the Republic of) (2) Mother's Pharmaceutical, Seoul, Korea (the Republic of) (3) College of Korean Medicine, Gachon University, Seongnam, Korea (the Republic of)

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia due to the reduction of sensitivity to insulin and the dysfunction of insulin-secreting in pancreatic beta-cells. The disease has been spread all over the world and affected over 300 million people. Although many anti-diabetic drugs are currently available to treat this chronic disease, they have limited long-term efficacy due to undesirable adverse effects. Hence, the strong need for novel anti-diabetic agents with a good safety still continues.

In connection with development of novel hypoglycemic agents, a dose dependent GSIS assay was conducted in an INS-1  $\beta$  cell line to screen a druggable in-house chemical library. We identified a potent hit compound with azacycle-based novel skeleton which showed equal insulin-secreting activity with that of gliclazide. The newly designed 40 azacycles were synthesized to develop more potent and safe analogs and then their biological activities were evaluated using GSIS and MTT assay on INS-1  $\beta$  cells. From the structure-activity relationship (SAR) studies, the electron donating group which substituted in amidobenzene ring plays a crucial part in insulin-secreting activity. Furthermore, mechanism studies on most potent compound revealed that our compounds act as agonists on PPAR $\gamma$  receptor.

### **MEDI 129**

#### **Optimization of 6-amino-3-methylpyrimidinones as potent, selective, and orally efficacious SHP2 inhibitors**

**Mark G. Palermo**<sup>1</sup>, mark.palermo@novartis.com, Patrick J. Sarver<sup>2</sup>, Michael Acker<sup>9</sup>, Jeffrey T. Bagdanoff<sup>3</sup>, Zhouliang Chen<sup>1</sup>, Michelle Fodor<sup>4</sup>, Jorge Garcia-Fortanet<sup>11</sup>, Huai-Xiang Hao<sup>4</sup>, Mitsunori Kato<sup>5</sup>, Robert Koenig<sup>6</sup>, Laura LaBonte<sup>7</sup>, Gang Liu<sup>1</sup>, Shumei Liu<sup>4</sup>, Chen Liu<sup>4</sup>, Morvarid Mohseni<sup>4</sup>, Martin Sendzick<sup>1</sup>, Travis Stams<sup>8</sup>, Ritesh B. Tichkule<sup>9</sup>, Christopher Towler<sup>9</sup>, Hongyun Wang<sup>9</sup>, Ping Wang<sup>9</sup>, Sarah L. Williams<sup>9</sup>, Bing Yu<sup>1</sup>, Matthew J. Lamarche<sup>10</sup>. (1) ONC/GDC, Novartis, Rindge, New Hampshire, United States (2) Princeton University, Princeton, New Jersey, United States (3) Medicinal Chemistry, Novartis, North Reading, Massachusetts, United States (4) Oncology, Novartis, Cambridge, Massachusetts, United States (5) Computer Aided Drug Discovery, Novartis Institutes for BioMedical Research, Cambridge, Massachusetts, United States (6) 2C-131-03, Novartis, Cambridge, Massachusetts, United States (7) PK Sciences, Novartis, Cambridge, Massachusetts, United States (8) CBT Protein Science, Novartis, Cambridge, Massachusetts, United States (9) Novartis Inst Biomed Res Inc, Cambridge, Massachusetts, United States (10) Novartis, Reading,

*Massachusetts, United States (11) Casma Therapeutics, Cambridge, Massachusetts, United States*

SHP2 is a non-receptor protein tyrosine phosphatase (PTP) within the MAPK pathway, involved in cell growth, survival, differentiation, and oncogenic transformation as well as a potential immune modulator due to its role in the programmed cell death PD-L1/PD-1 pathway. In this poster, we describe the optimization of a fused bicyclic hit for potency, selectivity, and physicochemical properties in order to expand the chemical diversity of allosteric SHP2 inhibitors and enhance our understanding of SAR and use of structure-based design. These studies led to the discovery of SHP394 (**1**), an orally efficacious inhibitor of SHP2, with high lipophilic efficiency, improved potency and enhanced pharmacokinetic properties. This work improves upon our previously described allosteric inhibitors, and exemplifies and extends the range of permissible chemical templates that inhibit SHP2 via the allosteric mechanism.

### **MEDI 130**

#### **Optimizing the anti-proliferative activity of CJ-15,208 in prostate cancer cells**

**Robyn Pescatore**, *ro.pescatore@wingate.edu*, Jane V. Aldrich. Medicinal Chemistry, University of Florida, Gainesville, Florida, United States

c-Myc, which is an important transcription factor that regulates various cellular functions such as cell growth and apoptosis, is commonly overexpressed in prostate cancer. We have demonstrated that the macrocyclic tetrapeptide natural product CJ-15,208 (*cyclo*[Phe-D-Pro-Phe-Trp]) and its D-Trp isomer decrease the levels of c-Myc protein and inhibit proliferation in PC-3 prostate cancer cells. We have screened over 50 analogues of our lead compounds for anti-proliferative activity in PC-3 prostate cancer cells and identified promising derivatives with enhanced anti-proliferative activity, revealing possible amino acid substitutions for optimization of the lead compounds' anti-proliferative activity. The results from this initial structure-activity relationship study of anti-proliferative activity will be presented.

### **MEDI 131**

#### **Finding new molecules for treatment of neurological and metabolic disorders by *in silico* analysis of phytoconstituents from traditional Indian and Russian medicines**

*Nikita Ionov*<sup>1,2</sup>, *Pavel Pogodin*<sup>1</sup>, *Anastassia Rudik*<sup>1</sup>, *Sergey Ivanov*<sup>1,2</sup>, *Alexey Lagunin*<sup>1,2</sup>, *Vladimir Poroikov*<sup>1</sup>, *Vladimir Luzhanin*<sup>3</sup>, *Maria Povydysh*<sup>3</sup>, *Rajesh Kumar Goel*<sup>4</sup>, *G. Narahari Sastry*<sup>5</sup>, **Dmitry Druzhilovskiy**<sup>1</sup>, *explorermf@yandex.ru*. (1) Department of Bioinformatics, Institute of Biomedical Chemistry, Moscow, Russian Federation (2) Department for Bioinformatics, Pirogov Russian National Research Medical University, Moscow, Russian Federation (3) Department for Pharmacognosy, Saint Petersburg State Chemical Pharmaceutical Academy, Moscow, Russian Federation (4) Department

*of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, India (5)  
Molecular Modeling Group, CSIR-Indian Institute of Chemical Technology, Hyderabad,  
India*

Natural products represent the auspicious source of medicines with improved safety and efficacy. In addition to their inherent biological activities provided as a "Gift of Mother Nature", they exhibit substantial structural diversity that creates great opportunities for discovery of new pharmaceutical agents.

In the framework of the Russian-Indian project, we created the pilot version of the database on Indian and Russian medicinal plants with significant information about their phytoconstituents and biological activities dedicated to the neurological and metabolic disorders.

The hidden pharmacological potential of individual phytocomponents from this database was analyzed using our ligand-based approach to prediction of biological activity spectra realized in the PASS software. We also examined the drug interaction between different phytoconstituents with our computer program PharmaExpert.

Comparison of the predicted biological activities with those currently known from literature was performed. Novel applications of separate phytoconstituents from the medicinal plants as well as their combinations were evaluated.

Similarities and differences between the pharmacological potential of Indian and Russian medicinal plants in the field of neurological and metabolic diseases will be discussed.

## **MEDI 132**

### **Development of tumor-targeting, light-activated chemotherapy with vitamin B<sub>12</sub>-protein kinase inhibitor conjugates**

**Liberty N. Gendron**<sup>2</sup>, *liberty.n.gendron@dartmouth.edu*, **Colter G. Sheveland**<sup>3</sup>, *cshevela@stu.norwich.edu*, **Thomas A. Shell**<sup>3</sup>, **Jennifer R. Shell**<sup>1</sup>, *jennifer.r.shell@dartmouth.edu*. (1) Thayer School of Engineering, Dartmouth College, Hanover, New Hampshire, United States (2) Saint Anselm College, Manchester, New Hampshire, United States (3) Chemistry and Biochemistry, Norwich University, Northfield, Vermont, United States

We have developed a drug delivery system whereby the drug is conjugated into an alkylcobalamin scaffold. Alkylcobalamins are structurally related to vitamin B<sub>12</sub> and are actively transported into tissue that require this vitamin by transcobalamin receptors (TCbIR). Multiple cancer types have enhanced expression of these receptors; therefore, the drug-cobalamin conjugate could be transported into the tumor via the TCbIR pathway. In fact, we were able to show the tumor targeting ability of the cobalamin platform *in vivo* with a fluorescently labeled cobalamin conjugate in two types of tumors shown to overexpress TCbIR in athymic nude mice. This delivery system provides light-activated release of chemotherapeutics which offers spatiotemporal control of drug activity. Due to the drug becoming active at the specific site that it is needed, such as a tumor, the potential side effects of that drug in organs at risk are mitigated. We have

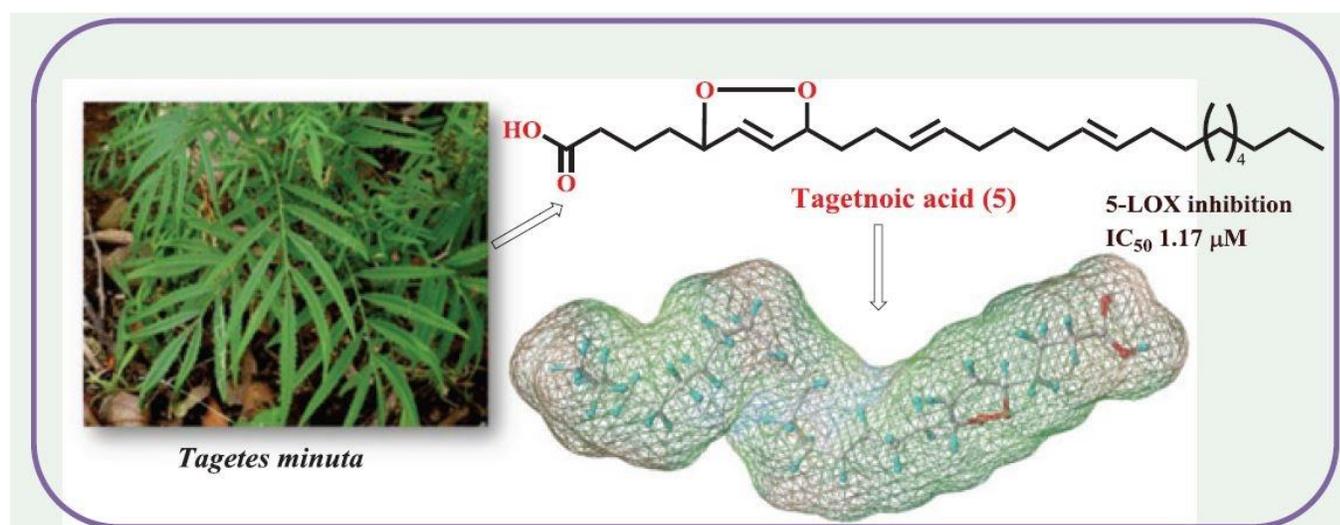
synthesized a series of protein kinase inhibitors conjugated to the cobalamin platform, including erlotinib and dasatinib, and demonstrated their ability to cause inhibition in a light dependent fashion. We hope to utilize these to investigate reduction of tumor margins in an in vivo model in a light-dependent fashion.

## MEDI 133

### Tagetnoic acid: A new lipoxygenase inhibitor peroxy fatty acid from *Tagetes minuta* growing in Saudi Arabia

**Maan T. Khayat**<sup>1</sup>, [maankhayat@yahoo.com](mailto:maankhayat@yahoo.com), Gamal A. Mohamed<sup>2</sup>, Sabrin R. Ibrahim<sup>3</sup>. (1) Pharmaceutical chemistry medicinal chemistry division, King Abdulaziz University Faculty of Pharmacy, Morgantown, West Virginia, United States (2) Department of Natural Products and Alternative Medicine, King Abdulaziz University, Jeddah, Makkah, Saudi Arabia (3) Department of Pharmacognosy and Pharmaceutical Chemistry, Taibah University, Madinah, Saudi Arabia

A new peroxy fatty acid, tagetnoic acid (5) [4-((3S,6S)-6-((3E,8E)-octadeca-3,8-dien-1-yl)-3,6-dihydro-1,2-dioxin-3-yl)butanoic acid] and four known metabolites: ecliptal (5-formyl-*a*-terthiophene) (1), 5-(4-hydroxybut-1-ynyl)-2,20-bithiophene (2), 22,23-dihydrospinaesterone (3), and stigmasterol (4) were separated from the n-hexane fraction of the aerial parts of *Tagetes minuta* L. (Asteraceae). Their chemical structures were verified using IR, UV, 2D and 1D NMR, and HRMS. Compounds 3–5 displayed potent lipoxygenase inhibitory potential with IC<sub>50</sub>s 2.26, 1.83, and 1.17 μM, respectively compared to indomethacin (IC<sub>50</sub> 0.89 μM). Moreover, molecular docking study revealed that the potent activity of 5 is due to H-bonding and hydrophobic interaction. The results of this study suggested that *Tagetes minuta* dietary consumption would be useful for the individuals at risk of acute and chronic inflammatory disorders.



## MEDI 134

### ***In silico* assessment of cardiovascular adverse effects of drug-drug interactions**

Sergey Ivanov<sup>1,2</sup>, Alexey Lagunin<sup>1,2</sup>, Dmitry Filimonov<sup>1</sup>, Vladimir Poroikov<sup>1</sup>, **Dmitry Druzhilovskiy<sup>1</sup>**, *explorermf@yandex.ru*. (1) Department of Bioinformatics, Institute of Biomedical Chemistry, Moscow, Russian Federation (2) Department for Bioinformatics, Pirogov Russian National Research Medical University, Moscow, Russian Federation

Adverse drug effects (ADEs) are one of the leading causes of death in developed countries, and the main reason for drug recalls from the market. The ADEs associated with action on the cardiovascular system are the most dangerous and widespread. Treatment of human diseases often requires the intake of several drugs, which can lead to drug-drug interactions (DDIs) causing an increase in the frequency and severity of adverse effects. Evaluation of ADEs, as well as the effect of DDIs on their manifestation, is a non-trivial task and requires numerous experimental and clinical studies.

To solve this problem, we developed a computational approach to assess the cardiovascular effects of DDIs. This approach is based on the analysis of FDA spontaneous reports (SRs) to identify DDIs with subsequent creation of structure-activity relationships (SARs) for pairs of drugs to predict five cardiovascular ADEs: myocardial infarction, ischemic stroke, ventricular tachycardia, cardiac failure, and arterial hypertension.

At the first stage of our approach, we applied L1-regularized logistic regression to SRs for the identification of pairs of drugs that interact with each other and cause ADEs more frequently than individual drugs (examples of synergy and additivity, “actives” in SAR models). Using the same method we also identified pairs of drugs that do not interact with each other (“inactives” in SAR models). At the second step, five SAR models were created based on the obtained information. We used probability estimates for 1554 human target calculated by PASS Targets software for each drug to create descriptors. Sum and difference of estimates were used as descriptors for drug pairs. To create SAR models we also used L1-regularized logistic regression. Accuracy values were calculated based on 5-fold cross-validation procedure.

The obtained datasets include on average 3500 drug pairs with active/inactive ratio 1:3. The average area under the ROC curve of obtained SAR models was 0.9, and the average balanced accuracy was 0.82. The predicted drug targets, which were taken as descriptors, can also be used to hypothesize the mechanisms of cardiovascular ADEs of DDIs. The created five SAR models can find practical application in the clinic for the selection of the safest combinations of drugs.

## MEDI 135

### **Novel macrocyclic tetrapeptide kappa opioid receptor ligands: Cytochrome P450 metabolism and interactions**

**Tanvir Khaliq**, *tanvirkhaliq@cop.ufl.edu*, **Jane V. Aldrich**,  
*jaldrich@cop.ufl.edu*. Department of Medicinal Chemistry, University of Florida,  
Gainesville, Florida, United States

We are pursuing novel macrocyclic tetrapeptides as kappa opioid receptor ligands as potential treatments for pain and addiction. Cyclic peptides are resistant to proteolytic degradation and hence can potentially display activity after systemic administration. We synthesized the natural product macrocyclic tetrapeptide, CJ-15,208 and its isomer, [D-Trp]CJ-15,208; both peptides exhibited potent *in vivo* opioid activity following oral administration to mice. Because of their promising lead-like properties, metabolism and pharmacokinetic properties of the peptides are being evaluated to facilitate their further development. These cyclic peptides are stable to proteolytic degradation, but can be oxidatively metabolized by cytochrome P450 enzymes (CYPs). In order to characterize the metabolic profile of the lead peptides, we evaluated their CYP metabolism using the most common isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Both peptides are metabolized specifically by 3A4. The details of the interactions of the compounds with CYPs will be presented.

## **MEDI 136**

### **AI-driven design of dual-pharmacophore libraries**

**Charles S. Bury**, *charles.bury@md.catapult.org.uk*, **John P. Overington**, **Andrew Pannifer**. Medicines Discovery Catapult, Alderley Edge, Cheshire, United Kingdom

The development of novel compounds containing multiple desired pharmacophores has provided a direct means to target several discrete drug targets simultaneously, thus mitigating the requirement for complex treatments administering several drugs in tandem in order to be effective. However, typically the resulting compounds are achieved by linearly fusing individual preselected pharmacophores together, rather than incorporating each into a desirable drug-like scaffold. This leads to compounds that can, by-design, artificially target multiple pathways simultaneously, yet may lack the drug-like qualities that enable such compounds to be readily absorbed and distributed to present a viable treatment strategy.

With the recent surge in popularity of generative deep learning methods, a diverse range of different neural network architectures have now been presented in the literature that exhibit great potential towards achieving a goal of high-throughput, automated, *de novo* drug design. In particular, generative AI models are now capable of directly targeting desired subregions of chemical space and/or distinct protein targets, as well as biasing towards the inclusion of particular molecular fragments or learned scaffold designs. Ultimately, this provides an effective means for generating diverse sets of novel compounds, whilst preserving the drug-like nature of the output molecules. Here it will be demonstrated how such neural networks can be utilised as a computational approach to aid the design of novel compounds containing multiple desired pharmacophores, whilst also crucially maintaining predicted activity towards each of several independent desired targets. The results of these generative

approaches will be compared against the most recent experimental benchmarks concerning the design of dual- and multi- pharmacophore inhibitors. It is suggested that such generative AI models may provide an efficient utility to advise multi-inhibitor design by optimising the selection of compatible pharmacophore pairings that will result in the most effective treatment response.

## **MEDI 137**

### **Development of potent and specific inhibitors for oncogenic kinase FGFR4**

**Renata Rezende Miranda**<sup>1,2</sup>, *rezendem@usc.edu*, Chao Zhang<sup>1,2</sup>. (1) Department of Chemistry, University of Southern California, Los Angeles, California, United States (2) Loker Hydrocarbon Research Institute, University of Southern California, Los Angeles, California, United States

The family of Fibroblast Growth Factor Receptors (FGFRs) is an important class of validated targets for cancer therapeutics as they play a crucial role in tumor proliferation, angiogenesis, migration, and survival. Mutations and overexpression of FGFRs and their ligands have been reported in cancers from several tissues, such as breast, lung, bladder, and liver. Amplification and activating mutations of FGFR4, for instance, have been described in 8% of rhabdomyosarcoma patients. Furthermore, it is estimated that 30% of patients with hepatocellular carcinoma, which accounts for most liver cancers, carry tumors with abnormally activated FGFR4 signaling. Although small-molecule inhibitors of FGFRs have been developed and evaluated in clinical trials for treating cancer, most of them are pan-FGFR inhibitors with promiscuous kinome activity. Sequence analysis reveals FGFR4 contains a rare cysteine residue within its ATP-binding site. This residue is unique to FGFR4 and is not found among the other members of the FGFR subfamily, despite their high homology. In order to develop new potent and selective drugs against FGFR4, we designed and synthesized electrophilic derivatives to covalently target this rare cysteine residue on FGFR4 (C552). Cp 1 showed highly potent inhibitory activity against recombinant wild-type FGFR4 kinase, with a half maximal inhibitory concentration (IC<sub>50</sub>) of 0.2 nM. Amongst 250 human kinases, Cp 1 (100 nM) caused 98% inhibition of FGFR4 and no significant inhibition (< 40%) of other kinases, demonstrating great specificity for FGFR4. Cocrystal structure of Cp 1 in complex with FGFR4 kinase confirmed the covalent interaction between the warhead of Cp 1 with the targeted cysteine residue. Modification of Cp 1 with a terminal alkyne group generated Probe 1, which labeled recombinant wild-type FGFR4 kinase at concentration as low as 1 nM. The same probe failed to label a mutant form of FGFR4 in which the cysteine was substituted with alanine (C552A). Probe 1 also showed selective labeling of overexpressed FGFR4 in HEK293 cells at concentration as low as 10 nM. In future work, we aim to fully characterize the potency, selectivity, target engagement, toxicity, and pharmacokinetics of Probe 1 *in vitro* and *in vivo* in order to elucidate valuable information about this poorly understood FGFR isoform.

## **MEDI 138**

## **Flexibility at different stages of mechanism of activation of the GPCR-prototype agrees with local motions explored by molecular dynamics simulations**

**Karla Gonzalez Ponce**, *karlaglezponce@gmail.com*, Abraham Madariaga, Karina Martinez Mayorga. *Physical Chemistry, Instituto de Quimica, UNAM, Mexico City, Mexico*

G protein-coupled receptors (GPCRs) are 7-helical transmembrane proteins that comprise the largest superfamily of plasma membrane receptors and are the primary target for pharmaceutical development. Upon ligand binding, the GPCR is capable to catalyze GDP–GTP exchange in heterotrimeric G proteins and regulate the intracellular level of secondary messengers.

Rhodopsin, the first protein structure solved by X-ray diffraction, is the primary model for studying GPCRs. As this protein is located at the human rod cells, the visual chromophore ligand (11-*cis*-retinal) is covalently bound to Lys 296 by a protonated Schiff base. This ligand in the dark state acts as an inverse agonist that is converted by light-induced isomerization to the all-*trans* agonist, driving the conformational transitions leading to receptor activation. In this mechanism, several intermediates are formed within milliseconds, such as bathorhodopsin, lumirhodopsin, and Meta I and Meta II states.

Experimental data have shown significant differences between the opsin (active-like state) and rhodopsin (inactive state). The primary difference in these states is that the opsin structure is obtained after the release of the all-*trans*-retinal so, thus becoming the apoprotein; while in rhodopsin (the inactive state), the protein is bound to the 11-*cis*-retinal.

These experimental information lead us to hypothesize that the difference in flexibility between rhodopsin and opsin is due to local fluctuations, at atomic level, which may be observable in the molecular dynamics simulations timescale.

The structures of rhodopsin and opsin were downloaded from the Protein Data Bank, and placed on a hydrated membrane bilayer at physiological conditions. All atom molecular dynamics simulations were performed for 100 ns. Root Mean Square Deviation (RMSD) of the backbone proteins and Root Mean Square Fluctuation (RMSF) of residues was analyzed and compared with results reported on literature.

### **MEDI 139**

#### **Drug delivery of xanthohumol to adipocytes using ultrasmall superparamagnetic iron oxide nanoparticles**

*Irاندokht Khaki Najafabad<sup>2</sup>, Janaiya Samuels<sup>2</sup>, Royce Dansby-Sparks<sup>3</sup>, Travis Fields<sup>2</sup>, Ajay Singh<sup>1</sup>, Srujana Raylam<sup>2</sup>, Rahul Deshmukh<sup>4</sup>, Vicky V. Mody<sup>2</sup>, vickymo@pcom.edu. (1) Pharmaceutical Sciences, South University, Savannah, Georgia, United States (2) Pharamceutical Sciences, Philadelphia College of Osteopathic Medicine, School of Pharamcy, Suwanee, Georgia, United States (3) Chemistry, University of North Georgia, Dahlonega, Georgia, United States (4)*

*Pharmaceutical Sciences, Rosalind Franklin University, College of Pharmacy, North 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-aminotripropylethoxysilane. The use of 3-APTES 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 viadicarboxylic 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 25mM 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 6.1mg 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 3.25mM significantly decreased adipogenesis compared to the XN as measured by decrease in the lipid content using AdipoRed<sup>TM</sup> lipid quantification assay.

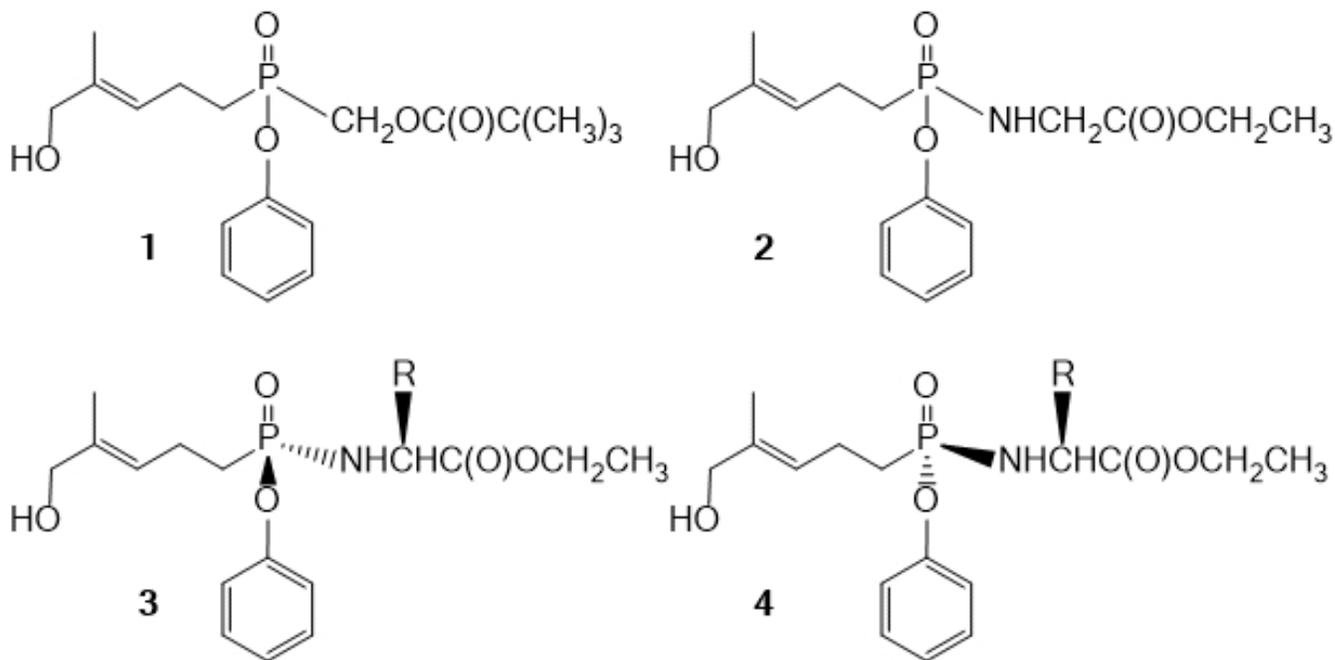
## **MEDI 140**

### **Nonracemic prodrugs of a butyrophilin ligand**

**Nicholas A. Lentini**<sup>1</sup>, *nicholas-lentini@uiowa.edu*, Chia-hung C. Hsiao<sup>2</sup>, Andrew J. Wiemer<sup>2</sup>, David F. Wiemer<sup>1</sup>. (1) Chemistry, Univ of Iowa, Iowa City, Iowa, United States (2) Pharmaceutical Sciences, University of Connecticut, Vernon, Connecticut, United States

The transmembrane protein butyrophilin functions as an intracellular receptor for small phosphorus-containing compounds and when ligand bound it stimulates proliferation of

$\gamma\delta$  T cells. Because the most potent natural ligand, (*E*)-4-hydroxy-3-methyl-but-2-enyl diphosphate is too unstable metabolically for potential clinical use, we have explored the preparation and biological activity of various phosphonate analogues. Our studies have uncovered potent prodrugs, including mixed acyloxy aryl esters (e.g. **1**) and aryl phosphoramidates (e.g. **2**), but in all previous cases the compounds were racemic. We now present the preparation of some nonracemic aryl phosphoramidates (e.g. **3** and **4**), along with our initial studies of their biological activity.



## MEDI 141

### Structural optimization of pyrrolopyrimidine RET kinase inhibitors

**Valeria Garcia**<sup>1</sup>, [valeria.garcia.esp96@gmail.com](mailto:valeria.garcia.esp96@gmail.com), **Sean Toenjes**<sup>2</sup>, **Sean M. Maddox**<sup>2</sup>, **gregory dawson**<sup>2</sup>, **Mariel M. Cardenas**<sup>2</sup>, **Jeffrey L. Gustafson**<sup>2</sup>. (1) Chemistry, San Diego State University, San Diego, California, United States (2) Chemistry and Biochemistry, San Diego State University, San Diego, California, United States

There are over 500 kinase proteins in the human genome, and their aberrant activity can lead to life-threatening diseases. Consequently, a dense amount of medicinal research has been focused on the development of small molecule kinase inhibitors. More than 80% of the FDA approved kinase inhibitors contain rapid interconverting chirality, also known as atropisomerism, and although they are considered to be achiral, they interact with their targeted proteins in an enantioselective fashion. This means that while one enantiomer contributes towards the desired activity, the other enantiomer can inhibit off-target proteins which may lead to adverse side effects in patients or muddled

biochemical signaling pathway experiments.

In research done previously in the Gustafson lab, exploiting atropisomerism was used as a selectivity filter and to increase the selectivity of pyrrolopyrimidine (PPY) Ret kinase inhibitors. In their report, they rigidified a bi-aryl axis by adding bulky substituents ortho to the chiral axis and observed that the (Ra)-atropisomer was 2-fold more selective towards Ret over Src. One drawback of this research was by rigidifying the chiral axis resulted in the loss of potency compared to the parent racemizing inhibitor (1857nM vs 128nM IC<sub>50</sub> towards Ret).

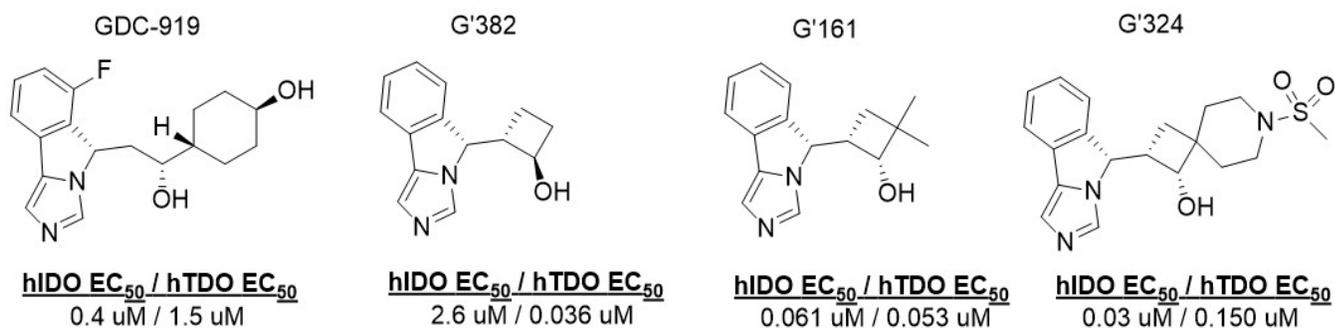
To further demonstrate that this strategy of exploiting atropisomerism as a selectivity filter we must optimize the inhibitors for both selectivity and potency. To do this, we utilized a molecular docking software called MOE to create a list of potential analogues that were calculated to be both selective and potent for Ret over Src. We then synthesized the molecules (15 scaffolds, 28 atropisomers) and separated the (Ra)- and (Sa)-atropisomers through chiral phase high liquid performance chromatography (HPLC). These isolable, stable atropisomers were then subjected to kinase inhibition assays to test the inhibition of the molecules. Structure activity relationships (SAR) showed a larger 'gate keeper' aryl ring and an electron neutral methyl group off the PPY increased potency towards Ret (17nM IC<sub>50</sub>) and selectivity (>100-fold Ret/Src and >500-fold Ret/Vegfr2). The lead inhibitor displayed cytotoxicity (IC<sub>50</sub> 2.5uM) in estrogen-deprived breast cancer cells (ED-MCF7) and showed elimination of Ret phosphorylation via western blots. Both the in silico and in vitro data suggest that we can obtain a higher potency while maintaining the selectivity in novel atropisomeric inhibitors.

## **MEDI 142**

### **Discovery and optimization of imidazoisoindole-based IDO/TDO dual inhibitors**

*Richard Pastor*<sup>1</sup>, *mpastor@gene.com*, *Brendan Parr*<sup>1</sup>, *Yichin Liu*<sup>2</sup>. (1) *Discovery Chemistry, Roche Inc, South San Francisco, California, United States* (2) *Biochemical Pharmacology, Roche Inc, South San Francisco, California, United States*

IDO and TDO are strongly implicated as cancer immunotherapy targets by the central role they play in the catabolism of tryptophan to kynurenine, a known immunosuppressive pathway, and their over-expression in a large number of tumor types. However, clinical results from recent trials with selective IDO inhibitors have been modest at best, suggesting IDO inhibition alone is not sufficient to achieve compelling clinical outcomes. Herein, we describe the discovery of novel, potent, and orally bio-available imidazoisoindole based small-molecule dual inhibitors of the human isoform of IDO and TDO. This chemical series was the result of a research collaboration with NewLink Genetics which evolved from GDC-919, an IDO selective clinical candidate. Through modification of the C5 substituent, we were able to identify TDO selective compounds, which was the initial aim of the research collaboration. Next, activity against IDO was gained through further modification of the same element to arrive at potent dual IDO/TDO inhibitors. Finally, through optimization of compound physical properties, potent and orally bio-available dual inhibitors were identified.



## MEDI 143

### Multi-approach strategy to improve the spectrum of ClpP activators

**Quentin Avila**, *quentin.ibere@gmail.com*, Adam S. Duerfeldt. Chemistry & Biochemistry, University of Oklahoma, Norman, Oklahoma, United States

The persistent and expedient evolution of multi-drug resistance, paired with a dwindling pipeline of therapeutic answers, amplifies the urgency for novel antimicrobials. New generations of current antimicrobials may provide short-lived solutions to resistance but are often susceptible to rapid cross-resistance evolution. However, therapeutics that exploit new targets provide modern challenges to bacteria; and thus, require the development of a completely new resistance regime, potentially lengthening the duration of action. One promising target that deserves further assessment is caseinolytic protease P (ClpP). Chemo-activation of this protease results in uncontrolled protein degradation and subsequent bacterial cell death. While known ClpP activators exhibit impressive potency against Gram-positive pathogens, they fail to cross Gram-negative membranes and/or are recognized by drug efflux pumps; thus, limiting activity to Gram-positive microbes and impeding their utility as broad-spectrum antibiotics. If ClpP activators, however, are administered with polymyxin B, a permeabilizing agent, or applied to efflux deficient cell lines, activity against Gram-negatives is observed. This demonstrates that if efflux incompatible and/or cell permeable ClpP activators can be developed, this class may establish itself as a first-in-class antibiotic. This poster will present our efforts towards overcoming the ineffectiveness of ClpP activating chemotypes against Gram-negatives. The results presented will center around two approaches: (1) structural diversification of N-acyl 3,5-difluorophenylalanines and (2) ClpP activator-cephalosporin hybrids. The first approach focuses on understanding the physicochemical and structural properties governing permeation and accumulation to allow the rational design of broader spectrum agents. The second approach leverages the cephalosporin core as a cleavable vehicle to improve the permeability of conjugated ClpP activators. Rationale, synthetic approach, and preliminary biological data will be presented for molecules arising from each strategy.

## MEDI 144

## **Development and characterization of hiPSC cortical neurons and their application to drug evaluation in CNS disease models**

**Kaveena Autar**<sup>2</sup>, [kautar@knights.ucf.edu](mailto:kautar@knights.ucf.edu), **Xiufang Guo**<sup>2</sup>, **Arindom Goswami**<sup>2</sup>, **Max Jackson**<sup>1</sup>, **John Rumsey**<sup>1</sup>, **Christopher Long**<sup>1</sup>, **James J. Hickman**<sup>3,1</sup>. (1) Hesperos, Inc., Orlando, Florida, United States (2) University of Central Florida, Orlando, Florida, United States (3) NanoScience Technology Center, University of Central Florida, Orlando, Florida, United States

The differentiation of functional cortical neurons from human induced pluripotent stem cells in vitro easily lends itself to a serum-free, drug delivery platform advantageous for testing novel chemicals for safety and efficacy in disease treatment. Initially, cortical neuron cultures were characterized morphologically by phase microscopy and immunocytochemistry and functionally by patch-clamp electrophysiology. Specifically, the expression of neuronal markers and neuronal activity increased throughout maturation. On day 0 of maturation, 50 percent of the culture expressed layer V cortical neuron marker *ctip2* and neuronal marker beta-III tubulin and displayed spontaneous and repetitive firing through whole-cell patch clamp. By day 28 of maturation, 90 percent of the culture expressed the aforementioned markers and displayed electrical activity. Subsequently, neurons were cultured on multi-electrode arrays (MEAs) to determine the effects of chemicals on neural circuit physiology for modeling brain disease phenotypes. In this system, we tested GABA<sub>A</sub> receptor antagonists and agonists as chemical convulsants or anti-convulsants, respectively. GABA<sub>A</sub> receptor antagonist administration enhanced spontaneous activity mimicking an epileptic phenotype, while GABA<sub>A</sub> receptor agonist administration quieted spontaneous activity. The versatility of this model lies in its ability to present an array of brain diseases characterized by functional brain deficits. Chemicals affecting receptor binding can be added to either enhance or inhibit neuronal activity. This serum-free, hiPSC cortical neuron model establishes a platform for the evaluation of neuron activity as well as a platform for drug testing in vitro.

### **MEDI 145**

#### **Effect of lithium at therapeutic and subtherapeutic doses in GSK3beta autonomous pathways at primary hippocampal neurons cell culture**

**Vanessa De-Paula**, [vanessajrp@hotmail.com](mailto:vanessajrp@hotmail.com), **Andre Barbosa**, **Orestes Forlenza**, **Helena Brentani**. Department of Psychiatry, University of Sao Paulo, Brazil, Sao Paulo, Brazil

*Introduction:* Low lithium concentration has a significant positive effect in synaptic plasticity and reduces cell toxicity. Lithium negatively regulates the expression and activity of glycogen synthase kinase 3b (GSK3b). GSK3b have different partners based on protein-protein interaction databases, here on called as the "GSKoma". The aim of the study is to evaluate the enrichment of the GSKoma in differentially expressed genes related to neuroprotection in hippocampal neurons with different doses of

lithium. *Methods:* Primary cultures of hippocampal neurons were treated for 7 days with lithium (0.02mM, 0.2mM and 2mM). The Agilent860k microarray platform were used. The samples were analyzed in the MeV, with a delta of 1.4 and FDR of 5% and R v3.4. GSKoma was constructed using PathCard and String program. *Results:* Up regulated genes were identified: 8 (0.02mM), 126 (0.2mM) and 739 (2mM). Down-regulated genes were identified: 36 (0.02mM), 1132 (0.2mM) and 1603 (2mM). GSKoma was made up of 182 proteins that directly interact with GSK3b. The results showed that probably GSK3b is not the main route of different doses of lithium on gene expression, since there was no significant enrichment of the GSKoma using MSET. Analyses of biological processes showed that the 0.02mM dose was related to: cortex tangential migration; forebrain degeneration of neurons and forebrain differentiation; the dose of 0.2mM ion transport, metal ions transport, ion transmembrane transport; 2mM response to stimulus and response to organic substance. Whereas the biological processes related to GSK3b block were: response to organic substance; response to oxygen containing compound; response to endogenous stimulus and response to organic cyclic compound. *Conclusion:* GSK3b pathway did not appear as the main event for the response to treatment with lithium in therapeutic and subtherapeutic doses.

## **MEDI 146**

### **Anti-diabetic activity of *Cissus rotundifolia* plant growing in Saudi Arabia**

**Saad Alshehri<sup>1</sup>**, *pharmacist15@hotmail.com*, **Fathi T. Halaweish<sup>2</sup>**. (1) South Dakota state university, Brookings, United States Minor Outlying Islands (2) South Dakota State Univ, Brookings, South Dakota, United States

Diabetes mellitus (DM) is a metabolic disease characterized by high levels of blood glucose resulting from low insulin production and uptake. Non-traditional treatment of diabetes from medicinal plants showed potential antidiabetic activity. *Cissus rotundifolia* (family, Vitaceae) is known plant in southwestern part of Saudi Arabia and used by people in the region to treat skin diseases, burns, and diabetes. Chemical and biological characteristics of *Cissus rotundifolia* active compounds are unknown. The aim of this study to investigate the chemical and biological properties of this medicinal plant using bio-assay guided separation. Aqueous methanol extract of *Cissus rotundifolia* was fractionated by partitioning against hexane and ethyl acetate. Methanol, ethyl acetate and hexane extracts are screened for antidiabetics activity using alpha-glycosidase assay at concentration of 12.5-50 mg/ml. Methanol extract showed a significant alpha-glucosidase inhibition percent of 58 % to 95%. Further LC separation afforded six compounds 1- 6 isolated and characterized using <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and 2D-NMR. Compound 3 (Butanedioic acid, 2-hydroxyl, 1-methyl ester) and compound 4 (4-methyl 1-vinyl 2-hydroxysuccinate) are identified the main constituent of methanol extract and showed a significant inhibition of alpha-glycosidase enzyme in range of 65% to 50% at concentration range from 1.00 – 0.25 mg/ml. The two isolated compounds identified with dicarboxylic group and hydroxyl group with similarity to malate structure (one of the main intermediates of citric acid cycle). This lead us to build hypothesis that investigation of the ability of the isolated compounds to inhibit gluconeogenesis process through

inhibition of the citric acid cycle that consider one of the main pathway to reduce the blood glucose level. Molecular docking study of the isolated compounds binding affinity to citric acid cycle enzymes was conducted. The docking results showed that butanedioic acid, 2-hydroxy-, 1-methyl ester has a significant consensus scores with high affinity binding to succinate dehydrogenase and citrate synthetase enzymes that play an important role in citric acid cycle. Isolated compounds showed inhibition of intestinal  $\alpha$ -glucosidase enzyme and binding affinity to citric acid cycle enzymes indicate potential antidiabetic properties that may decrease of hepatic glucose by decreasing **gluconeogenesis**. The docking result and antidiabetic activity of alpha-glucosidase inhibition will be presented.

## **MEDI 147**

### **Development of a thermal shift assay for evaluating inhibitor candidates targeting viral hemagglutinin and neuraminidase**

*Allison de Moya, [aldemoya@davidson.edu](mailto:aldemoya@ davidson.edu), Scott A. Whitney, Lesa Offermann, **Nicole L. Snyder**, [nisnyder@davidson.edu](mailto:nisnyder@davidson.edu). Chemistry, Davidson College, Davidson, North Carolina, United States*

Influenza is a contagious respiratory virus that is responsible for millions of infections and thousands of deaths globally each year. The influenza virus infects host cells by binding to cell surface sialic acid using a hemagglutinin spike protein (HA). After infection and replication, the virus is released from the host cell with the help of a second protein, neuraminidase (NA). Our interest in developing new inhibitors for HA and NA led us to consider the feasibility of using a thermal shift assay for the rapid evaluation of inhibitor candidates. In this poster we present our preliminary results on the development of a thermal shift assay for evaluating HA and NA, including challenges and opportunities for the use of this technique as a rapid screening tool.

## **MEDI 148**

### **Identifying of the molecular target for the potent antimicrobial agent TI-I-100 to treat drug resistance bacteria**

*V. V. N. Phani Babu Tiruveedhula<sup>1,2</sup>, [tiruvee2@uwm.edu](mailto:tiruvee2@uwm.edu), Revathi Kodali<sup>1</sup>, Ianlan Han<sup>1</sup>, Leggy Arnold<sup>3</sup>, James M. Cook<sup>4</sup>. (1) Chemistry and Biochemistry, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin, United States (2) T3 BioScience LLC, Mequon, Wisconsin, United States (3) University of Wisconsin Milwaukee, Milwaukee, Wisconsin, United States (4) Univ of Wisconsin, Milwaukee, Wisconsin, United States*

The alarming increase in bacterial resistance over the last decade, coupled with the lack of new classes of antibiotics to treat resistant infections, is a growing healthcare threat. In continued efforts to develop new potent antimicrobial agents, a novel class of acrylic esters was synthesized. To determine the molecular target for this class of compounds, the novel alkyne TI-I-100 was designed as a substrate for the copper catalyzed azide-

alkyne 1,3-dipolar cycloaddition (CuAAC). Gratifyingly, TI-I-100 exhibited promising MIC values of 0.25-4.0  $\mu\text{g/mL}$  against clinically significant antibiotic-resistant strains such as MRSA, MDR VISA, and VRE. Consequently, this stimulated the search for the molecular target employing the CuAAC reaction using the Click-iT Plus Alexa Fluor Picolyl Azide Toolkit with fluorescently tagged Alexa Fluor 647 picolyl azide (AF647) within *Staphylococcus aureus* lysate. This permitted experiments to identify *S. aureus* proteins that had been covalently modified by the alkyne, TI-I-100 to be seen on SDS-PAGE under fluorescence. Encouraged by the results, AF647 was replaced with biotin azide in order to isolate the targeted proteins using streptavidin beads. Later, the purified protein fractions were subjected to peptide mass fingerprinting for protein identification and results will be presented.

## MEDI 149

### Pharmacophore generation of $\mu$ -opioid receptor biased-ligands: Uncovering structural features from molecular modeling analysis

**Bruno Hernández**<sup>1</sup>, [brukiks37@gmail.com](mailto:brukiks37@gmail.com), **Abraham Madariaga**<sup>2</sup>, **Karina Martinez Mayorga**<sup>3</sup>. (1) *Physicochemistry, Instituto de Química, Universidad Nacional Autónoma de México, City of Mexico, Mexico* (2) *Physical Chemistry, Universidad Nacional Autónoma de México, Mexico City, Mexico* (3) *Physical Chemistry, Instituto de Química, UNAM, Scottsdale, Arizona, United States*

The number of deaths by opioid overdose has increased drastically recently. A growing number of research groups have gathered efforts to discover and develop novel molecules, aiming the reduction of adverse effects of opioid analgesics, without sacrificing the therapeutic benefits. Chronic and post-operative pain is mainly handled with  $\mu$ -opioid receptor (MOR) agonists, such as morphine. However, the misuse of these substances is accompanied by undesirable overdose consequences, for instance respiratory suppression and tolerance. At molecular level, ligand binding at the orthosteric site of the receptor, may trigger two different signaling pathways: Gi-protein dependent mechanism or recruitment of  $\beta$ -arrestins 1 and 2. Previous experiments suggest that  $\beta$ -arrestins recruitment after MOR activation could be related to adverse effects. In contrast, the Gi-protein pathway is considered as the desirable signaling cascade. Few molecules, e.g. herkinorin, promote Gi protein signaling pathway over  $\beta$ -arrestins recruitment, a process called biased signaling or functional selectivity. Thus, the improvement of efficient strategies for the discovery of MOR biased ligands on this and other G-protein coupled receptors are warranted. In previous work, we have generated a protein-ligand interaction fingerprint (PLIF) based on docking and molecular dynamics analysis of several biased ligands. This chemoinformatic tool is intended to detect biased ligands on large databases. Given the increase number of new biased ligands identified in the last few years, it is expected that enhanced descriptions of the functional selectivity phenomenon will emerge based on new ligand-based approaches such as pharmacophore modeling. In this work, we analyzed the main interactions of several recently reported MOR biased ligands. This allowed the generation of new pharmacophoric features which fine-tune the selection resulted from

PLIF-filtered sets. Ligand interactions with the  $\mu$ -opioid receptor were obtained by docking analysis for all compounds and molecular dynamics for the most potent ones. The results suggest that the new biased compounds have a similar interaction profile than the known biased ligands, according to the previous results obtained by PLIF analysis. Altogether the information obtained in this work provides a framework for future discovery and development of innovative MOR biased-ligands.

## **MEDI 150**

### **Nucleic acid nano-vehicles designed form flexible tetra-U/T helix linking motif**

*Emil F. Khisamutdinov, kemil@bsu.edu. Chemistry, Ball State University, Yorktown, Indiana, United States*

RNA nanotechnology employs synthetically modified ribonucleic acid to engineer highly stable nanostructures in one, two, and three dimensions for medical applications. Despite the tremendous advantages in this field, it is uncertain whether chemically modified RNA nanoparticles and their metabolic products are toxic to an organism creating significant problem in further applications. In contrast, we used naturally occurring nucleic acids and developed RNA/DNA hybrid approach to address questions related to assembly efficiency, thermal and enzymatic stability, as well as exploited their potential to serve as a cargo for delivery of silencing RNA. A computer-assisted *de novo* RNA tetra-uracil/thymine (tetra-U/T) helix linking module (motif) was fabricated to construct four functional equilateral triangles of ~12 nm size using RNA, DNA and RNA/DNA mixtures. We demonstrate their enzymatic and thermodynamic stabilities, immunostimulatory activity and siRNA delivery can be regulated by the ratio of DNA and RNA within the triangular nano-scaffold. We also demonstrate that tetra-U/T motif has great potential in the fabrication of rectangular, pentagonal, and hexagonal nanostructures confirmed by AFM, representing the power of simplicity of RNA/DNA approach for RNA nanotechnology and nanomedicine community. The technique shown here for a simple design to precisely tune physicochemical properties adds a new angle to exploit RNA/DNA hybrid nanoparticles in a clinical setting.

## **MEDI 151**

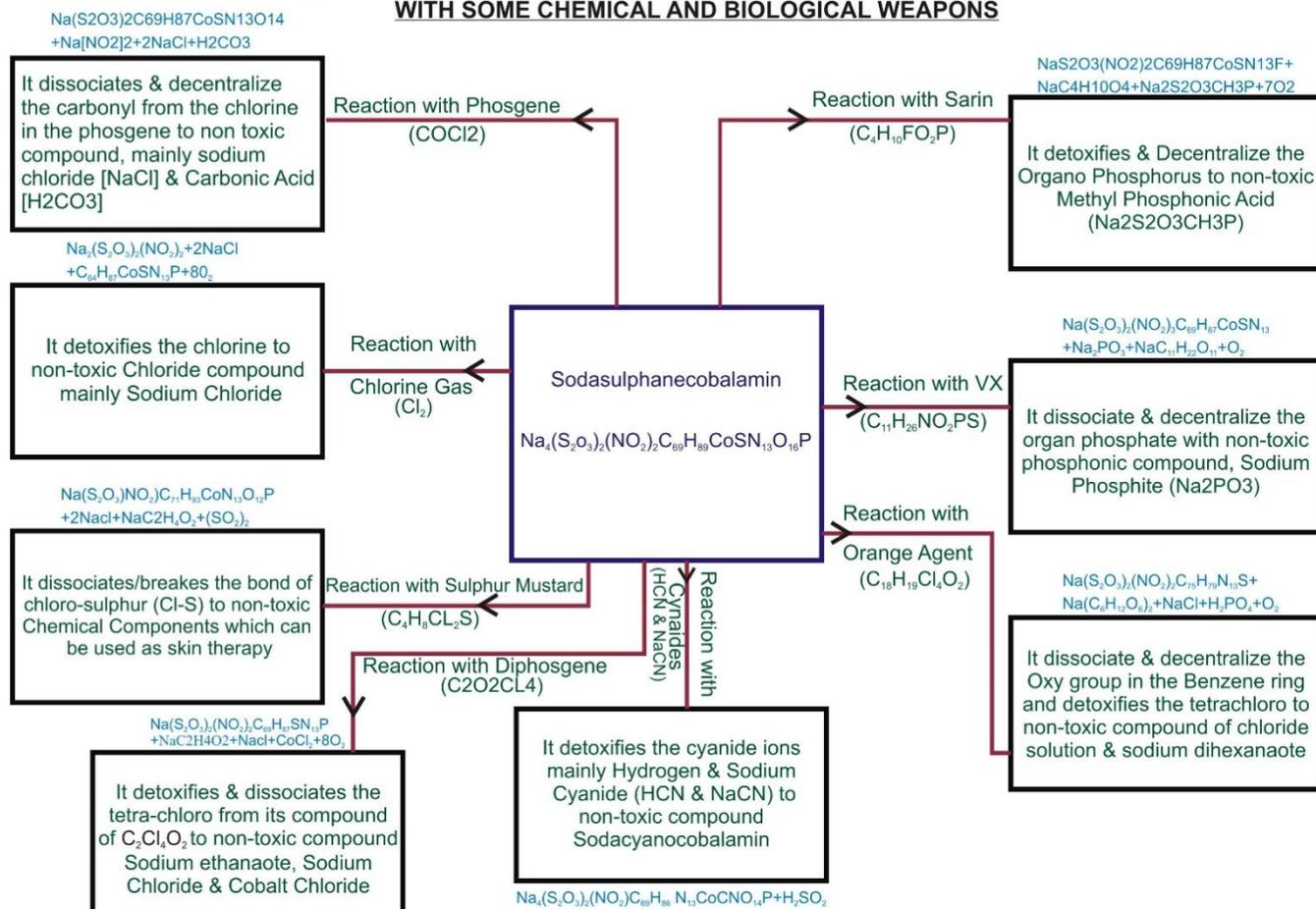
### **Drug development on chemical therapeutics/antidote for chemical and biological warfare agents/toxic agents**

*Salako N. Olatunji, salakoolatunji9@gmail.com. FEDERAL INSTITUTE OF INDUSTRIAL RESEARCH OSHODI , FIIRO, Sango Ota, LAGOS, Nigeria*

SodaSulphanecobalamin ( $\text{Na}_4\text{S}_5\text{CoC}_{69}\text{N}_{15}\text{H}_{89}\text{O}_{26}$ ) is an antidote for Chemical and Biological warfare agents, which detoxify and decentralized the toxic substances in any chemical based threat mainly, classical chemical agent threat categories include vesicant or blister agents (e.g., sulfur mustard), blood agents (e.g., cyanide), respiratory agents (e.g., phosgene), and nerve agents (e.g., GA or Tabun, GB or Sarin, GD or

Soman, and VX) as well as lung damaging agents (Chlorine, diphosgene). It dissociate the toxic components in each chemical weapons, either nerves agent, blister agent or mustard gas to a nontoxic substance when administered and doesn't have any adverse effects unlike Atropine (which has little effect on nicotinic effect, such as muscle twitching, flaccidity) and other antidotes been tested for neutralizing or countermeasures for a particular chemical based threat. It displaces the Cyanides to a free toxic compound, thiocyanocobalamin .It removes the burns when the sulfur mustard is been contacted through skin, and eye The antidote (SodaSulphanecobalamin) which is sulfur drug group (H-S) bends the mustard makes the anditodal removes mustard from the body, of which can be used as treatment for Organic Arsenical. It also added the amide group of protein when used. However, recent studies shows that this antidote can serve as a replacement for the antidote of Orange agent (2, 3, 4, 7-tetra chlorobenzodioxin) which displaced millions of Vietnam Citizens during the World War II and displaces chlorobenzo to sodium benzoate and saline.Nerve agents developed in the 1930s and 1940s were stockpiled during the Cold War. More recently, nerve agents have been used in the Iran–Iraq War in the 1980s, the Japanese terrorist attacks by the Aum Shinrikyo cult in 1995 and attacks in Syria in 2017. Recently, the Salisbury and Amesbury Nerve attack ( Novichok) on March 4<sup>th</sup> and July 2018 respectively ,when SodaSulphanecobalamin is been used for nerves agent antidotal , it dissociates organophosphate to phosphoric acid which helps in metabolism of the body.

**REACTION PATHWAY/FLOW CHART OF SODASULPHANECOBALAMIN  
WITH SOME CHEMICAL AND BIOLOGICAL WEAPONS**



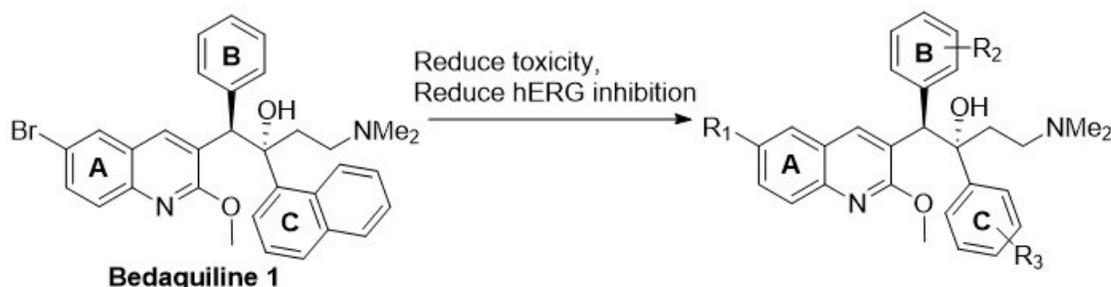
**MEDI 152**

**Next-generation bedaquiline for the treatment of tuberculosis**

**Peter J. Choi**<sup>3</sup>, *p.choi@auckland.ac.nz*, Hamish Sutherland<sup>3</sup>, Amy Tong<sup>3</sup>, Daniel Conole<sup>3</sup>, Adrian Blaser<sup>3</sup>, Christopher B. Cooper<sup>1</sup>, Scott G. Franzblau<sup>2</sup>, Anna M. Upton<sup>1</sup>, William A. Denny<sup>3</sup>, Brian D. Palmer<sup>3</sup>. (1) Global Alliance for TB Drug Development, New York, New York, United States (2) Institute for Tuberculosis Research, University of Illinois at Chicago, Chicago, Illinois, United States (3) Cancer Society Research Centre, University of Auckland, Auckland, New Zealand

Bedaquiline is a 2012 FDA approved drug for the treatment of resistant tuberculosis (TB). It is the first TB drug in 40 years with a novel mechanism of action through inhibition of the mycobacterial ATP synthase enzyme. It demonstrates excellent efficacy against TB, but induces phospholipidosis at high doses, has a long terminal elimination half-life and exhibits potent hERG channel inhibition, resulting in clinical QTc interval prolongation. These serious side effects and drawbacks initiated the development of a second generation analogue.

In collaboration with Global Alliance against Tuberculosis drug development, a number of second generation analogues of bedaquiline have been prepared and evaluated for their use as less toxic, more potent second generation compounds. SAR of new analogues and the selection process towards the preclinical candidate will be presented.



## MEDI 153

### Inhibition of Dengue virus protease by chemical constituents of a clove: From food ingredient to medicine

**Muhammad Saeed**, [sobisaeed77@gmail.com](mailto:sobisaeed77@gmail.com). Chemistry and Chemical Engineering, Lahore University of Management Sciences, Lahore, Punjab, Pakistan

Dengue virus (DENV) infections are rampant in tropical and subtropical regions of the World with millions of people at risk. There is no specific antiviral treatment available against these infections, hitherto. Amongst the different potential therapeutic targets, DENV protease, NS3pro that functions when bound by its cofactor NS2B is considered an important target due to its crucial role in the viral replication cycle. We are reporting here a potent DENV protease inhibitor, eugenin, isolated from a spice, cloves, that is a food ingredient widely used in many parts of the world. Eugenin and two other compounds isobiflorin and biflorin were isolated from cloves, *Syzygium aromaticum*, which inhibited DENV protease *in vitro*. The IC<sub>50</sub> values of eugenin was determined to be  $0.0947 \pm 0.025 \mu\text{M}$  (n = 3) for DENV2 isotype and  $7.53 \pm 1.13 \mu\text{M}$  (n = 3) for DENV3 isotype; isobiflorin was found to be  $58.9 \pm 1.25 \mu\text{M}$  (n = 3) for DENV2 and  $218.9 \pm 1.33 \mu\text{M}$  (n = 3) for DENV3; and biflorin was found to be  $89.6 \pm 4.41 \mu\text{M}$  (n = 3) for DENV2 and  $336.9 \pm 1.20 \mu\text{M}$  (n = 3) for DENV3, respectively. Computational docking and saturation transfer difference (STD) NMR spectroscopy provided atomic-level details of the binding of these molecules to the recombinant DENV NS2BNS3pro enzymes and suggested extensive interactions mediated by a network of H bonds and hydrophobic contacts. These inhibitors, being the constituents of food ingredients, are highly promising in the context of anti-viral therapeutics development against DENV.

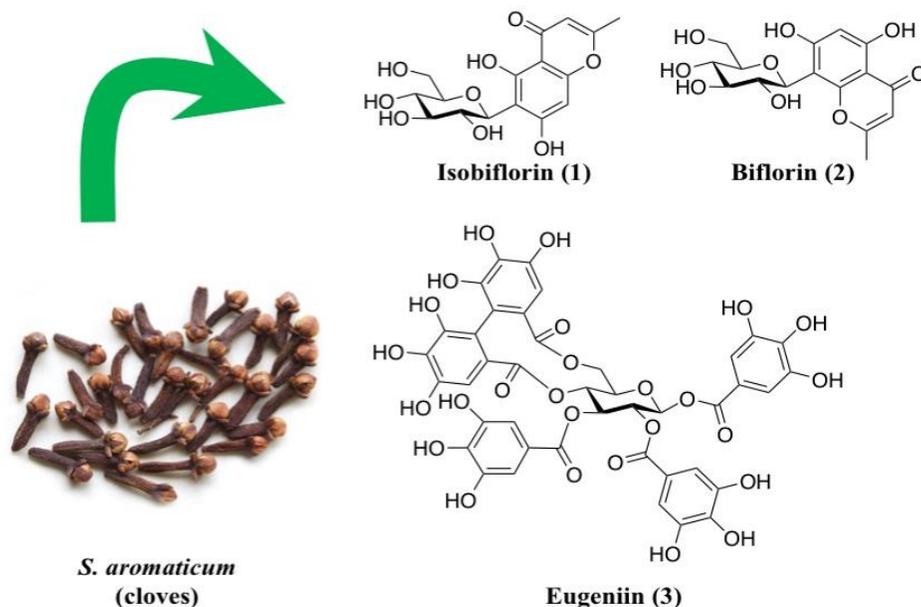


Figure 1. Chemical structures of isobiflorin, biflorin and eugenin isolated from cloves

## MEDI 154

### Development of novel C3-analogs of galeterone for prostate cancer therapy

**Purushottamachar Puranik**<sup>1,2</sup>, *porshottam@gmail.com*, Francis N. Murigi<sup>3</sup>, Andrew K. Kwegyir-Afful<sup>5</sup>, Senthilmurugan Ramalingam<sup>1</sup>, Vidya P. Ramamurthy<sup>1</sup>, Vincent C. Njar<sup>4,2</sup>. (1) Pharmacology, University of Maryland Baltimore, Gaithersburg, Maryland, United States (2) University of Maryland, Center of Biomolecular Therapeutics (CBT), Rockville, Maryland, United States (3) Division of Hematologic Malignancies, Cellular Therapy, Duke Cancer Institute DUMC, Durham, North Carolina, United States (4) University of Maryland School of Medicine, Baltimore, Maryland, United States (5) Center of Veterinary Medicine (CVM) in the office of new animal drugs evaluation (ONADE) in the division of human food safety (DHFS), US Food and Drug Administration, Rockville, Maryland, United States

Anti-prostate cancer (PC) agents Abiraterone (abi) and galeterone (gal) are 3-OH- $\Delta^5$ -C17-heterocycles substituted steroids. Their structural feature mimic endogenous precursors (dehydroepiandrosterone and pregnenolone) of the androgens {Testosterone (T) and dihydrotestosterone (DHT)} in the steroidogenesis pathway. These agents inhibit the 17-lyase enzyme (CYP17A1) which is responsible for steroid-C17 modification. Unlike abi, gal is unique due to its multi-target activities such as AR antagonism and induction of AR degradation. In the androgen axis the 3 $\beta$ -

hydroxysteroid dehydrogenase ( $3\beta$ -HSD) is another important enzyme which converts 3-OH- $\Delta^5$  steroids to 3-oxo- $\Delta^4$  (T) which is further converted to potent androgen (DHT) by the action of  $5\alpha$ -reductase enzyme.  $3\beta$ -HSD also known for metabolism of abi and gal due to their structural similarity to endogenous ligands. Consequently, both abi and gal have short half-lives in mice (1.5 h and 45 min respectively). These two agents also suffer from lower oral bioavailability (37 and ~19% in mouse, respectively), and thus, the need high therapeutic oral doses (1000 and 2550 mg/day, respectively) for the treatment of men with PC. Despite of the modest pharmacokinetics profile, abi was approved by the FDA for clinical use. Abi's robust efficacy in the clinic may be due to the superior anti-PC activity of its first/major metabolite (3-OH- $\Delta^4$ -Abi). Unfortunately, gal's first/major metabolite (3-oxo- $\Delta^4$ -gal) is not as potent as 3-OH- $\Delta^4$ -Abi, which may be a reason for its failure in the phase III clinical trials. In the current study, we have synthesized various C3-analogs of gal and determined their anti-PC activities. We will be present the rationale for the design, their synthesis, *in vitro* SAR and *in vivo* anti-PC activities, pharmacokinetics, toxicity profiles of the most active compounds, VNPP414 and VNPP433- $3\beta$ . Simple modification at metabolic soft spot markedly improved half-lives, oral absorption and acceptable toxicity profiles. Our results support advancing VNPP433- $3\beta$  to the clinic.

## MEDI 155

### Design, synthesis, and evaluation of quinazoline derivatives as FAK inhibitor with antiproliferative and antiangiogenic activity on cancer induced chick embryo

**Amita Verma**, [amitaverma.dr@gmail.com](mailto:amitaverma.dr@gmail.com), Prateek Pathak, parjanya K. Shukla, vikas kumar. Sam Higginbottom University of Agriculture, Technology and Sciences, Allahabad, India

#### Background:

Focal adhesion kinase (FAK) is essential in embryonic angiogenesis by regulating endothelial cell survival and up-regulated in many cancers. Angiogenesis is a complex biological process which promotes tumor growth and metastasis. Indeed, FAK inhibitors are presently being developed for the treatment of cancer. Considering that, present study deals with designing quinazoline derivatives (QDs) as a potential inhibitor of FAK for anti-cancer activity.

**Methods:** QDs were designed by molinspiration and FORZE V10 software and compared with known anticancer agent vandetanib. Docking studies were performed by Auto dock 4.2 on focal adhesion kinase (FAK protein). Designed QD were synthesized through multistep reaction and characterized by UV, IR, NMR and Mass spectroscopy. *In-vitro* anti-cancer activity was performed on HeLa cell lines (cervical cancer) and Hep G2 (Hepatocellular carcinoma) by MTT assay and further antiangiogenic inhibition was performed on chick embryo through CAM (chick chorioallantoic membrane model) assay.

**Results:** All the designed analogues showed considerable bioavailability and field similarity. Docking studies revealed that 12j (semicarbazide group substitution on the side chain of 1,3,5 triazine skeleton of quinazoline) exhibited hydrogen bond

interactions: N7, N10, N11 with LEU 840 and N9 with GLU917 and inhibit FAK with Ki of 1.55  $\mu$ M. In cytotoxic assay, IC<sub>50</sub> report clearly marked that 12j has significant proliferative inhibition against HeLa (6.65  $\mu$ M) and HEP G2 (29.35  $\mu$ M). *In-ovo* result explored that 8j showed promising activity (1.91 $\pm$ 0.01) ( $p > 0.05$ ) against HeLa induced egg cell whereas marginal score against HepG2 cancer cells. All analogues were active against cancer induced chick embryo and non-toxic to the normal cells.

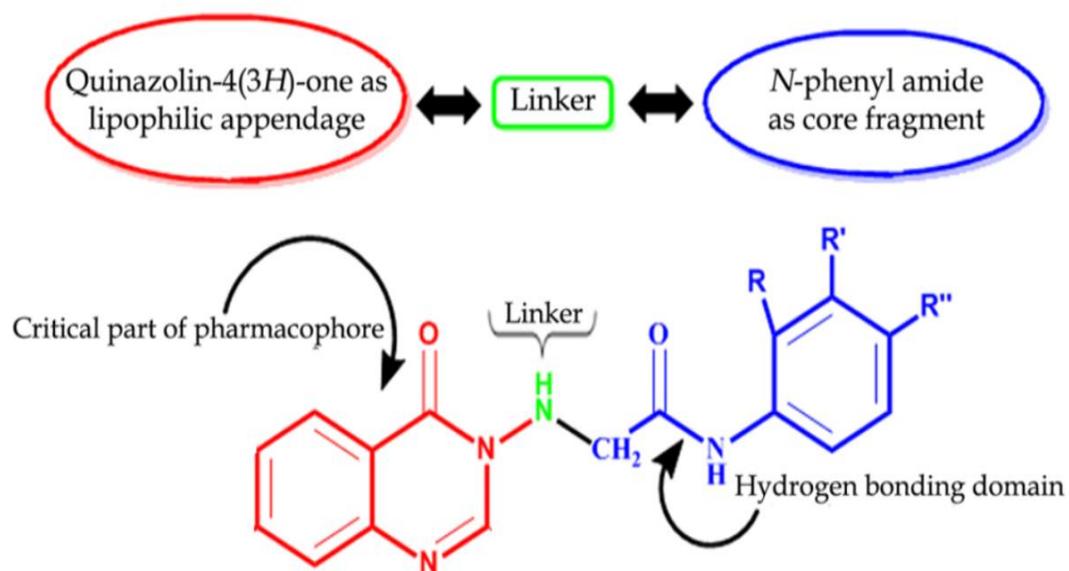
**Conclusions:** In conclusion, we have reported that QDs could serve as a lead for future drug discovery in cancer therapy because of potent inhibitor of FAK with considerable bioavailability.

## MEDI 156

### Pharmacoinformatic-based structural exploration, synthesis, and bioevaluation of selective Gly/NMDA antagonists: Potential ligands to treat intractable epilepsy

*Vinodkumar G. Ugale*, [vinod.ugale@rediffmail.com](mailto:vinod.ugale@rediffmail.com), SANJAY BARI. Department of Pharmaceutical Chemistry, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur (Dhule)-425405 Maharashtra., Shirpur (Dhule), Maharashtra, India

Gly/NMDA receptor has known as potential target for the treatment of pharmacoresistant epilepsy. Herein, we have employed multiple pharmacoinformatic methods to identify selective Gly/NMDA antagonists. A potent set of quinoxalines were used for generation of 3D-QSAR model and validated by chemometric protocols such as cross validation, validation by an external set, decoy set and Y-randomization test. The validated 3D-QSAR model was used to screen virtual hits from ZINC database by pharmacophore mapping and docking process. The PubChem and SciFinder search tools were employed to arrive at potential leads as Gly/NMDA antagonists. After careful concern of pharmacophoric features, we have designed potential selective antagonists. We have synthesized sixteen different 2-((7-chloro-4-oxoquinazolin-3(4*H*)-yl)amino)-*N*-substituted phenylacetamides by utilizing fragment modification approach and evaluated for antiseizure activity. A single step one-pot method for synthesizing substituted quinazolinone in presence of *p*-toluene sulfonic acid was carried out. The *N*-alkylation reaction between quinazolinone and 2-chloro-*N*-(substituted phenyl)acetamides affords targeted compounds. The synthesized compounds were characterized by different spectral methods. Compound **3d** emerge as archetype with excellent action in mice against electroshock, chemically induced and pharmaco-resistant 6Hz preclinical seizure models with no symptoms of neurotoxicity and hepatotoxicity (**ED<sub>50</sub> = 21.7 mg/kg**, MES; **ED<sub>50</sub> = 29.2 mg/kg**, scPTZ; **ED<sub>50</sub> = 33.9 mg/kg**, 6Hz; **TD<sub>50</sub> = 325.9 mg/kg**). The promising antiseizure activity of synthesized molecules, through computational studies and no toxicity symptoms make us to anticipate their emergence as valid leads for further chemical optimization as potential ligands to treat intractable epilepsy.



**Figure 1:** Structural exploration of quinazolin-4(3H)-ones as antiseizure agents by fragment modification approach.

## MEDI 157

### Identification of dibutyrate prodrug of antiviral deoxynojirimycin derivative IHVR-19029

**Yanming Du**<sup>1</sup>, [yanming.du@bblumberg.org](mailto:yanming.du@bblumberg.org), **Huagang Lu**<sup>1</sup>, **Gia Guo**<sup>1</sup>, **Huixin Luo**<sup>1</sup>, **Qing Su**<sup>1</sup>, **Nicky Hwang**<sup>1</sup>, **Julia Ma**<sup>1</sup>, **Xuexiang Zhang**<sup>1</sup>, **Sandra Bixler**<sup>2</sup>, **Travis Warren**<sup>2</sup>, **Sina Bavar**<sup>2</sup>, **Ju-Tao Guo**<sup>1</sup>, **Timothy Block**<sup>1</sup>, **jinhong Chang**<sup>1</sup>. (1) Baruch S. Blumberg Institute, Doylestown, Pennsylvania, United States (2) Army Medical Research Institute of Infectious Diseases, Frederick, Maryland, United States

We discovered a novel N-alkyl-ureanyl-deoxynojirimycin, IHVR-19029, that has been demonstrated to significantly protect mice from lethal infection of Marburg and Ebola virus when administered via injection route through inhibition of the host endoplasmic reticulum (ER)  $\alpha$ -glucosidases I and II. However, the major obstacles toward development of oral available IHVR-19029 are their short plasma half-life, low oral bioavailability and inhibition of carbohydrate-metabolizing gut glucosidases, which results in osmotic diarrhea side effect. To overcome these problems, several types of prodrugs were designed and synthesized, including ester, carbonate, and amino acid prodrugs each with fully protection or partial protection of the four hydroxyl groups on DNJ core of IHVR-19029. As enzymatic assays showed, all the prodrugs lost the ability to inhibit ER  $\alpha$ -glucosidases I and II, suggesting that these ester prodrugs would have reduced activity against GI  $\alpha$ -glucosidases, and potentially overcome the off-target effects of the parent compound. In addition, *in vitro* ADME profiling studies demonstrated that while all the prodrugs remained intact in simulated gastric fluid, most of them subjected to rapid conversion to the parent drug either within the circulation

and/or inside the cells. Pharmacokinetic profiling of the representative acetate, butyrates, isobutyrate prodrugs in mice demonstrated that orally delivered dibutyrate prodrug can be very rapidly and efficiently metabolized leading to the significantly increased overall exposure to parent compound than that of direct administration of parent compound. The selected prodrugs will be advanced into animal efficacy studies against Ebola virus infection.

## **MEDI 158**

### **Multiple quantitative structure-activity relationships (QSARs) analysis for $\gamma$ -secretase inhibitors**

*Vaishali Patil<sup>1</sup>, vaishuwise@gmail.com, Neeraj Masand<sup>2</sup>. (1) KIET School of Pharmacy, KIET Group of Institutions, Meerut, Uttar Pradesh, India (2) Dept. of Pharmacy, LLRM Medical College, Meerut, UP, India*

In the present work, QSAR (Quantitative StructureActivity Relationship) models for  $\gamma$ -secretase inhibitory activity of two series of sulphonamides were developed as per the OECD guidelines. The newly developed multiple QSAR models are easy to interpret and have been successful in identification of many molecular descriptors, which could be highly useful for future use of these models by QSAR experts. The multiple QSAR models satisfy threshold values for many statistical parameters such as  $R^2 = 0.82$  to  $0.85$ ,  $Q^2 = 0.76$  to  $0.84$ , etc. thereby assuring good external predictive ability of the models. The multiple QSAR and pharmacophoric models successfully identified that the substituted-benzenesulfonamide moiety, presence of H-bond acceptor, bond distance and some other pharmacophoric features that govern the activity of sulphonamides analogs. The results could be very useful to synthetic/medicinal chemists for future modifications of selected sulphonamides as drug candidates.

## **MEDI 159**

### **Potent, non-carboxylesterase-labile pro-drugs of the enolase inhibitor HEX for the treatment of ENO1-deleted glioblastoma**

*Victoria C. Yan<sup>1</sup>, yan22v@mtholyoke.edu, Elliot S. Ballato<sup>1,2</sup>, Kristine L. Yang<sup>1,2</sup>, Dimitra K. Georgiou<sup>1</sup>, Kenisha Arthur<sup>1</sup>, Pakriti Shrestha<sup>1,3</sup>, Sunada Khakha<sup>1</sup>, Jeffrey Ackroyd<sup>1</sup>, Florian L. Muller<sup>1</sup>. (1) The University of Texas MD Anderson Cancer Center, Houston, Texas, United States (2) Chemistry, Rice University, Houston, Texas, United States (3) Chemistry, Mount Holyoke College, South Hadley, Massachusetts, United States*

Genomic deletions are ubiquitous in the cancer genome, often inactivating tumor suppressor genes. An unintended consequence of these deletions is the co-deletion of nearby chromosomal neighbors that are irrelevant to tumor progression. Our lab has pioneered a novel therapeutic strategy that targets tumor suppressor deletions by exploiting vulnerabilities generated by the co-deletion of neighboring metabolic

housekeeping genes with critical but normally redundant functions. One promising passenger deletion is of the glycolytic enzyme ENO1 in a subset of glioblastomas. Cancers harboring the deletion of ENO1 are dramatically sensitized to inhibition of its redundant paralog, ENO2.

Our current endeavors towards bringing this concept to the clinic aim to improve our small molecule ENO2 inhibitor, HEX. HEX is substrate-competitive Enolase inhibitor with a  $K_i$  of 63 nM for ENO2 versus 250 nM for ENO1. We recently reported the synthesis of a pivaloyloxymethyl (POM) prodrug derivative, POMHEX, to mask the anionic phosphate moiety for improved cellular permeability and blood-brain-barrier passage. Our data indicate that POMHEX is effective in cell-based systems, with an  $IC_{50}$  of ~40 nM. Strikingly, treatment with POMHEX in intracranial xenografted mouse models eradicates *ENO1*-homozygously deleted tumors in up to 40% of cases. Animals are effectively cured without tumor recurrence—even after discontinuation of the drug. However, its sub-optimal pharmacokinetic (PK) properties portend significantly lower concentrations of POMHEX in the brain relative to visceral organs. This is largely due to the high levels of carboxylesterase activity in mouse plasma, resulting in premature cleavage of the first POM group prior to cellular entry.

In response to this issue, we have focused on synthesizing non-carboxylesterase-labile pro-drug derivatives of HEX. Preliminary data indicate that protecting HEX with both a benzylamine and a pivalic thioester (VCY13) yield the most promising results. Head-to-head comparison of VCY13 to POMHEX reveals greater cell-based potency, with an  $IC_{50}$  of ~38 nM. Importantly, bioactivation of VCY13 is not contingent upon carboxylesterase activity, which points to enhanced PK. Our present efforts thus involve examining the pharmacological consequences of altering the sterics on the thioester moiety while testing the *in vivo* stability of various thioester-benzylamine-protected compounds in mouse models.

## **MEDI 160**

### **Rational design, synthesis, and *in-vitro* screening of novel tankyrase inhibitors for the treatment of cancer**

**Bhumika D. Patel**, *bhumika.patel@nirmauni.ac.in*, Ankit Patel, Hardik G. Bhatt. *Pharmaceutical Chemistry, Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat, India*

Tankyrase, Poly (ADP-ribose) polymerase5 (PARP5), a member of PARP protein superfamily, is an emerging novel target for the treatment of colon, breast, bladder, gastric cancers etc. It plays a key role in Wnt signaling which is an essential pathway for adult homeostasis and embryonic development like regeneration of skin, gut, hair and bone marrow. It has been observed that Wnt and their downstream effectors are directly or indirectly involved in tumor initiation, growth, and metastasis. Tankyrase is the enzyme which controls the level of Axin, one of the key component of Wnt signaling. Inhibition of tankyrase activity promotes Axin stabilization and attenuates Wnt signaling

in cancer cells which in turn controls cell proliferation and/or metastasis of cancer. During the past few years, there has been an increased interest in the development of selective small-molecular tankyrase inhibitors and few molecules are currently in the preclinical phase. To design such new molecules, *in-silico* pharmacophore modeling (DISCOtech Module, SybylX), 3D-QSAR (CoMFA and CoMSIA), virtual screening, molecular docking (Surflex, SybylX) and ADMET prediction (OSIRIS property explorer) studies were performed to identify potential hits which could be optimized into leads and further synthesized. Based on the results of computational studies, a series of substituted quinazolin-4-one was synthesized and characterized. *In-vitro* cell viability MTT assay was performed to screen all the synthesized molecules against APC wild-type (HCT116) and APC mutant (SW480, SW620, HT29) colon cancer cell lines using doxorubicin as standard. Compound **AP-9** and **AP-10** gave best results in APC mutant SW480 cell line with  $IC_{50}$  40.23  $\mu$ M and 43.45  $\mu$ M respectively which was found better than doxorubicin ( $IC_{50}$  64.05  $\mu$ M). Further *in-vitro* studies of both the compounds are under progress.

## **MEDI 161**

### **Novel diphenylbutylpiperidine analogs to treat lung cancer**

**Md Ashraf Uz Zaman**, *md.ashraf@ttuhsc.edu*, Md Sanaullah Sajib, Constantinos M. Mikelis, Nadezhda German. Department of Pharmaceutical Sciences, SOP, Texas Tech University HSC, Amarillo, Texas, United States

Diphenylbutylpiperidines are the well-known class of first-generation antipsychotics. It includes several agents: penfluridol, clopimozide, fluspirilene, and pimozide. In addition to the intended use, this class of compounds was shown to kill cancer cells *in vitro*, providing a new repurposing prospective. Penfluridol had shown no cardiac toxicity, a common side effect for this class, and has been evaluated in various cancer models. However, no work was done to assess the CNS-receptors mediated neurotoxicity of this drug. We have established that a 10 mg/kg dose of PFL in mice, either i.p. or oral, equals to the 1  $\mu$ M level of this drug in the brain. In our assessment of the binding profile of PFL, we observed that 1  $\mu$ M is enough to block a majority of CNS receptors (Tab. 1), which could lead to neurotoxicity in patients undergoing chemotherapy with this compound. .

By overlapping antipsychotic and anticancer pharmacophores of PFL, we have designed and synthesized a series of analogs that were further evaluated for CNS activity, ability to cross the BBB and cytotoxicity. Our lead compounds PF131 ( $IC_{50}$  = 5.6  $\mu$ M) and PF331 ( $IC_{50}$  = 2.7  $\mu$ M) showed optimized toxicity profile in *in vitro* (CNS binding profile, Table 1) and *in vivo* (acute and chronic toxicity) models. Tissue analysis showed that 10 mg/kg i.p. dose provides at least 50  $\mu$ M concentration of PF331 in the lungs of CB57B6 mice (Fig. 1A). Hence, we used lung cancer xenograft model to analyze its *in vivo* efficacy and observed 80% reduction in tumor size (Fig. 1B). Initial mechanistic studies suggested that anticancer effect is partially attributed to an overactivation of mTOR pathway. More studies are conducted to understand proposed mechanism. In

conclusion, a novel diphenylbutylpiperidine analog with the reduced toxicity and ability to significantly reduce tumor size *in vivo* was identified.

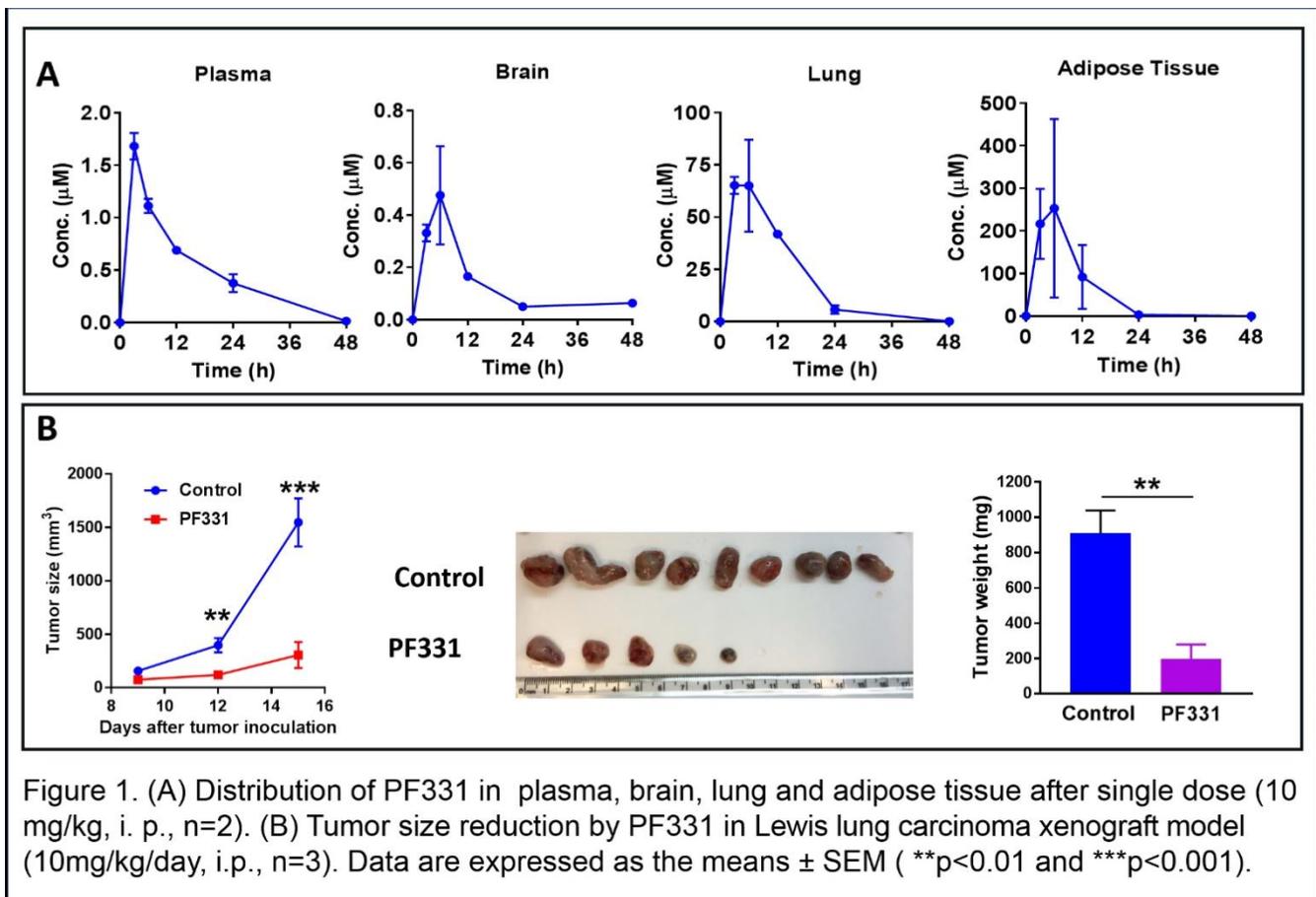


Figure 1. (A) Distribution of PF331 in plasma, brain, lung and adipose tissue after single dose (10 mg/kg, i. p., n=2). (B) Tumor size reduction by PF331 in Lewis lung carcinoma xenograft model (10mg/kg/day, i.p., n=3). Data are expressed as the means ± SEM ( \*\*p<0.01 and \*\*\*p<0.001).

Figure 1

	5HT1A	5HT1D	5HT2A	5HT2B	5HT2C	5HT5a	5HT6	5HT7	D1	D2	D3	D4	D5	KOR	MOR	DOR	H1	H2	NET	SERT	DAT
PFL	356	3560	361	184	881	>10 <sup>4</sup>	>10 <sup>4</sup>	280	147	159	136	>10 <sup>4</sup>	125	>10 <sup>4</sup>	867	1714	>10 <sup>4</sup>	>10 <sup>4</sup>	588	>10 <sup>4</sup>	1714
PF121	1262	752	164	177	402	ND	1680	1574	300	148	474	25	437	667	902	1558	814	252	902	903	1191
PF131	1395	844	1000	423	1712	894	1671	969	798	194	209	385	529	2669	356	1413	ND	546	77	428	529
PF141	1363	NA	1105	ND	1603	ND	ND	ND	ND	317	552	1643	ND	1021	328	ND	718	526	ND	ND	ND
PF151	1094	1074	6059	509	1126	4152	1670	812	>10 <sup>4</sup>	550	782	>10 <sup>4</sup>	744	>10 <sup>4</sup>	>10 <sup>4</sup>	>10 <sup>4</sup>	NA	NA	458	>10 <sup>4</sup>	>10 <sup>4</sup>
PF211	481	628	1000	374	2131	NA	1695	326	135	38	62	58	121	1328	70	1526	ND	278	518	1180	121
PF331	>10 <sup>4</sup>	>10 <sup>4</sup>	900	729	740	4973	1400	949	>10 <sup>4</sup>	417	437	459	623	>10 <sup>4</sup>	8253	>10 <sup>4</sup>	7031	NA	1438	1314	622
PF431	901	NA	889	NA	2548	ND	ND	ND	ND	460	ND	132	ND	1705	536	NA	718	401	ND	ND	ND

**Table 2.** Binding activity (K<sub>i</sub>, nM) of penfluridol and its analogs at CNS receptors. (n=4). ND - not determined, NA - not active

Table 1

## MEDI 162

### Discovery of novel toll-like receptor 7 antagonists

**Shuangshuang Jiang**<sup>1</sup>, *jss15@mails.tsinghua.edu.cn*, **Hekai Chen**<sup>1</sup>, **Hang H. Yin**<sup>1,2</sup>. (1) School of Pharmaceutical Sciences, Center of Basic Molecular Science, Department of Chemistry, Tsinghua University, Beijing, China (2) Chemistry and Biochemistry, University of Colorado Boulder, Boulder, Colorado, United States

Toll-like receptors (TLRs) are highly conserved transmembrane proteins which detect pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). TLRs play a vital role in the innate immune system. Ten different kinds of TLRs (TLR1-10) have been identified in human. Among these, TLR7 and TLR8 both locate in the endosome, where they recognize viral ssRNA and synthetic tricyclic imidazoquinoline derivatives. Due to their phylogenetical and structural similarity, especially the sequence and structure homology, we have faced great challenges in the development of antagonists targeting TLR7 alone. In this study, we have discovered the first TLR7 small molecule antagonist **S-38** (IC<sub>50</sub> = 340 nM) with negligible cytotoxicity. In THP-1 cells, compound **S-38** inhibited R848-induced production of the production of pro-inflammatory cytokines (TNF- $\alpha$ , IL-6 and IL-1 $\beta$ ) in a dose-dependent manner. Moreover, in our test with clinical samples, **S-38** also showed potent inflammation-suppressing activities by preventing the production of TNF- $\alpha$  in peripheral blood mononuclear cells (PBMCs) harvested from donors. In conclusion, we have successfully developed the first TLR7 small molecule antagonist which could be used as a chemical probe to understand the biological relevance of TLR7 in different pathogenesis processes. Our effort in the discovery of TLR7 antagonist may contribute to the development of novel therapeutic strategies for autoimmune diseases.

## MEDI 163

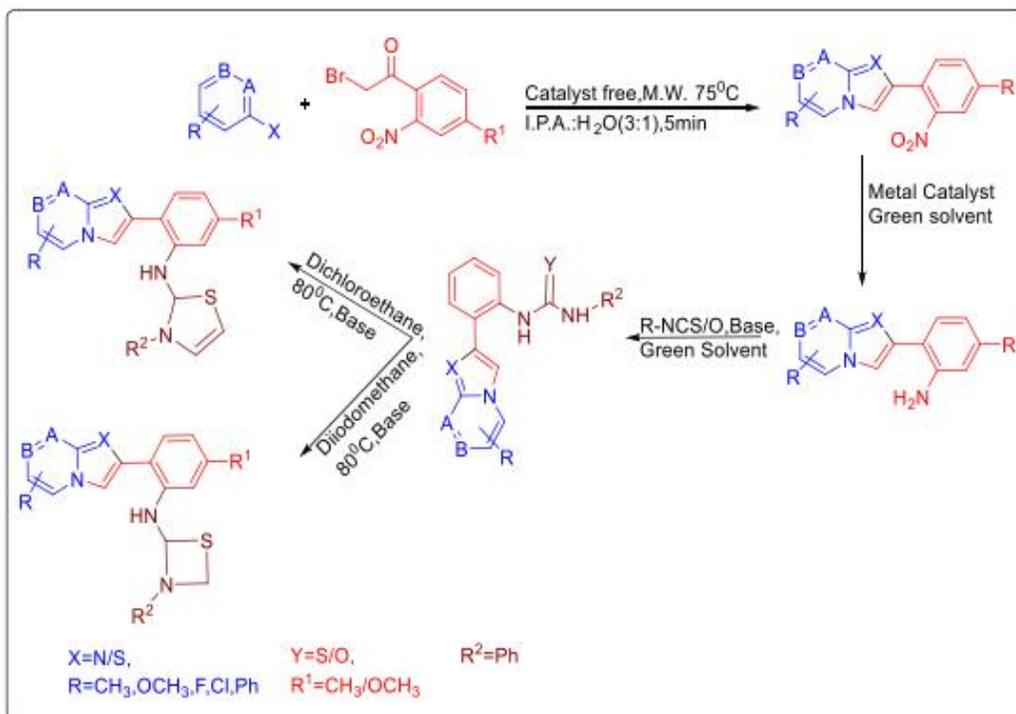
### Green synthetic approach to access thiazetid-2-imine and thiazolidin-2-imine fused pyrazolo-pyrimidine scaffold as hybrid bifunctional molecules: Structure-based optimization and evaluation of calcium dependent protein kinase1(CDPK1) inhibition

**Nishanth Rao**, *nishanth.ramdas@gmail.com*. department of chemistry, vellore institute of technology, Sangareddy, Telangana, India

Antibiotic resistance is a threatening issue being faced by the world today. It is an intrinsic part of bacterial evolution whose genetic basis arise via, chromosomal mutation of bacteria or by the acquisition of resistance genes from other bacteria by horizontal gene transfer [HGT] and by the production of  $\beta$ -lactamase. To some extent, bifunctional and hybrid antimicrobials are considered to be the successful outcome of research towards bacterial resistance. MCB-3861 is one such example of fluoroquinolone-oxazolidinone hybrid anti-microbial with a 4-hydroxy piperidinyl linker. It shows resistance against several clinically relevant gram-positive pathogens, including

vancomycin-Resistant Enterococci (VRE), *E. faecalis* S. *pneumonia*. calcium dependent protein kinase1(CDPK1) is an essential enzyme in the opportunistic pathogen *Toxoplasma gondii*. It controls multiple processes such as adhesin secretion, motility, invasion, of *Toxoplasma gondii*. Considering an amide in a general view resonance on nitrogen atom attains planar structure with  $sp^2$  hybridization which gives best overlap of orbitals with the adjacent carbonyl carbon atom making it less electrophilic and less reactive. Contrarily extensive literature survey on SAR of the lactam containing anti microbials reveals that, 4-5 ring system in penicillin prevents nitrogen atom in lactam ring from attaining  $sp$  hybridization. In addition actual ideal bond angle ( $109.5^\circ$ ) of the  $sp^3$ , hybridized carbon atom in lactam ring is constricted to  $90^\circ$  leading to angle strain making it susceptible to degradation by  $\beta$ -lactamase. From our preliminary work, we found that imidazo [1,2-a]pyridine/pyrimidine/pyrazine derivatives with methyl and methoxy substitutions would be active against gram positive and gram negative bacteria. In this context we underpinned a design to synthesize hybrid antimicrobials by inception of thia/oxazetid-2-imine and thia/oxazolidine-2-imine moieties to methyl or methoxy substituted imidazo/ thiazo pyridine/ pyrimidine/pyrazine derivatives and explore structure activity relationship of CDPK1 with a goal of increasing selectivity .

### Graphical Abstract:



## MEDI 164

### Development of inhibitors of the pore forming protein perforin for the treatment of leukaemia

**Jiney Jose**<sup>1,2</sup>, [jineyjjj@gmail.com](mailto:jineyjjj@gmail.com), Julie Spicer<sup>3</sup>, Christian K. Miller<sup>1,2</sup>, Patrick D. O'Connor<sup>1</sup>, Anna Giddens<sup>1</sup>, Hediah Akhlaghi<sup>4</sup>, Joseph Trapani<sup>4</sup>, William A. Denny<sup>5</sup>. (1) Auckland Cancer Society Research Centre, Faculty of Medical and Health Science University of Auckland, Auckland, New Zealand (2) Maurice Wilkins Centre, University of Auckland, Auckland, New Zealand (3) Auckland Med Schl Cancer Soc Res, The University of Auckland, Auckland, New Zealand (4) Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia (5) Cancer Society Research Centre, University of Auckland, Auckland, New Zealand

Treatment of leukaemia remains a formidable challenge despite therapeutic advances. Bone marrow transplant (BMT) can be curative in the treatment of leukaemia; long term survival is >70% for a matched graft, however in the case of a mismatch survival is <40%. In recent years, the use of BMT therapy has increased, leading to a larger pool of mismatched patients requiring treatment and resulting in a medical need that is largely unmet.

Our research group has been investigating the role of perforin, a pore forming protein used by cytotoxic effector cells in the immune system to kill virus-infected or transformed cells. However these 'killer' cells have also been implicated in graft rejection in mismatched patients where they kill foreign donor cells. Therefore we are trying to inhibit perforin function to prevent graft rejection in BMT and improve overall patient survival. This represents a novel new approach to immunosuppression as there are currently no drugs on the market that specifically target perforin function. Herein we present our synthetic effort towards development of inhibitors of perforin and the *in vitro* activity of a human T lymphocyte cell line.

## MEDI 165

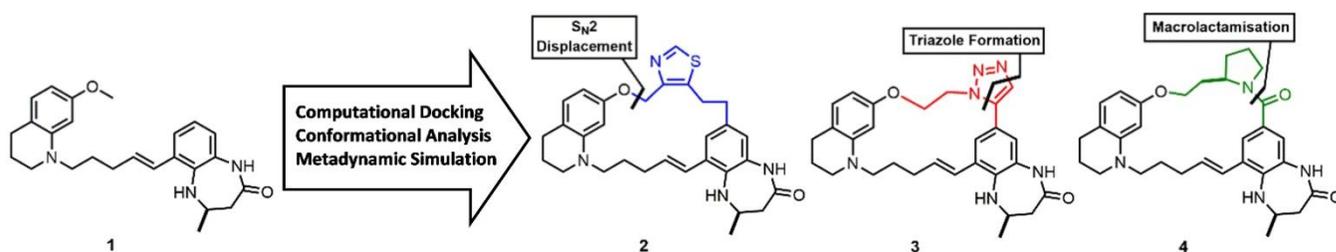
### Design and synthesis of macrocyclic CREBBP bromodomain ligands

**Mustafa Moroglu**<sup>1</sup>, [mustafa.moroglu@chem.ox.ac.uk](mailto:mustafa.moroglu@chem.ox.ac.uk), Matthew D. Selby<sup>2</sup>, James Reuberson<sup>2</sup>, William Pitt<sup>2</sup>, James Clayton<sup>1</sup>, Stuart J. Conway<sup>1</sup>. (1) Department of Chemistry, University of Oxford, Oxford, United Kingdom (2) UCB, Slough Berkshire, United Kingdom

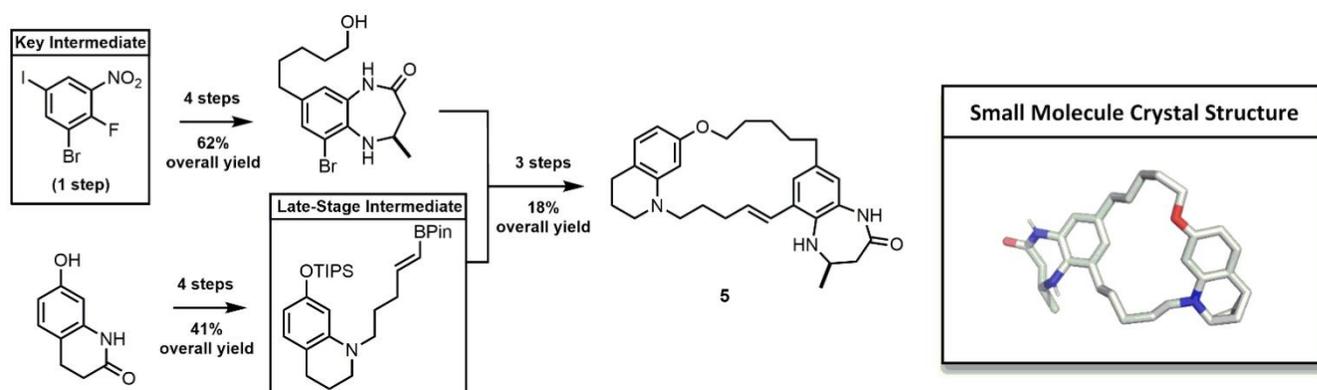
Cyclic AMP responsive element binding protein, binding protein (CREBBP) is a transcriptional coactivator with an epigenetic 'reader' bromodomain that binds to acetylated lysine residues (KAc) of histone proteins. CREBBP has been indicated as a potential oncology target. Our group has identified nanomolar potent compounds, including ligand **1**, for the CREBBP bromodomain, with moderate selectivity against BRD4(1), which is a member of the bromodomain and extra terminal domain (BET) family of bromodomains. The protein bound conformation of ligand **1** differs

substantially from its solution state conformation. This project explores the hypothesis that constraining ligand **1** as a macrocycle, which adopts a solution state conformation that is closer to the protein bound structure, would result in an increased affinity and selectivity over other bromodomain targets. Computational rationale (through docking, conformational analysis and metadynamic simulations) led to the design of macrocycles **2–4** for synthetic preparation (**Figure 1**).

Macrocycles **2–4** would explore three alternative macrocyclisation strategies;  $S_N2$  displacement, triazole formation and macrolactamisation, respectively. In addition, a macrocycle with a fully saturated carbon linker was chosen for synthetic preparation, to validate the computational design and explore the importance of rigidifying the ring. Synthetic preparation of macrocycle **5** followed a 12 step convergent synthesis, with key, late-stage intermediates used for the preparation of macrocycles **2–4** (**Scheme 1**). Testing the affinity of macrocycles **2–4** for the CREBBP bromodomain will provide a good insight to the benefits of macrocyclic ligand design in medicinal chemistry.



**Figure 1.** Computationally designed macrocyclic ligands **2–4** for the CREBBP bromodomain based on ligand **1**.

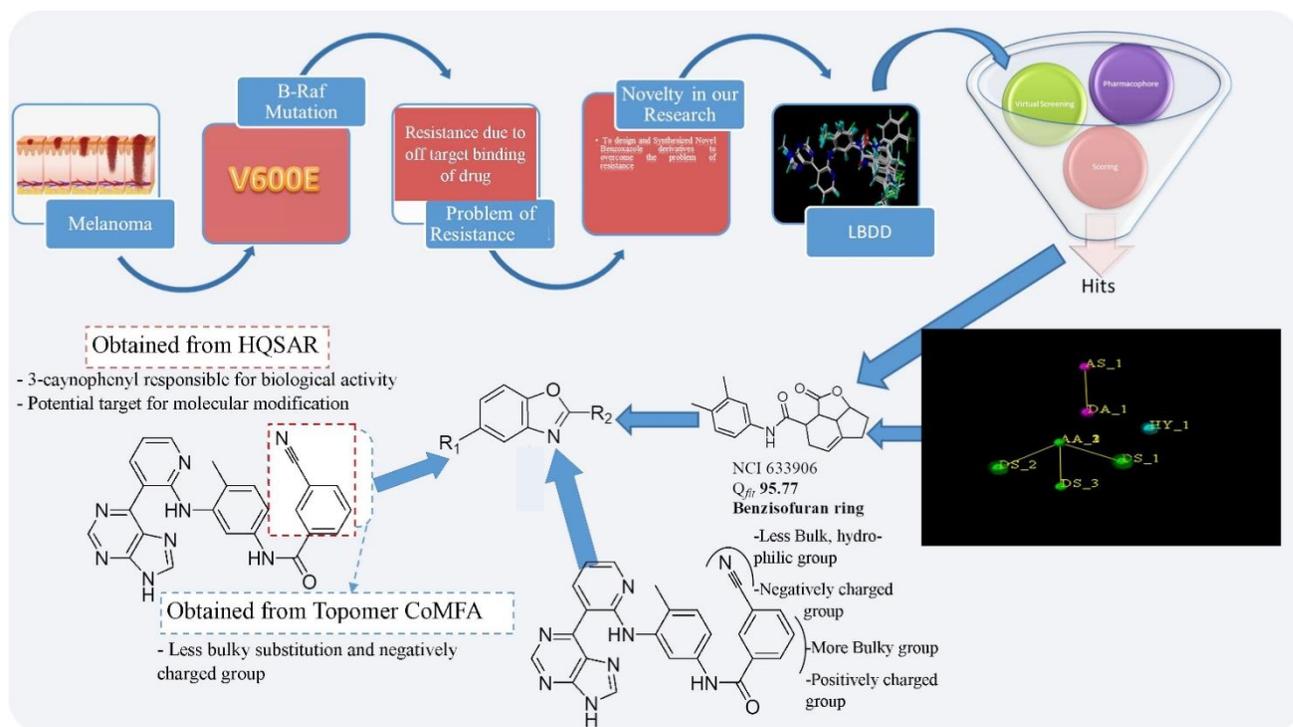


**Scheme 1.** 12 Step convergent synthesis for the preparation of macrocycle **5**.

## **Design and synthesis of novel benzoxazole derivatives as B-Raf kinase inhibitor for the treatment of skin cancer**

**Jaydeepsinh P. Chavda**, jaydeepsinh3636@gmail.com, Kevin v. Shah, Hardik G. Bhatt. *Pharmaceutical Chemistry, Institute of Pharmacy, Ahmedabad, Gujarat, India*

Cancer is the second leading cause of death after cardiovascular disease. Melanoma is more aggressive than most other types of cancer. B-Raf belongs to the serine/threonine kinase family playing an essential role in cell growth proliferation. Almost 70% B-Raf mutation found in melanoma cancer. Hence, B-Raf is the excellent target for the treatment of melanoma cancer. To design novel B-Raf kinase inhibitors, various computational approaches like pharmacophore modelling, virtual screening, 3D-QSAR (CoMFA, CoMSIA, HQSAR, and Topomer CoMFA) and molecular docking were used. Pharmacophore model was generated using 10 structurally diverse molecules using DiscoTech module and best-generated model was refined with GASP module of Sybyl X. The refined best pharmacophore model with nine features; one hydrophobic region, three donor sites, three acceptor atom, one donor atom, and one acceptor site, was used as a query for virtual screening in the NCI database. Virtual hits from NCI database was further screened by applying the Lipinski's filter, removal of counter ions / duplicate structures that resulted into 11485 hits. 3D-QSAR study was also performed on purinyl-pyridine derivatives. Benzoxazole moiety was selected from features of best pharmacophoric model and bioisosteric replacement of core ring of virtual hit molecules, while various substitutes were incorporated based upon contour map analysis of 3D-QSAR studies. Molecular docking study of novel benzoxazole derivatives were carried out by using GOLD 5.2. Among, all designed molecules, few compounds showing good docking score as compared to the marketed available B-Raf inhibitor, Vemurafenib, were synthesized and characterised. All synthesized molecules were evaluated for *in vitro* cytotoxicity studies on various cell lines and potent molecule is under investigation for *in vivo* pharmacological models for skin cancer. In future, this study will be explored to develop hit to lead generation of novel inhibitor against mutated B-Raf for effective skin cancer therapy.



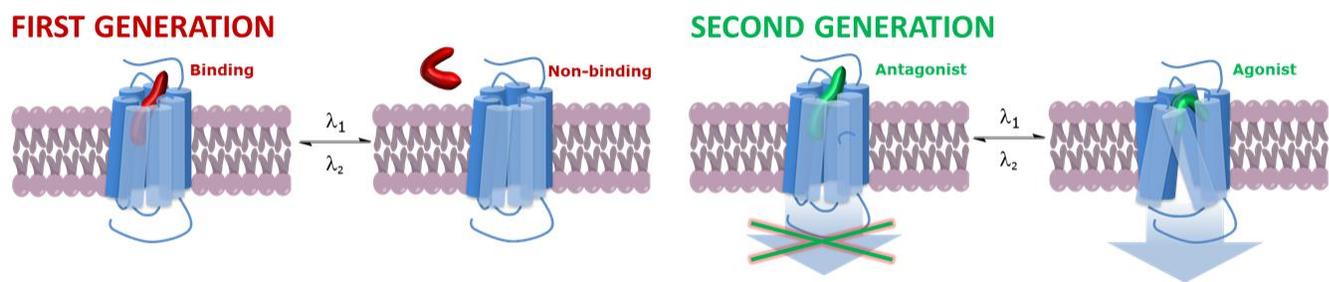
## Designing of Novel Scaffold

### MEDI 167

## Photopharmacology for GPCR receptor proteins: 1<sup>st</sup> and 2<sup>nd</sup> generation chemical biology tools

**Maikel Wijtmans**, *wijtmans@few.vu.nl*. Dept of Pharmacochemistry, Vrije Universiteit, Amsterdam, Netherlands

Photopharmacology is a discipline that uses photoswitchable ligands as pharmacological tool compounds to yield spatiotemporal control of protein activity with light. However, photopharmacology in the G protein-coupled receptor (GPCR) field is still in its infancy. In this presentation, our general approach towards GPCR photopharmacology will be discussed as well as recent contributions from our laboratory including several series of photoisomerisable azobenzene-based GPCR ligands. First-generation series involve photoswitchable antagonist or agonist ligands that shift affinity/potency for an aminergic GPCR. In a second-generation series, we incorporated a change in the ligand efficacy for a peptidergic GPCR upon illumination, thus establishing a photoswitch from antagonism to agonism. Our contributions deliver a toolbox of compounds capable of photomodulating GPCR signaling in complementary ways.



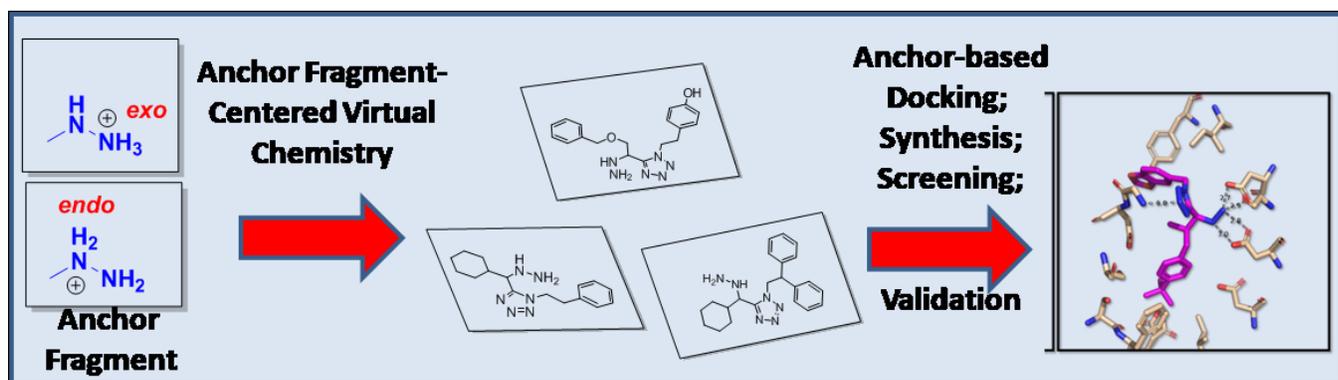
## MEDI 168

### Inhibitors for Asp-proteases: Anchor-based virtual screening, innovative chemistry, and protein crystallography

**Markella Konstantinidou**<sup>1</sup>, [konsmark@hotmail.com](mailto:konsmark@hotmail.com), **Francesca Magari**<sup>2</sup>, **Fandi Sutanto**<sup>1</sup>, **Muhammet Unver**<sup>3</sup>, **Varsha Jumde**<sup>3</sup>, **Carlos J. Camacho**<sup>4</sup>, **Gerhard Klebe**<sup>2</sup>, **Anna Hirsch**<sup>3</sup>, **Alexander Doemling**<sup>1</sup>. (1) Department of Drug Design, University of Groningen, Groningen, Netherlands (2) Department of Pharmaceutical Chemistry, Philipps University Marburg, Marburg, Germany (3) Helmholtz Institute for Pharmaceutical Research, Saarland, Germany (4) University of Pittsburgh, Pittsburgh, Pennsylvania, United States

Computer-aided drug design has become an essential aspect of drug discovery, significantly accelerating the processes of discovery and lead optimization. Here, we focus on anchor-centered docking approaches. A few years ago, we introduced the pharmacophore-based virtual screening platform ANCHOR.QUERY (<http://anchorquery.ccbb.pitt.edu/>), which includes novel compounds that can be easily synthesized using multi-component reactions and commercially available starting materials. ANCHOR.QUERY was successfully applied to the protein–protein interaction of p53–MDM2 and the discovery of allosteric inhibitors of the PDK1 kinase. However, ANCHOR.QUERY was made for the design of small molecule PPI antagonists and therefore, it is based on the often overarching energy contribution of deeply buried large amino acid side chains in the receptor pockets, often called “hot spots”. Often an energetically hot spot consists of a synthetic fragment in which case the amino acid side chain centered ANCHOR.QUERY database cannot be employed.

Here, we describe the development of a docking protocol for tailor-made virtual libraries with flexible fragments as anchor points. In a case study on aspartic proteases we designed a novel warhead which is incorporated in an easily accessible multi-component reaction scaffold. Initial screening and protein crystallography-supported hits could be rapidly improved towards more potent binders in a small number of optimization rounds. The pipeline of anchor-centred docking, innovative chemistry and screening will be applicable in many different targets for the discovery of novel leads.

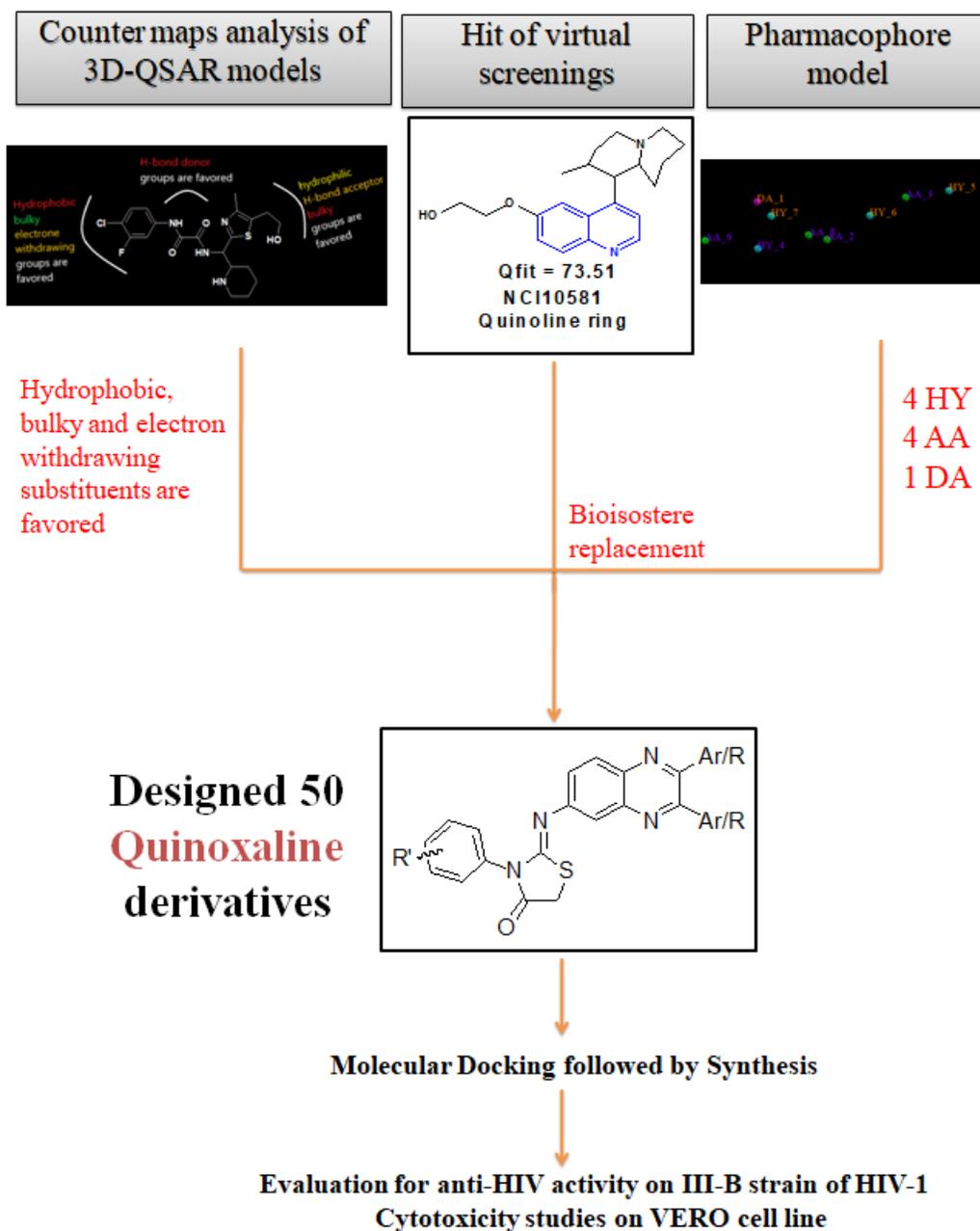


## MEDI 169

### Designing and synthesis of novel scaffold by adopting ligand- and structure-based approaches as HIV-1 entry inhibitor specially targeting to viral glycoprotein Gp120

**Kevin v. Shah**, [kevinshah1712@gmail.com](mailto:kevinshah1712@gmail.com), Jaydeepsinh P. Chavda, Hardik G. Bhatt. Pharmaceutical Chemistry, Institute of Pharmacy, Gandhinagar, Gujarat, India

Severe adverse effect and drug resistance are major drawbacks in the treatment of HIV. The improvement in the novel therapeutics will boost in a number of new drugs available and will expand the scope of combination therapy. Drugs aimed to viral elements instead of cellular components emerge as good tactics which would avoid the disruption of the normal function of the host cell leads to less side effects. Hence, present research work had been made to develop a HIV-1 entry inhibitors targeting HIV-1 envelope glycoprotein gp120. In ligand-based approach, pharmacophore modeling, virtual screening and 3D-QSAR (CoMFA, CoMSIA and HQSAR) studies were performed. Molecular docking study was utilized as the structure-based approach. Pharmacophore model was generated using 9 diverse molecules, using GALAHAD module of Sybyl X. The best model containing nine features viz. 4 hydrophobic, 4 acceptor atoms, 1 donor atom, was used as the query for virtual screening in the NCI database. Virtual hits from NCI database was further screened by applying Lipinski's filter, removal of duplicate structures/counter ion that result into around 40800 hits. 3D-QSAR studies were conducted on 29 phenyl oxalamide derivatives. Quinoxaline ring was selected from features of best pharmacophoric model and bioisosteric replacement of core ring of virtual hit molecules, while various substitutions were incorporated based upon counter map analysis of 3D-QSAR studies. Molecular docking study of novel Quinoxaline derivatives was carried out by using GOLD 5.2. Among all designed compounds, few compounds showing good docking score as standard gp120 inhibitors; were synthesized and characterized. These derivatives were evaluated for anti-HIV activity on III-B strain of HIV-1 and cytotoxicity studies were performed on VERO cell line. In future, this study will be explored for hit to lead generation of novel inhibitor against HIV infection.



## MEDI 170

Developing a chemical probe: Thieno[3,2-*d*]pyrimidines, selective and potent inhibitors of protein kinase DRAK2/STK17B

*Alfredo Picado*, [alfredopicadov@gmail.com](mailto:alfredopicadov@gmail.com), Carrow Wells, David Drewry. School of Pharmacy, University of North Carolina-Chapel Hill, Chapel Hill, North Carolina, United States

The Structural Genomics Consortium at the University of North Carolina (SGC-UNC) is focused on generating high quality chemical probes for understudied kinases and releasing them into the public domain. As part of this effort, a set of inhibitors targeting the serine/threonine kinase DRAK2/STK17B (DAPK-related apoptosis-inducing protein kinase 2) were recently developed. DRAK2 is an understudied kinase belonging to the Death-associated protein kinase (DAPK) family that also includes DAPK1, DAPK2, DAPK3, and DRAK1. Despite the paucity of research around DRAK2, we do know that it is expressed in T cells and B cells and its over expression has been linked to autoimmune diseases such as multiple sclerosis and type 1 diabetes. Currently no selective and potent inhibitors have been reported targeting DRAK2, so identification of a chemical probe for this kinase would help elucidate the role this kinase plays in disease.

Our investigation of DRAK2 originated with the selectivity profiling of thienopyrimidine acid analog donated by Pfizer (PFE-PKIS 43), initially synthesized as part of a TPL2 inhibitor program. This profiling revealed a high quality DRAK2 inhibitor, binding to DRAK2 at 3.8nM and only to 2 kinases in a panel of 403 kinases. We obtained a co-crystal structure of PFE-PKIS 43/DRAK2 in order to facilitate compound design. This shown a key back-pocket interaction of the carboxylic acid moiety with lysine-62, which could contribute to its potency and selectivity.

We utilized the co-crystal structure to further optimize for DRAK2. We modified the pendant phenyl ring, the core ring system, and the carboxylic acid moiety. These changes resulted in a set of thieno[3,2-*d*]pyrimidine DRAK2 inhibitors that demonstrate a range of binding affinities. The most potent compounds have  $K_d$  values below 50 nM and cellular potency ( $IC_{50}$ ) below 300 nM. These analogs have also demonstrate cellular off-target selectivity, improved mouse microsomal metabolic stability, and good permeability and solubility. To our knowledge, this is the first chemotype to be both potent and selective *in vitro* against DRAK2.

Experiments are ongoing to evaluate the effect of these analogs and respective negative controls as DRAK2 inhibitors in human T-cells as well efforts to generate phenotypic output on human primary cells.

## **MEDI 171**

### **PROTAC small-molecule degraders of AR protein**

**Xin Han**<sup>1,2</sup>, [xinhan@umich.edu](mailto:xinhan@umich.edu), **Chao Wang**<sup>1,2</sup>, **Chong Qin**<sup>1,2</sup>, **Weiguo Xiang**<sup>1,2</sup>, **Ester Fernandez-Salas**<sup>1,2</sup>, **Chao-Yie Yang**<sup>1,2</sup>, **Mi Wang**<sup>1,2</sup>, **Lijie Zhao**<sup>1,2</sup>, **Tianfeng Xu**<sup>1,2</sup>, **Jeanne Stuckey**<sup>3</sup>, **Shaomeng Wang**<sup>1,2</sup>. (1) Internal Medicine, University of Michigan, Ann Arbor, Michigan, United States (2) The Rogel Cancer Center, University of Michigan, Ann Arbor, Michigan, United States (3) Life Sciences Institute, University of Michigan, Ann Arbor, Michigan, United States

Androgen receptor (AR) is a validated therapeutic target for the treatment of metastatic castration-resistant prostate cancer (mCRPC). In the present study, we report our design, synthesis and biological characterization of small-molecule AR degraders designed based upon the proteolysis targeting chimera (PROTAC) concept. Through extensive optimization of the AR antagonist portion, the E3 ligase portion and the linker portion, we have successfully obtained highly potent PROTAC AR degraders, as exemplified by compounds **ARD-61** and **ARD-69**. In vitro, both of these two compounds effectively induce degradation of AR protein in AR-positive prostate cancer cell lines (LNCAP, VCAP and 22RV1) and achieves DC<sub>50</sub> values of around 1 nM. Importantly, they are capable of reducing the AR protein level by >95% in AR-positive prostate cancer cell lines. **ARD-61** and **ARD-69** are highly potent and effective in inhibition of cell growth in AR-positive prostate cancer cell lines and is >10-100 times more potent than its corresponding AR antagonists. Both of them are very effective in suppressing the expression of PSA, TMPRSS2 and FKBP5 genes in both LNCAP and VCAP cell lines in a dose-dependent manner and is capable of reducing the mRNA level of both PSA and TMPRSS2 genes by >50% at 10 nM. They can also inhibit Enzalutamide-resistant cell growth efficiently. In vivo, **ARD-61** showed potent AR degradation effects and anti-tumor activities in multiple murine xenograft tumors models in severe combined immunodeficiency (SCID) mice at well-tolerated dosing schedules. Our data suggest that further optimization of these compounds may yield a new class of promising agents for the treatment of mCRPC by inducing degradation of AR protein.

## **MEDI 172**

### **Design, synthesis, and application of GLP1 agonist-ASO conjugates to gene silencing in pancreatic beta cells**

*Laurent Knerr<sup>1</sup>, laurent.knerr@astrazeneca.com, Ahlke Hayen<sup>1</sup>, Maria Ölwegård-Halvarsson<sup>1</sup>, Punit P. Seth<sup>2</sup>, Thazha P. Prakash<sup>2</sup>, William J. Drury<sup>2</sup>, Carina ämmälä<sup>1</sup>, Ingela Ahlstedt<sup>1</sup>, Pia Stillemark-Billton<sup>1</sup>, Charlotte Wennberg-Huldt<sup>1</sup>, Eva-Marie Andersson<sup>1</sup>, Eric Valeur<sup>1</sup>, Rasmus Jansson-Löfmark<sup>1</sup>, David Janzén<sup>1</sup>, Linda Sundström<sup>1</sup>, Johan Meuller<sup>1</sup>, Josefine Claesson<sup>1</sup>, Patrik Andersson<sup>1</sup>, Camilla Johansson<sup>1</sup>, Richard G. Iee<sup>2</sup>, Brett P. Monia<sup>2</sup>, Shalini Andersson<sup>1</sup>, Anders Björkbom<sup>1</sup>, Erika Cavallin<sup>1</sup>, Xueqing Li<sup>1</sup>. (1) AstraZeneca, Gothenburg, Sweden (2) Ionis Pharmaceuticals, Carlsbad, California, United States*

Antisense oligonucleotide (ASO) have been under clinical investigation over the last 30 years. The development and optimization of their chemistry has led to a recent increased number of FDA approvals and clearly confirmed the value of this alternative therapeutical approach. However, their broad application is still hampered by their limited productive uptake by cells outside the liver. While numerous targeted delivery approaches have been studied to circumvent this issue, the selective application of ASOs to extra hepatic targets remains a formidable challenge. We will report on a novel strategy based on ASO conjugation to a glucagon like peptide receptor (GLP1R) agonist. This approach has enabled the successful productive internalization of ASO conjugate in pancreatic beta cells - a cell type so far refractory to

ASO uptake - and translated into remarkable selectivity for gene silencing in the targeted cell population compared to liver.<sup>1</sup>

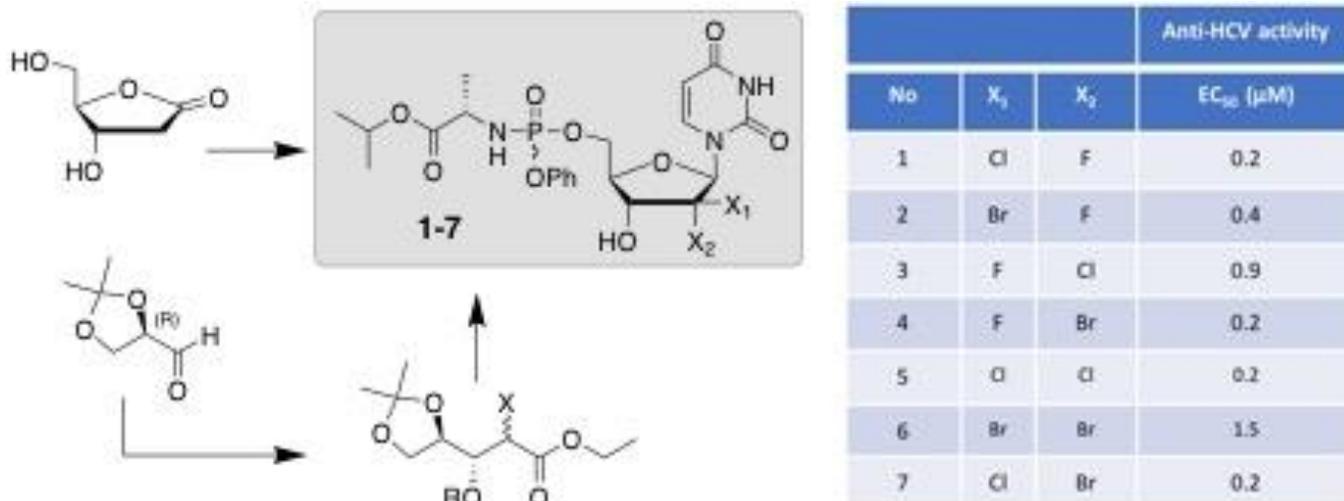
The presentation will encompass the design of these conjugates with emphasis on the impact of the chemistries of the different components: ASO, targeting peptide and linker. We will outline the challenges associated with the synthesis and profiling of these novel conjugates as well as the future perspective for this novel ASO delivery method.

## **MEDI 173**

### **Synthetic efforts towards the preparation of 2'-dihalogenated nucleotide prodrugs**

**Seema P. Mengshetti**, *seema.mengshetti@emory.edu*, Longhu Zhou, Ozkan Sari, Coralie De Shutter, Shaoman Zhou, Zhe Chen, Hongwang Zhang, Ahmed Khalil, Hao Li, Reuben Ovadia, Mahesh Kasthuri, Franck Amblard, Raymond F. Schinazi. Center for AIDS Research, Laboratory of Biochemical Pharmacology, Department of Pediatrics, Emory University School of Medicine, Atlanta-30322, Georgia, United States

Nucleoside analogs constitute an important class of drugs, as they are the basis for most treatment strategies against extremely important human pathogens such as herpes simplex virus (HSV), varicella zoster virus (VZV), human cytomegalovirus (HCMV), human immunodeficiency virus (HIV) hepatitis C virus (HCV), hepatitis B virus (HBV) and also cancer. Among them 2'-halogenated nucleosides analogs have drawn special attention which led to the approval of Gemcitabine (2'-deoxy, 2',2'-difluorocytidine) and Clofarabine (2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine) for cancer along with Sofosbuvir, a monophosphate prodrug of 2'-deoxy, 2'-β-methyl-2'-α-F uridine, for the treatment of HCV. In our search for new antivirals, we studied in details the influence of different combination of halogens at the 2'-position by preparing and evaluating 2'-β-Cl,2'-α-F (**1**), 2'-β-Br,2'-α-F- (**2**), 2'-α-Cl,2'-β-F (**3**), 2'-α-Br,2'-β-F- (**4**), 2'-diCl (**5**), 2'-diBr (**6**) and 2'-α-Br,2'-β-Cl (**7**) uridine monophosphate prodrugs. Synthesis of these compound was either achieved from deoxyribonolactone or by using stereo-selective aldolisation and halogenation reactions. Interestingly, all of the dihalogenated compounds displayed selective inhibition of HCV (GT1b) in a subgenomic HCV replicon system.

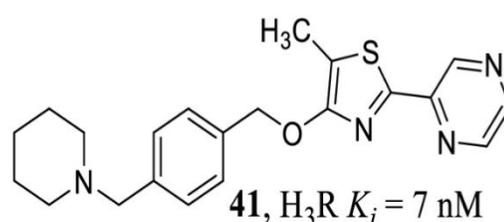
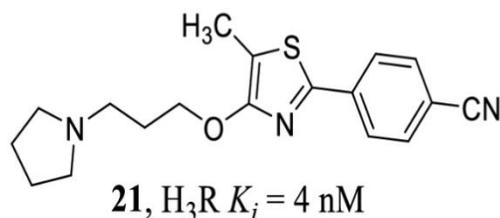
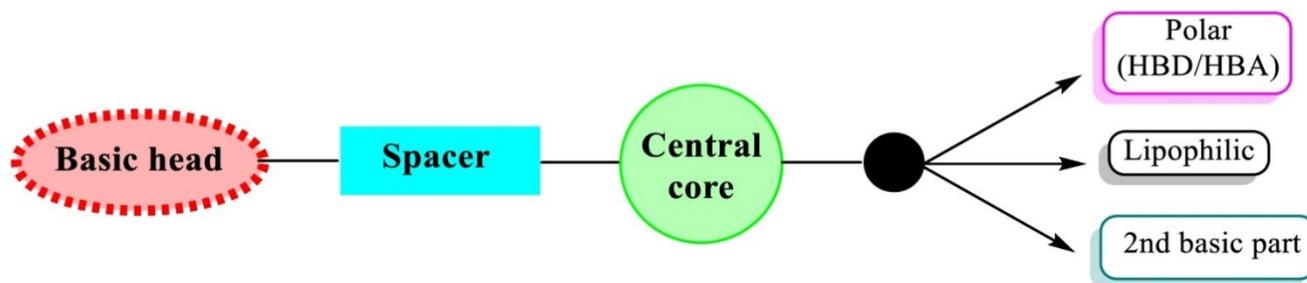


## MEDI 174

### Design, synthesis, and biological evaluation of novel oxadiazole- and thiazole-based histamine H<sub>3</sub>R ligands

**Mohammad A. Khanfar**<sup>1</sup>, *mhm512@hotmail.com*, **Holger Stark**<sup>2</sup>. (1) Alfaisal University, Amman, Jordan (2) Heinrich Heine University Düsseldorf, Düsseldorf, Germany

Histamine H<sub>3</sub> receptor (H<sub>3</sub>R) is largely expressed in the CNS and modulation of the H<sub>3</sub>R function can affect histamine synthesis and liberation, and modulate the release of many other neurotransmitters. Targeting H<sub>3</sub>R with antagonists/inverse agonists may have therapeutic applications in neurodegenerative disorders, gastrointestinal and inflammatory diseases. This prompted us to design and synthesize azole-based H<sub>3</sub>R ligands, i.e. having oxadiazole- or thiazole-based core structures. While ligands of oxadiazole scaffold were almost inactive, thiazole-based ligands were very potent and several exhibited binding affinities in a nanomolar concentration range. Ligands combining 4-cyanophenyl moiety as arbitrary region, para-xylene or piperidine carbamoyl linkers, and/or pyrrolidine or piperidine basic heads were found to be the most active within this series of thiazole-based H<sub>3</sub>R ligands. The most active ligands were in silico screened for ADMET properties and drug-likeness. They fulfilled Lipinski's and Veber's rules and exhibited potential activities for oral administration, blood-brain barrier penetration, low hepatotoxicity, combined with an overall good toxicity profile.



## MEDI 175

### Design and optimization of a first-in-class NACK inhibitor: A novel path to notch inhibition

**Tanya T. Kelley**<sup>1</sup>, [ttk7@miami.edu](mailto:ttk7@miami.edu), Xiaoxia Zhu<sup>2</sup>, Anthony J. Capobianco<sup>2</sup>, Stephan Schürer<sup>1,3</sup>. (1) Molecular and Cellular Pharmacology, University of Miami Miller School of Medicine, Miami, Florida, United States (2) Department of Surgery, University of Miami Miller School of Medicine, Miami, Florida, United States (3) Center for Computational Science, University of Miami, Coral Gables, Florida, United States

Notch Activation Complex Kinase (NACK) is a key player in Notch-mediated tumorigenesis and is an attractive novel target for the treatment of esophageal adenocarcinoma. NACK, annotated in the kinome as SgK223, is an atypical pseudokinase and an established Notch transcriptional co-activator. However, there is no known endogenous or exogenous ligand, no existing co-crystal structure and no reported biological data. To identify a scaffold for NACK inhibition, an artificial intelligence (AI) multitask classification approach was employed. Over 6 million commercially available compounds were screened against established kinase machine learning classifiers, and nearly 8000 were prioritized based on the predicted probability of being active. A homology structure model of the NACK kinase domain was generated and further optimized by all-atom explicit water molecular dynamics (MD) simulations, followed by virtual screening of prioritized compounds. Top-scoring compounds were purchased and screened in *in-vitro* and *in-vivo* assays. Commercially available compound Z271-0326 (iNACK) displayed the best inhibitory activity and was further validated in rodent models. A robust novel chemical synthesis for iNACK was accomplished in six steps with an overall yield of 26%. Current efforts are aimed towards optimizing iNACK into the first NACK molecular probe. We optimized our virtual NACK kinase domain structure model *via* MD simulations, and performed *in-silico*

structure-activity relationship (SAR) studies to better understand putative binding interactions. A second SAR library was recently designed and synthesized with the goal of improving binding affinity and inhibitory activity. Preliminary assay results demonstrate that analogue UM-73 has a 4-fold increase in affinity with an IC<sub>50</sub> of 330 nm in cells. We will continue to optimize iNACK through future SAR studies to further enhance inhibitory activity, while balancing affinity with favorable ADMET properties. Thus, arriving at a First-in-Class advanced preclinical NACK inhibitor.

## **MEDI 176**

### **Anthrax antitoxin lead optimization via bioisosteric replacement and other *in silico* strategies**

**Connor McDermott**, *mcderr108@umn.edu*, Elizabeth A. Ambrose. Medicinal Chemistry, University of Minnesota, Saint Paul, Minnesota, United States

*Bacillus anthracis*, the causative agent of the deadly bacterial infection anthrax, is a well-known bioterrorism agent in need of effective countermeasures. Current treatment options include antibiotics and antibody-based therapeutics, but neither directly targets the primary cause of the lethality of these infections: the lethal factor (LF), a zinc-metalloprotease and component of the tripartite exotoxin that the bacteria secrete. LF, which interferes with cellular immune defense mechanisms and induces endothelial cell apoptosis, has therefore become a popular target for the development of new anthrax therapeutics; however, no LF inhibitors have yet been approved to treat anthrax. Recently, we performed a large-scale experimental high-throughput screen and identified two promising small molecules active against LF. Here we report the structures of these hits as well as efforts to increase their solubility for structural biology studies while retaining their inhibitory activity towards LF, primarily via targeted bioisosteric replacement and a variety of virtual screening techniques. We also employed biophysical fragment-based screening to identify functional groups that increase inhibitory activity against LF, and these results are presented herein. Finally, we report new structural biology data crucial in elucidating the binding modes of our novel compounds as well as key structural features that contribute to strong and specific LF inhibition.

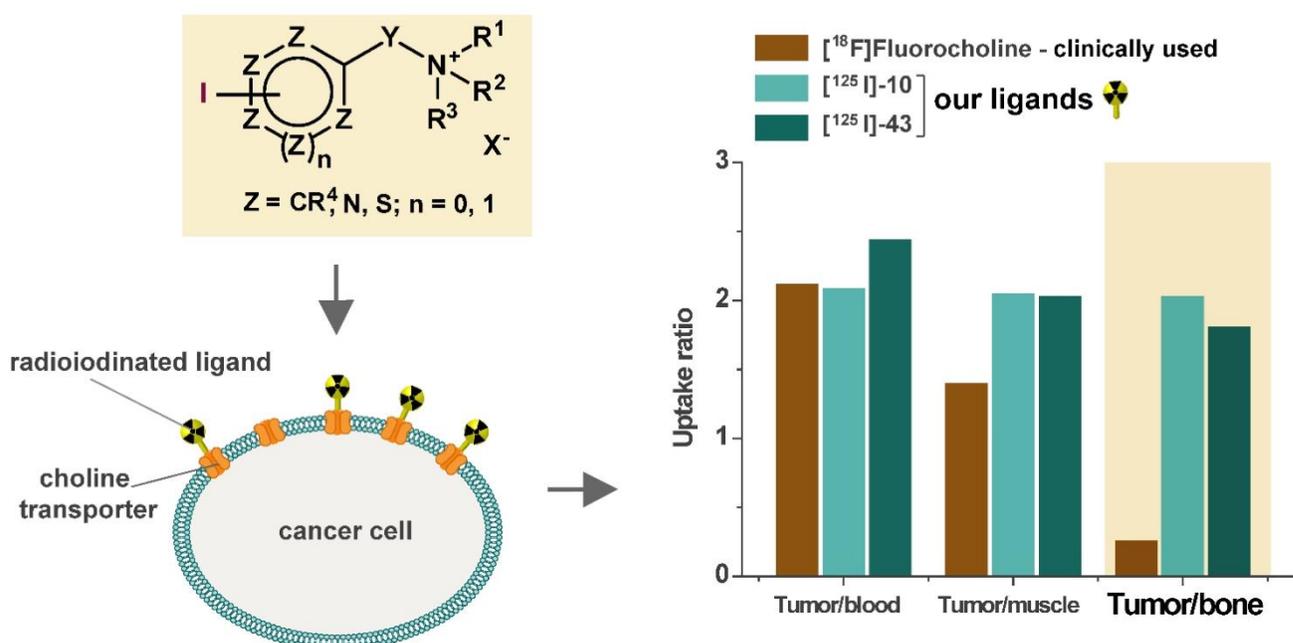
## **MEDI 177**

### **Radioiodinated aromatic choline analog tracers**

**Pavel Svec**<sup>1</sup>, *prion2@seznam.cz*, Zbynek Novy<sup>2</sup>, Jan Kucka<sup>1</sup>, Milos Petrik<sup>2</sup>, Ondrej Sedlacek<sup>1</sup>, Marian Hajdich<sup>2</sup>, Martin Hruby<sup>1</sup>. (1) Institute of Macromolecular Chemistry, CAS, Prague, Czechia (2) Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacký University Olomouc, Olomouc, Czechia

Current medicine and the field of cancer management increasingly profits from radionuclide imaging methods. In our research, we introduce a conceptually novel

series of radioiodinated ligands, which are applicable in diagnostics and potentially also in therapy (theranostics) of diseases related to pathological expression or function of choline transport proteins (ChTs). Compared to  $^{11}\text{C}$  and  $^{18}\text{F}$ -labeled choline derivatives already used in clinical practice for imaging mainly in prostate cancer patients, the herein described iodinated compounds are applicable for both positron emission tomography (PET) and single-photon emission tomography (SPECT) as well as for therapy depending on the iodine isotope selection. Some of the 50 compounds presented in this work possess considerably higher binding affinities towards ChTs (nanomolar ligands) than fluorocholeline or the natural ligand - choline. Biodistribution data acquired for eighteen  $^{125}\text{I}$ -labeled ligands in murine human prostate cancer xenograft model (PC-3 cells) revealed two compounds which exhibit significantly improved biodistribution profile in comparison with clinically used [ $^{18}\text{F}$ ]fluorocholeline. Interestingly, all tested radioiodinated ligands displayed tumor-to-bone uptake ratios superior to [ $^{18}\text{F}$ ]fluorocholeline. Furthermore, unlike  $^{11}\text{C}$  and  $^{18}\text{F}$ -labeled choline derivatives, the presented iodinated ligands can be prepared in their radiolabeled form by a facile palladium-catalyzed isotopic exchange in aqueous environment under mild conditions.



## MEDI 178

### Evolution of commercially available compounds for HTS

**Dmitriy Volochnyuk**<sup>1,3</sup>, [d.volochnyuk@gmail.com](mailto:d.volochnyuk@gmail.com), **Sergey Ryabukhin**<sup>2,4</sup>, **Yurii Moroz**<sup>4</sup>. (1) Enamine LTD, Kiev, Ukraine (2) Enamine Ltd, Kyiv, Ukraine (3) IOCh NASU, Kiev, Ukraine (4) Taras Shevchenko National University of Kyiv, Kiev, Ukraine

The content, size, and quality of compound collections used in HTS campaigns are fundamental to the success of the project; the most advanced screening technologies and the most physiologically relevant assays were though defeated by low quality of compound collections. The question, however, remains whether the available purchasable space allows to create a high-quality compound library for the HTS project that is comparable with selections from the Big Pharma repositories. While several analyses of the chemical space covered by suppliers' compound libraries (SCL) have been published recently, the aforementioned question remains unanswered. The starting point of the study was generation of the chemical space covered by purchasable screening compounds using ZINC database of **16,902,208** unique structures including stereoisomers.

In this talk, we shall describe:

- a critical revision of the existing VCL from the user's standpoint and whether it competes with the available Big Pharma collections in supporting compound novelty, diversity, and quality;
- evaluation of possibility to easily create the high-quality compound library without involving cost-demanding compound management through a limited number of vendors. Such approach will include the vendor's selection;
- compound management optimization in the case of consolidated libraries from different vendors. To simplify compound management, we studied relationship between the quality of the selected sets and number of the suppliers.

From our analysis it would appear that over the last 10 years the market has evolved to meet these demands, with new compounds from many suppliers meeting modern physiochemical properties. At the moment it is not possible to purchase an ideal one-million compound set (50K scaffolds, minimum of 20 compounds per scaffold).

However, it would appear that an ideal 500K set can be purchased. If sample logistics is an issue then we have shown that it is possible to purchase the 500k set from only six suppliers, with a 350K set available from just three suppliers. Many large companies have been through similar exercises and have built their screening decks accordingly. If you are considering building a screening deck *ab initio* then it is possible to achieve this from purchasable space.

## **MEDI 179**

### **Chemical tools to probe the role of bromodomains in the parasite *Trypanosoma cruzi***

**Corentine Laurin**<sup>1</sup>, [corentine.laurin@gmail.com](mailto:corentine.laurin@gmail.com), **Matthias Schiedel**<sup>1</sup>, **Anthony K. Chan**<sup>1</sup>, **Philip G. Humphreys**<sup>2</sup>, **Jon T. Sea**<sup>2</sup>, **Stuart J. Conway**<sup>3</sup>. (1) Chemistry, University of Oxford, Oxford, Oxfordshire, United Kingdom (2) GlaxoSmithKline, Stevenage, United Kingdom (3) Department of Chemistry, University of Oxford, Oxford, United Kingdom

Chagas disease is a chronic infection caused by the parasite *Trypanosoma cruzi* (*T. cruzi*) and is transmitted to mammals by hematophagous triatominae insects, often known as "kissing bugs". The development of the parasite in the heart muscle or digestive tract causes severe damage, resulting in organ failure. The current treatments,

benznidazole and nifurtimox, have a limited efficacy, show heavy side effects, and developing resistance. Increasing evidence shows that epigenetic targets play a crucial role in the parasitic life cycle of protozoan parasites.<sup>1</sup> Our research focuses on post-translational modifications (PTMs) of histone tails, especially acetylation. Bromodomains (BDs) are readers of the acetylated lysine residues. The bromodomains of the *T. cruzi* parasite have been briefly described in the literature, but their function remains uncharacterised. The life cycle of the parasite is complex and is thought to rely heavily on epigenetic control, hence our main interest is to validate the *T. cruzi* bromodomains as therapeutic targets.

Optimisation of expression and purification protocols of the bromodomain containing factors (BDFs) protein constructs in *E. coli* was followed by the development of a waterLOGSY-based assay to screen acetyl-lysine mimic containing compounds. The binding of the hits was further characterised by <sup>1</sup>H ligand-observed protein titration to obtain  $K_D$ , as well as by <sup>19</sup>F NMR. A known human bromodomain ligand was characterised to have a  $K_D$  value between 25 and 55  $\mu$ M, and is the current highest affinity ligand for *TcBDF3* identified by <sup>1</sup>H NMR. A focused library of analogues was synthesised to validate the binding of the chosen acetyl-lysine mimicking motif, then several probes were designed to develop new assays for *T. cruzi* bromodomains. Firstly, diazirine-derived probes were synthesised to produce photo-activatable covalent binders that can be monitored by protein mass spectrometry. Additionally, four fluorescent probes, with varying linkers, were synthesised to establish a fluorescent polarisation assay.

In summary, photo-activatable diazirines, and fluorescent probes were synthesised to provide tool compounds for further assay development to study the *T. cruzi* bromodomains. Identified ligands will show validation of bromodomains of *T. cruzi* as targets for Chagas disease. This will have wide implications in the use epigenetics targets to treat parasites more broadly.

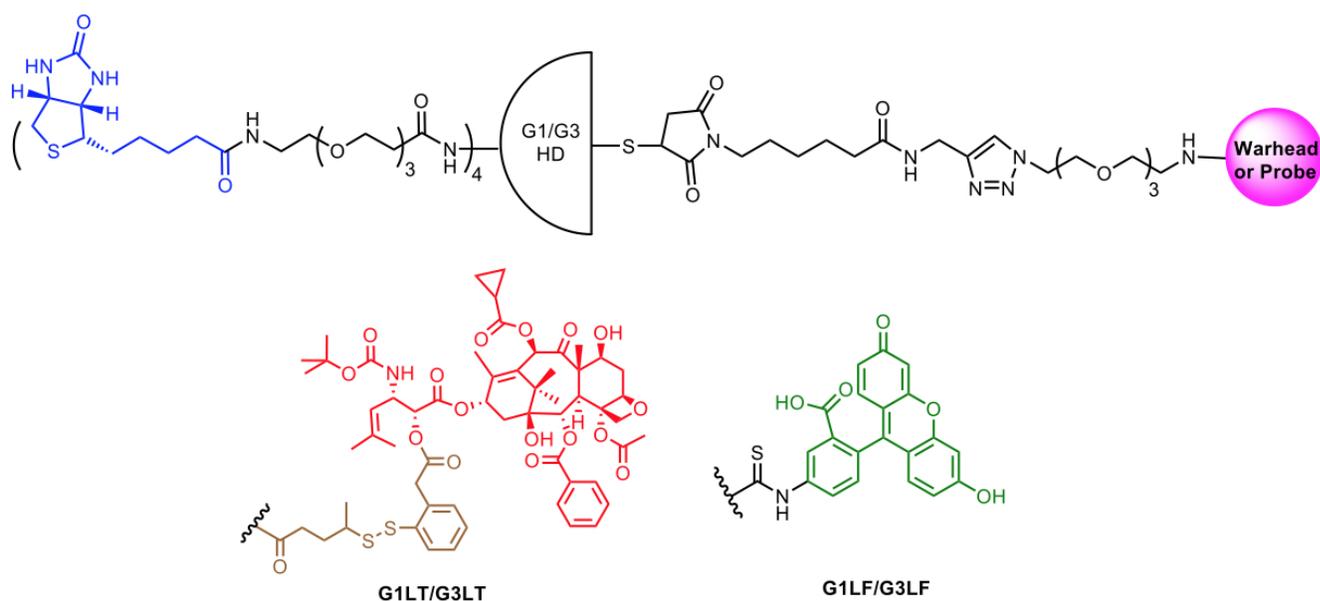
## **MEDI 180**

### **PAMAM-half-dendron-based drug conjugates as efficient tumor-targeted drug-delivery system for a new-generation taxoid**

**Yi Sun**<sup>1</sup>, *yi.sun@stonybrook.edu*, Longfei Wei<sup>1</sup>, Yaozhong Zhang<sup>1</sup>, Iwao Ojima<sup>1,2</sup>. (1) Chemistry Department, Stony Brook University, Stony Brook, New York, United States (2) Institute of Chemical Biology and Drug Discovery, Stony Brook, New York, United States

Cancer remains the second leading cause of death in the United States. In spite of tremendous efforts, there is still no common cure for cancer. Over the past decades, significant advancements have been made in the development of tumor-targeted drug delivery systems (TTDDS) to distinguish cancer cells from normal cells. Vitamin receptors such as folate receptors (FRs) and biotin receptors (BRs) are overexpressed on the surface of various cancer cell lines to maintain rapid cancer cell growth, which

can be used as cancer-specific biomarkers. Dendrimers are well-defined macromolecules, which can be used to increase the number of payload, and improve targeting efficacy as well as other biological and physiological properties. Based on these potentially advantageous features, PAMAM dendrimer-based drug conjugates were designed and synthesized by conjugating a biotin-PEGylated G3/G1 PAMAM half-dendron, a disulfide-based smart linker and a new-generation taxoid or a fluorescent probe (**Figure 1**). Biological evaluations (MTT, CFM and flow-cytometry analyses) of these drug conjugates against various cancer cell lines indicated substantially enhanced receptor-mediated endocytosis (RME) and excellent BR-specific cytotoxicity, i.e., selectivity to cancer cells.



**Figure 1.** PAMAM-Half-Dendron-Based Tumor-Targeted Drug Delivery Systems

## MEDI 181

### *In-silico* designing and synthesis of novel and selective hits as Poly ADP-Ribose Polymerase 1 (PARP1) inhibitors for treatment of solid tumours

**Priyancy G. Jain**<sup>1</sup>, 17mph406@nirmauni.ac.in, **Bhumika D. Patel**<sup>2</sup>. (1) Pharmaceutical Chemistry, Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat, India (2) Pharmaceutical Chemistry, Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat, India

Poly ADP-Ribose Polymerase 1 (PARP1) is known as one of the potential target for treatment of breast and ovarian cancer. There are currently three FDA approved PARP1 inhibitors namely Olaparib, Rucaparib and Niraparib in market while Veliparib and Talazoparib are in late stage of clinical development. All these molecules are non-

selective PARP1 inhibitors with concurrent inhibition of PARP2 with similar potency which may cause toxicities like acute myeloid leukemia, myelodysplastic syndrome and GI toxicity. Overall, looking at the success rate of PARP1 inhibitors into various solid tumours, there is an urge of novel and selective PARP1 inhibitors. To design such new inhibitors, many *in-silico* studies have been performed. Initially, 3D-QSAR study of a series of 2, 3-Dihydrobenzofuran-7-carboxamide derivatives was carried out using 23 molecules in training set and 8 in test set and significant model generated using distill based alignment. Contour map analysis of best COMFA and COMSIA model suggested hydrogen bond acceptor, steric and hydrophobic features as important ligand features. A ligand based pharmacophore model was also developed using DISCOtech module of SYBYL.X and the best scored model contains three features; Donor atom, Acceptor atom, and Hydrophobic. The predictive power of pharmacophore model was then validated using GH score and ROC curve method. Virtual screening of NCI database against validated pharmacophore retrieved 15,503 hits after applying Lipinski's rule. The novel PARP1 inhibitor scaffold was designed by combined results of contour maps, pharmacophore and virtual hit structures. Total 50 novel structures of substituted benzo-oxazinone derivatives were designed and refined by docking into the crystal structure of PARP1 (PDB-5DS3) and PARP2 (PDB-5DSY). The ones which showed higher GOLDScore in PARP1 over PARP2 were selected for *in-silico* ADMET prediction using OSIRIS property explorer. Finally, by looking into the overall leadlikeness and synthetic feasibility, the virtual hits were selected for synthesis.

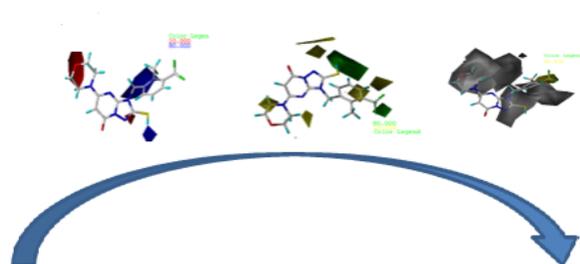
## **MEDI 182**

### **Ligand-based drug design and synthesis of novel phosphoinositide 3-kinase (PI<sub>3</sub>K) beta inhibitors for the treatment of lung cancer**

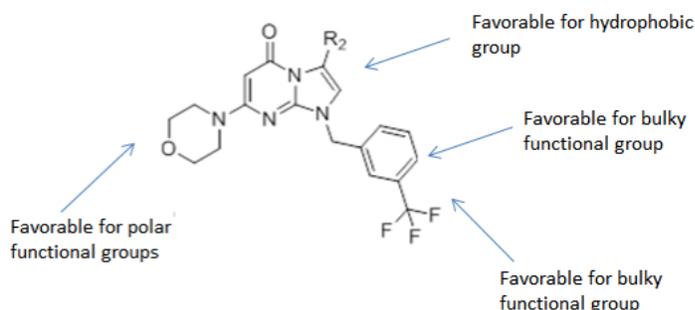
**Shreya r. Mehta**<sup>1</sup>, shreyamehta36@gmail.com, Manjunath Ghate<sup>2</sup>, Palak Parikh<sup>1</sup>. (1) pharmaceutical chemistry, Nirma university of pharmacy, Ahmedabad, India (2) pharmaceutical chemistry, Nirma university of pharmacy, Ahmedabad, International, India

As per WHO, lung cancer is the leading causes of death among all other types of cancer. Drug resistant and selectivity is the major problem in the treatment of lung cancer. PI3K is the mammalian target of rapamycin which involves PI3K/AKT/mTOR pathway. To design such new inhibitors many *in-silico* studies have been performed. In this present research, 3D-QSAR studies by taking 43 synthetic PI3K beta inhibitors which were selected from the series of imidazo [1,2-a]pyrimidin-5(1H)-ones with improved isoform selectivity and excellent inhibition of downstream phosphorylation of AKT has been identified. Ligand based approach CoMFA and CoMSIA were applied for the identification of salient features of pyrimidine containing moiety for PI3k inhibition. Three different alignments were used to obtain best QSAR model, from which Distill alignment was found to be best model. In CoMFA, Leave one out cross validated co-efficient, Conventional co-efficient and predicted co-relation co-efficient values found to be 0.603, 0.986, and 0.61 respectively. Likewise in CoMSIA,  $q^2$ ,  $r^2$  ncv, and  $r^2$  pred were proved to be 0.562, 0.895, and 0.687 respectively. A ligand based pharmacophore

model was developed using GALAHAD module of Sybyl-X. The best model generated 3 types of pharmacophoric features namely hydrogen bond donor, hydrogen bond acceptor, and one hydrophobic. The predictive power of Pharmacophore model was then validated using GH score and ROC curve method. Finally the model was screened against NCI library and total 8,505 hits were obtained after applying Lipinski's rule of 5. Important features of imidazo-pyrimidine were identified by different counter-maps which are then synthesized as potent molecules for the treatment of cancer.



### Identification of important features required for PI3K inhibition



## MEDI 183

### Targeting membrane-bound dimer of cRaf kinase in search of anti-cancer drugs

**Priyanka Srivastava**<sup>1</sup>, [priyanka.p.srivastava@uth.tmc.edu](mailto:priyanka.p.srivastava@uth.tmc.edu), **John Hancock**<sup>1</sup>, **Alemayehu Gorge Abebe**<sup>2</sup>. (1) Integrative Biology and Pharmacology, UTHealth, Houston, Texas, United States (2) Integrative Biology and Pharmacology, The University of Texas Medical School - Houston, Houston, Texas, United States

Raf kinases are downstream effectors of Ras proteins and are key players of the MAPK signaling pathway involved in a variety of cell signaling processes. Auto-inhibited cytosolic Raf is recruited to the plasma membrane by Ras for its normal function. Paradoxical activation is a serious problem in cancer patients where Raf-specific drug activates the MAPK signaling abnormally in a more aggressive manner. Majority of Raf-specific drugs target the ATP-binding pocket. Studies have demonstrated enhanced Raf dimerization by Raf-specific drugs and a predominant signaling via cRaf isoform of Raf

(of three Raf kinases, a-, b- and cRaf) as primary causes that underlies the observed paradoxical activation. Disrupting Raf dimers will serve as a promising alternative strategy to abrogate abnormal MAPK signaling. My recent study based upon a sequence and structure-based bioinformatics analysis combined with microsecond-level all-atom molecular dynamics (MD) simulations revealed three distinct regions of the catalytic kinase domain of monomeric cRaf in direct contact with the membrane. cRaf dimer, on the other hand, although interacted with the membrane directly but transiently and peripherally as compared to the monomer. This was followed by performing probe-based MD simulation on the membrane-bound cRaf monomer and dimer (pMD-membrane). pMD is a methodology to identify small-molecule ligand-binding pockets in membrane-bound or water-soluble proteins. pMD was also performed on the monomer and dimers of cRaf in solution (pMD-solution). Binding free energy maps obtained from the pMD-membrane- and pMD-solution-derived conformational ensembles will be discussed with a focus on the cRaf dimer interface and may possibly yield potential ligand-binding pockets. To my knowledge, this is the first study that will utilize a membrane-dynamics guided conformational ensemble to probe for the potential ligand-binding pockets in Raf kinases.

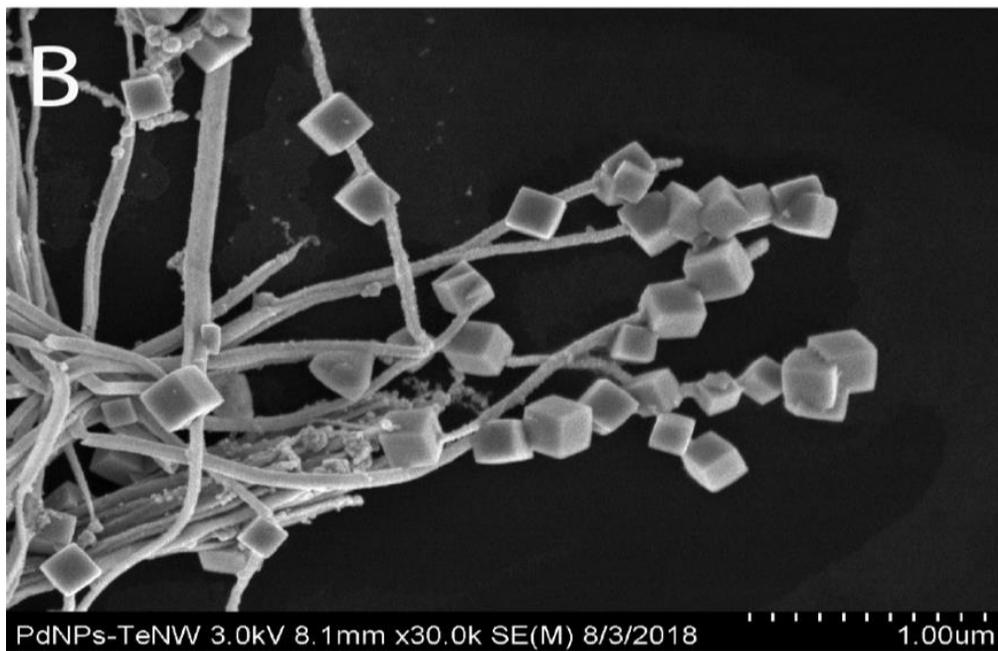
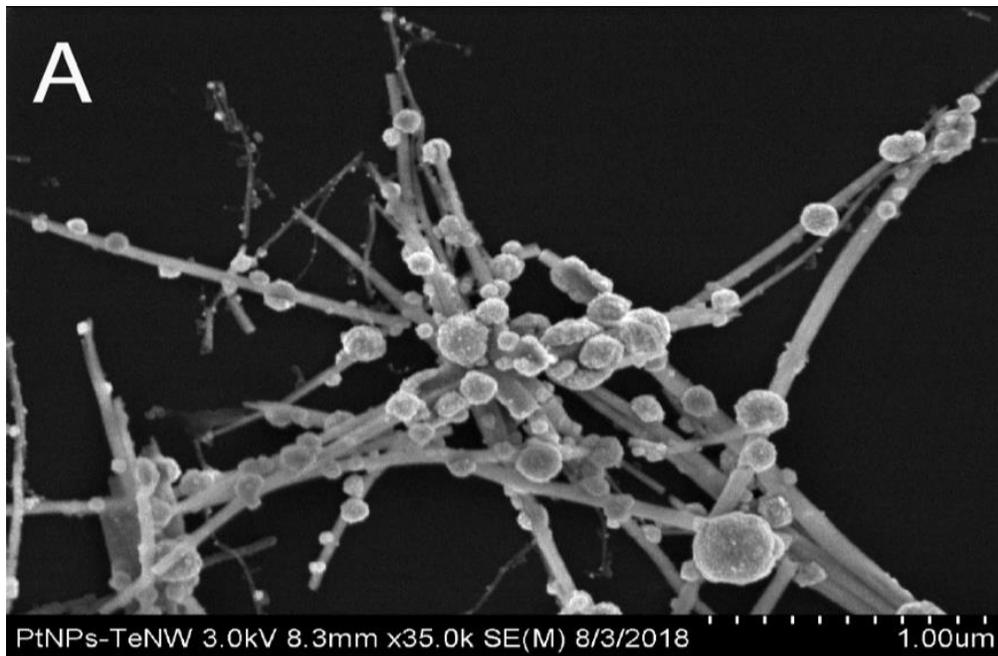
## **MEDI 184**

### **Green synthesis of a synergetic structure of tellurium nanowires and metallic nanoparticles for biomedical applications**

**Ada Vernet Crua**, *vernetcrua.a@husky.neu.edu*, **David Medina Cruz**, **Thomas Webster**, **BOHAN ZHANG**. *Chemical Engineering, Northeastern University, Boston, Massachusetts, United States*

Health care system is facing significant concerns nowadays such as antimicrobial resistance and cancer. New approaches should be considered, and nanotechnology has been found as a powerful solution to them. Current synthetic methodologies for production of nanoparticles, based on physicochemical standards are known to be easy-to-get and straightforward. Nevertheless, there is a cost associated with the limitations that should be overcome from these approaches, such as the production of toxic by-products or the lack of biocompatibility of the products. Therefore, new methods are needed, and green chemistry offers itself as a suitable and novel answer, achieving a safe and environmentally-friendly design. In this research, tellurium nanowires were synthesized using a green synthesis methodology (TeNWs). Once purified, TeNWs were used as a template for the growth of metallic nanoparticles (such as platinum -Pt- and palladium -Pd- ) in a quick method with no need of additional reducing agent at room temperature. The structure containing both metallic nanoparticles and nanowires was known as synergy and showed interesting behaviour. Besides, biocompatibility and anticancer tests of both structures – the synergy and the nanowires - with human tissue were accomplished, growing human dermal fibroblast (HDF) cells and melanoma cells in media in the presence of both nanosystems. Furthermore, antibacterial properties were tested against *Escherichia Coli* and *Staphylococcus Aureus*. The experiments were

done with the aim to elucidate an improved behavior in the use of synergetic structures thus, to use them in promising biomedical applications.



SEM characterization of two synergetic nanostructures PtNP-TeNWs (A) and PdNP-TeNWs (B).

## **Intracellular paired agent imaging enables personalized medicine for cancer patients**

**Lei Wang**<sup>1</sup>, [wanglei@ohsu.edu](mailto:wanglei@ohsu.edu), **Emily Schultz**<sup>1</sup>, **Allison Solanki**<sup>1</sup>, **Kenneth Tichauer**<sup>2</sup>, **Kimberley S. Samkoe**<sup>3</sup>, **Summer L. Gibbs**<sup>1</sup>. (1) Biomedical Engineering, Oregon Health & Science University, Portland, Oregon, United States (2) Illinois Institute of Technology, Chicago, Illinois, United States (3) Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, United States

Patients with advanced cancers die because their cancers develop resistance to all available therapeutic strategies. “Personalized cancer medicine” strives to use biomarker-matched molecularly targeted therapies to overcome known resistance mechanisms. However, monotherapies with targeted agents directed to known genetic mutations have rarely resulted in long-term cures. Protein-based resistance mechanisms, such as adaptive resistance, involve reprogramming of cell signaling pathways in response to molecular targeted therapies, and as such limit the duration of therapeutic efficacy. Non-genetic resistance mechanisms are not well understood on an individual patient level because they involve complex and dynamic interactions within the signaling pathway phosphoproteome. A large body of work has been carried out to characterize phosphoproteome changes of individual tumors in response to therapy; however, current methods suffer from lack of sensitivity and specificity to accurately predict outcomes. To overcome this difficulty, our group has developed a novel imaging platform to quantify phosphorylation status termed ***intracellular paired agent imaging (iPAI)***. iPAI is a fluorescence-based approach that utilizes fluorophore-labeled small molecule therapeutics as imaging agents to measure phosphorylated proteins. Herein, we have developed fluorescently labeled, spectrally distinct, paired targeted and untargeted derivatives of the kinase inhibitor Erlotinib. The similarities of the iPAI targeted and untargeted agents to the parent drug were characterized using competitive binding and cytotoxicity assays in cancer cell lines with varied epidermal growth factor receptor (EGFR) expression. Validation for the quantification of the protein phosphorylation using iPAI has been completed by comparing to phospho-specific antibody staining in a panel of EGFR overexpressing cancer cell lines. Additionally, we have demonstrated our ability to quantify the phosphorylation status of EGFR in treated and untreated cells using our iPAI technology. Synthesis of additional iPAI agents for other proteins in the EGFR signaling cascade are ongoing enabling quantification of the phosphorylation status of the treated protein as well as downstream proteins in future studies. We anticipate that iPAI will enable future prediction of personalized cancer therapy for patients based on their treated and downstream protein phosphorylation response.

**MEDI 186**

**Catalytic allylic oxidation of cyclic enamides and 3,4\_dihydro\_2H\_pyran by TBHP**

**Ranad Humeidi**<sup>1,2</sup>, *ranadhumeidi1995@gmail.com*, Yang Yu<sup>2</sup>, Michael Doyle<sup>2</sup>. (1) Broad Institute of MIT and Harvard, Cambridge, Massachusetts, United States (2) University of Texas at San Antonio, San Antonio, Texas, United States

Allylic oxidation of heteroatom substituted cyclic alkenes by tert-butyl hydroperoxide (70% TBHP in water) using catalytic dirhodium caprolactamate [Rh<sub>2</sub>(cap)<sub>4</sub>] forms enone products with a variety of 2-substituted cyclic enamides and 3,4-dihydro-2H-pyrans. These reactions occur under mild reaction conditions, are operationally convenient to execute, and are effective for product formation with as low as 0.25 mol% catalyst loading. With heteroatom stabilization of the intermediate allylic free radical two sites for oxidative product formation are possible, and the selectivity of the oxidative process varies with the heteroatom when R = H. Cyclic enamides produce 4-piperidones in good yields when R = alkyl or aryl, but oxidation of 2H-pyrans also gives alkyl cleavage products. Alternative catalysts for TBHP oxidations show comparable selectivities but give lower product yields.

## **MEDI 187**

### **Exploring novel E3 ligase binders for targeted protein degradation**

**Yoshihide Tomata**, *yoshihide.tomata@fimecs.com*, Kanae Gamo, Naomi Kitamoto, Yusuke Tominari. FIMECS, Inc., Fujisawa, Kanagawa, Japan

Strategy of targeted protein degradation is a fundamentally different mechanism from existing molecular-targeted therapy and makes it possible to drug the current undruggable and high value targets. Since it is not possible to degrade all targets by a particular E3 ligase binder, selection of the appropriate E3 binder is one of the most important factors in realizing the degradation of the selected drug target. We have already generated novel XIAP binders with unique pharmacophore and developed diversity-oriented synthetic platform, "RaPPIDS™". Furthermore, we have continued to seek other novel E3 binders. In this presentation we introduce degrader compounds conjugated with our E3 ligase binders. In addition, we also report the results of in vitro degradation activity and in vivo efficacy regarding our IRAK-M program.

## **MEDI 188**

### **BD2-selective BET inhibition induces cell death in pediatric tumor cell lines**

**Peter J. Slavish**<sup>1</sup>, *jslavish67@gmail.com*, Nancy Martinez<sup>1</sup>, Anang Shela<sup>2</sup>. (1) Chemical Biology & Therapeutics, St Jude Children's Research Hospital, Memphis, Tennessee, United States (2) Chemical Biology Therapeutics, MS1000, Saint Jude Children's Research Hospital, Memphis, Tennessee, United States

Aberrant BET (bromodomain and extra-terminal) protein expression has been linked to the upregulation of oncoproteins, such as Myc, which drive tumorigenesis. Since the discovery that inhibiting BET proteins can reduce oncoprotein expression in vitro and in

vivo, many pan-BET inhibitors have been generated and are being developed for clinical use. However, there are safety concerns associated with pan-BET inhibitors; hence the development of BET bromodomain selective probes that can discriminate between the first domain (BD1) and second domain (BD2) is important in chemical biology and drug discovery. Herein, we report the synthesis and biological characterization of such a molecule, SJ849018. This compound demonstrates enthalpy-driven binding and slow dissociation from BD2, but binds to BD1 with significantly reduced affinity. We demonstrate that SJ849018 inhibits Myc-RNA and protein expression similar to the pan-BET inhibitor, (+)-JQ1, and microarray analyses confirm that SJ849018 alters global gene expression at lower concentrations than observed with the latter. Furthermore, SJ849018 is cytotoxic to a panel of pediatric cancer cell lines, demonstrating better, or comparable, activity to (+)-JQ1. Our results strongly suggest that inhibition of a single BET bromodomain (BD2) can result in the same cellular effects observed with pan-BET inhibitors and that such agents may have reduced toxicity. Further structural refinement of SJ849018 lead to another interesting intra-BET selective probes--SJ870471. Co-crystallization results with SJ870471 and both binding domains provides rationale for the observed BD2-selectivity. Though broadly less active than JQ1 in a panel of pediatric tumor cell types, SJ870471 does show exceptional activity in a subset of our panel. Investigations to explain the observed BD2-sensitivity of these tumors is ongoing.

## **MEDI 189**

### **Development of polymer-based nanoparticulate intranasal lipopeptide vaccine constructs against group A streptococcus**

*Reshma Jayprakash Nevagi, rjnevagi@gmail.com, Wei Dai, Zeinab Khalil, Waleed Hussein, Robert Capon, Mariusz Skwarczynski, Istvan Toth. University of Queensland, Brisbane, Queensland, Australia*

Group A streptococcus (GAS) is a gram-positive bacterium that is responsible for broad range of human diseases such as pharyngitis, impetigo, pneumonia, bacteremia, toxic shock syndrome, acute rheumatic fever (ARF) and rheumatic heart disease (RHD). Vaccines, rather than antibiotics, are expected to be efficacious for the prevention of GAS related infections. So far, there is no commercial vaccine available against GAS. Traditional vaccines composed of live/attenuated or killed microorganism have been effective against diseases such as influenza, smallpox and chicken pox. However, whole organism-based vaccine is not feasible for GAS due to existence of more than 200 serotypes. Cell surface M-protein is the major virulent factor of GAS. But, M-protein based vaccine is predicted to induce autoimmune response due to structural similarity with human cardiac myosin. Thus, synthetic peptide vaccines based on epitopes derived from conserved region of M-protein are expected to be efficient to provide protection against GAS. However, peptide epitopes alone are poorly immunogenic due to lack of pathogen associated structural patterns. Hence, adjuvants are often included in peptide vaccine to trigger immune response against peptide antigen. Lipids and polymers are known to possess adjuvanting property. Therefore, we developed a GAS

peptide vaccine based on lipid and polymers combination strategy. We synthesised lipopeptides that included lipid moiety, GAS B-cell peptide epitope J8 (QAEDKVKQSREAKKQVEKALKQLEDKVQ) and universal T-helper epitope PADRE (AKFVAAWTLKAAA), which were further formulated into polymeric nanoparticles. For that purpose, lipopeptides were conjugated to anionic polymer via copper(I)-catalyzed azide alkyne cycloaddition (CuAAC) “click” reaction. These anionic lipopeptide conjugates formed nanoparticles (200 nm, + 40 mV) via ionic-complexation with a cationic polymer, trimethyl chitosan. The lipopeptides formulated into nanoparticles were able to induce high systemic and mucosal IgG antibody titers upon intranasal immunisation in mice. The produced serum antibodies were opsonic against five strains of GAS.

## **MEDI 190**

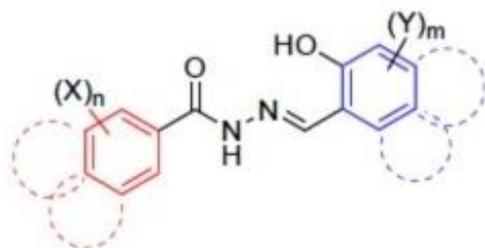
### **SAR of novel anti-fungal agents targeting the synthesis of fungal GlcCer**

**Krupanandan Haranahalli**<sup>1</sup>, [krupaharanahalli@gmail.com](mailto:krupaharanahalli@gmail.com), **Cristina Lazzarin**<sup>2</sup>, **Yi Sun**<sup>3</sup>, **Maurizio Del Poeta**<sup>2</sup>, **Iwao Ojima**<sup>4</sup>. (1) Institute of Chemical Biology and Drug Discovery, Stony Brook University, Stony Brook, New York, United States (2) Molecular Genetics and Microbiology, Stony Brook University, Stony Brook, New York, United States (3) Chemistry Department, Stony Brook University, Mount Sinai, New York, United States (4) Chem Dept/ICBDD, Stony Brook University, Stony Brook, New York, United States

According to recent statistics, nearly 300 million people are affected by serious fungal infections globally. current anti-fungal agents possessing serious drawbacks such as drug-drug interactions, toxicity and narrow spectrum of activity and with an increase in the emergence of resistant strains of fungi to these drugs, there is a desperate need for the development of new antifungal agents with novel mechanisms of action. Previously our labs reported the identification of acylhydrazone analogs BHBM and D13 that displayed potent antifungal activities by inhibiting the synthesis of sphingolipid GlcCer in *C. neoformans*. Based on the structures of BHBM and D13, extensive SAR studies were carried out by synthesizing a library of ~300 N-(aromatic acyl)-2-hydroxyarylhyazones which led to the identification of several lead compounds that displayed excellent MIC<sub>80</sub>, *in vitro* killing activity and high selectivity indices. One of the lead compounds P3G8 that displayed excellent MIC<sub>80</sub> of 0.06 µg/mL (48 h incubation), was found to be fungicidal at the same concentration and completely eradicated *C. neoformans* cells in 72 hours. It was further tested *in vivo* in a mouse model of cryptococcosis, and resulted in 100% survival of infected mice. Herein, we present the SAR study and biological evaluation of the lead compounds.



**BHBM** -  $R_1 = \text{CH}_3$ ,  $R_2 = R_3 = \text{H}$ ;  $R_1' = R_2' = \text{H}$ ,  $R_3' = \text{Br}$   
**D13** -  $R_1 = R_2 = \text{H}$ ,  $R_3 = \text{Br}$ ;  $R_1' = R_3' = \text{Br}$ ,  $R_2' = \text{H}$



## MEDI 191

### Encapsulation and controlled release of antimetabolite drug 6-thioguanine from aluminum metal-organic framework

Cole Grinnell<sup>1</sup>, Rena Lapidus<sup>2</sup>, **Alexander Samokhvalov**<sup>1</sup>,  
 Alexandr.Samokhvalov@morgan.edu. (1) Chemistry Department, Morgan State University, Baltimore, Maryland, United States (2) School of Medicine, University of Maryland, Baltimore, Maryland, United States

6-Thioguanine (6-TG) is an FDA-approved antimetabolite leukemia drug, which however has short plasma half-life (~20 min.) and low bioavailability (~30%). For the prolonged delivery, 6-TG should be encapsulated on the suitable non-toxic insoluble carrier. Metal-Organic Frameworks, MOFs are promising for encapsulation of small-molecule drugs by sorption and controlled delivery. We report recent studies of encapsulation of 6-TG by sorption on non-toxic, stable, water-insoluble aluminum MOF (Al-MOF) Basolite A100. Sorption of 6-TG on Basolite A100 from the FDA-approved solvent dimethyl sulfoxide (DMSO) results in the ternary sorption complex A100/DMSO/6-TG or the stoichiometric binary complex A100/DMSO. We describe the spectroscopic, thermal, and structural characterization of sorption complexes, kinetics of *in-vitro* delivery of 6-TG, and cytotoxicity. To study chemical bonding of drug molecules in the complexes, we utilized solid-state front face (FF) 3-dimensional fluorescence emission spectroscopy at 25 °C. The spectra of Basolite A100 show the distinct emission bands in the near-UV and visible range due to monomers of benzenedicarboxylate (BDC) linker and ligand-to-ligand charge transfer (LLCT). After encapsulation of 6-TG and DMSO, the fluorescence spectra undergo selective quenching due to specific binding of co-adsorbates 6-TG and DMSO. From the data by

differential scanning calorimetry (DSC), DMSO is strongly bound to linkers in Basolite A100, but is promptly released (<30 min.) from the complex to simulated bodily fluid (SBF) at 37 °C and pH 7.4. The release of 6-TG from the ternary complex proceeds on a >24 h. time scale. While pure 6-TG undergoes hydrolysis, the 6-TG in the ternary complex features the favorable kinetic profile of pre-programmed delivery with an increase of concentration. The cytotoxicity tests with acute myeloid leukemia (AML) MV4-11 cells indicate the substantial toxicity of the ternary complex. The water-stable and non-toxic Al-MOF Basolite A100 is promising for encapsulation and time-programmed delivery of small-molecule drugs.

## **MEDI 192**

### **Modification of hydroxynaphthoquinone scaffold in search of antimicrobial and antineoplastic agents**

*Emerson Smith, Thomas Maloney, Michael Humphrey, Caleb Ray, **Irosha N. Nawarathne**, irosha.nawarathne@lyon.edu. Chemistry, Lyon College, Batesville, Arkansas, United States*

Naturally occurring and synthetically derived hydroxynaphthoquinones (juglone, lawsone, phthiocol, plumbagin, laphachol) have a wide range of pharmacological uses such as anti-bacterial, anti-fungal, anti-viral, anti-parasitic, anti-inflammatory, anti-proliferative, anti-cancer, and anti-tubercular. The naphthoquinone scaffold is present in the core structure of important therapeutics and biologically active natural products already. Taking advantage of Michael addition reactions, substituents were incorporated to the hydroxynaphthoquinone scaffold to create multitudes of 1,4-naphthoquinones. The analogues were tested for their antimicrobial and anticancer properties. In this presentation, development of these novel hydroxynaphthoquinones utilizing an interesting chemical approach will be discussed along with their biological activities.

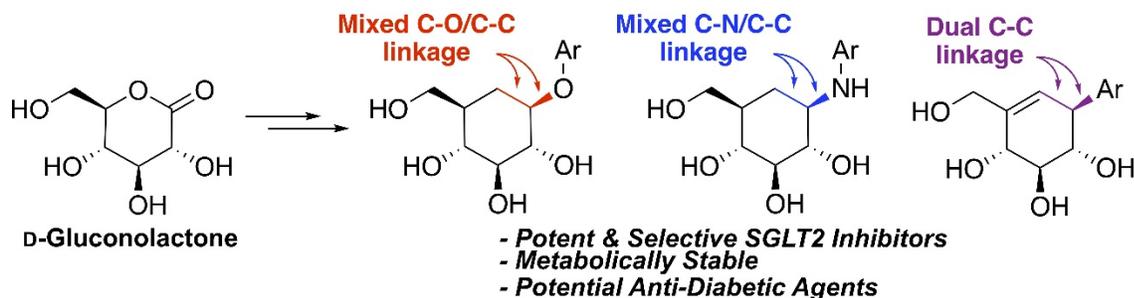
## **MEDI 193**

### **Design, syntheses, and SAR studies of carbasugar SGLT2 inhibitors**

***Wai-Lung Ng**<sup>2,1,3</sup>, chemwlng@hotmail.com, Ho Chuen Li<sup>2</sup>, Virginia K.-M. Lau<sup>4</sup>, Anthony K. Chan<sup>6</sup>, Judy Chan<sup>4</sup>, Clara B.-S. lau<sup>4</sup>, Tony K. Shing<sup>5,2</sup>. (1) Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, Massachusetts, United States (2) Department of Chemistry, The Chinese University of Hong Kong, Hong Kong, Hong Kong (3) Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States (4) Institute of Chinese Medicine, Hong Kong, Hong Kong (5) Department of Chemistry, Keio University, Yokohama, Japan (6) Department of Chemistry, University of Oxford, Oxford, United Kingdom*

The current therapeutic agents are not effective enough to treat patients with Type 2 diabetes mellitus (T2DM) satisfactorily. Also, there are many side effects associated with them. Thus, we set out to investigate novel small-molecule carbohydrate mimics as

potential antidiabetic agents to supplement the existing medication. Selective inhibition of the transporter protein sodium-glucose cotransporter 2 (SGLT2) has emerged as a promising way to control blood glucose level in T2DM patients. We have pioneered the design and synthesis of some novel carbasugars (pseudosugars), in which the endocyclic oxygen atom was replaced with a methylene unit to render the molecule free from glycosidase degradation. Our synthetic targets are the carbocyclic analogues of sergliflozin and dapagliflozin, which are readily accessible via various transition metal-catalyzed cross-coupling reactions. We herein describe our novel synthetic approaches towards carbasugar SGLT2 inhibitors and discuss their SAR.



## MEDI 194

### Synthesis and characterization of NIR dye-doped nanoparticles for *in vivo* medical imaging

**Christine Schneider**<sup>1</sup>, [christine.b.schneider@uni-wuerzburg.de](mailto:christine.b.schneider@uni-wuerzburg.de), **Sofia Dembski**<sup>2,1</sup>, **Franziska Miller**<sup>3</sup>, **Timon Riess**<sup>4</sup>, **Jithin Jose**<sup>4</sup>. (1) Department Tissue Engineering and Regenerative Medicine (TERM), University Hospital Wuerzburg, Wuerzburg, Germany (2) Translational Center Regenerative Therapies TLZ-RT, Fraunhofer Institute for Silicate Research ISC, Wuerzburg, Germany (3) BMBF NanoMatFutur Group NANO-ID, Department Chemical Technology of Materials Synthesis, Julius-Maximilians-University Wuerzburg, Wuerzburg, Germany (4) FUJIFILM VisualSonics Inc., Toronto, Ontario, Canada

Nanoparticles (NPs) are promising tools for a wide spectrum of biological and medical applications. They can be used as carrier and delivery systems for active agents such as biomolecules, dyes and a wide range of sensitive substances and also contribute to the stabilization of these compounds *in vivo*. Real time non-destructive imaging screening *in vivo* can be performed by means of fluorescent based methods. Near infrared (NIR) dyes are perfectly suited for this purpose. They are very promising for tissue labeling because of the fact that in the IR range there is significantly lower background fluorescence than in the visible range. Another feature of tissue is the so called transparent "NIR-window" at wavelengths from 650 nm to 1350 nm. One major disadvantage of most organic NIR dyes is their very fast degradation *in vivo*, so long-term investigations are not feasible. To stabilize these dyes, one option is to encapsulate the dye molecules into a NP matrix.

Here, we present our recent research activities in the field of medical diagnostics concerning the encapsulation of NIR dyes, e.g. Indocyanine Green (ICG) and IRDye® 800CW, into NPs for in vivo imaging. Our work is focused on the synthesis and characterization of NP carrier systems on the basis of e.g. amorphous silica and liposomes and has successfully been demonstrated. These NPs are synthesized via wet-chemical synthesis and doped with different NIR dyes. The choice of silica and liposomes as a basis of the NPs is motivated by their high biocompatibility, biodegradability and the possibility of surface modifications.

The characterization of the NPs is done by conventional methods such as transmission electron microscopy (TEM), dynamic light scattering (DLS), fluorescence and absorption spectroscopy. The focus here was on the investigation of stability of the encapsulated NIR dyes under different storage and physiological conditions. In addition to a greater stability, the photoacoustic effect of NIR dye doped NPs has been demonstrated.

In summary, the synthesis of different NP systems on the basis of amorphous silica and liposomes and the encapsulation of different NIR dyes was successfully demonstrated. With the confirmation of the stability of the encapsulated dyes in the NP matrix and their photoacoustic activity they have shown their potential in the field of medical imaging.

## **MEDI 195**

### **Dynamic DNA-encoded library technology: Discovery of kinesin-1 activators and inhibitors**

*Michael Thompson<sup>1</sup>, michael.thompson@dynabind.com, Francesco Reddavid<sup>1</sup>, Stephan Heiden<sup>1</sup>, Meiyang Cu<sup>2</sup>, Yixin Zhang<sup>2</sup>. (1) DyNABind GmbH, Dresden, Germany (2) TU Dresden, Dresden, Germany*

DNA-Encoded Library (DEL) technology is an increasingly prominent drug discovery approach based on simultaneous screening of potentially huge numbers of compounds against a protein target of interest in a general binding assay. Each compound is tagged with a unique DNA strand which functions as an identifying barcode. Compared to more traditional high-throughput screening approaches, DEL operates at significantly reduced costs, creating new opportunities for drug discovery groups of any organizational size. We have developed the first application of a dynamic DEL system, wherein two DNA strands featuring universally complementary annealing regions can be randomly combined to present two binding moieties to the target, with the DNA interactions designed to be intrinsically unstable, driving constant reshuffling of the molecular pairs until they are stabilized by sufficiently strong binding to the protein target. This system was designed to overcome limitations in library construction and data quality, allowing the preparation of equimolar libraries without side products or truncates.

Benchmarking this platform against a conventional system showed over 30 times improved signal-to-noise ratios with reduced false positive rates. Using this platform, we have created multiple libraries based on both fragment and small molecule moieties, offering over 120 million highly diverse and medicinally relevant compounds for discovery which we have deployed against a broad range of targets, including

proteases, cytokines, multiple enzyme families and GPCRs.

Here we present results of hit discovery and validation using our platform against the human motor protein kinesin-1. Targeting of kinesin family proteins is of interest due to implications in both cancer and neurodegenerative disease. Application of our platform revealed hits which were investigated in a functional assay to reveal multiple structurally separated inhibitors, as well as an activator. Of particular interest is the activator, which is the first known direct activator of kinesin-1.

## **MEDI 196**

### **Design and synthesis of quinazolinone derivatives lacking toxicity producing attributes as glucokinase activators**

**Saurabh C. Khadse**, *khadse\_s@rediffmail.com*. *Pharmaceutical Chemistry, R C Patel Institute of Pharmaceutical Education & Research, Near Balaji Girls Hostel, MAHARASHTRA, India*

Discovery of small molecule glucokinase (GK) activator (GKA), RO-28-1675, an phenylacetamide derivative led to discovery of several amides and other small molecules which promised to lower the blood sugar level through activation of GK enzyme. But these compounds failed to pass beyond the trials due to the toxicities associated with them. These toxicities were attributed to some structural residues like thiazole ring, primary aromatic amino group present in these molecules. Therefore, it was thought to divert from the present set of GKA scaffold and construct newer lead to activate glucokinase enzyme. In this endeavour, quinazolinone compounds were designed based on direct drug design study and were synthesized in satisfactory yields. The docking studies, carried in Glide module, with ligands and standard RO-281675 provided results that indicated expected interactions of the ligands in the allosteric site of GK. Oral administration of a single dose of synthesized quinazolinones caused a significant reduction in blood glucose in the wistar rat after oral glucose challenge. However, EC<sub>50</sub> values obtained by conducting human GK activation assay suggest less-ability of quinazolinone compounds to stimulate GK for the conversion of glucose to glucose-6-phosphate.

## **MEDI 197**

### **Novel, odorranalectin-based, opioid-like peptides: Synthesis, intranasal delivery to brain, and activity against opioid receptors**

**Ramanjaneyulu Rayala**<sup>1</sup>, *rrayala@fau.edu*, *Brandon Williams*<sup>1</sup>, *Shahayra Majumder*<sup>2</sup>, *Jay P. McLaughlin*<sup>2</sup>, *Predrag Cudic*<sup>1</sup>. (1) *Chemistry, Florida Atlantic University, Jupiter, Florida, United States* (2) *Pharmacodynamics, University of Florida, Gainesville, Florida, United States*

Pain is a very common problem affecting almost every person in our society, especially the ones with moderate-to-severe chronic pain requiring opioid therapy, as opioids are

associated with the risk of addiction and overdose. It is challenging to treat central nervous system diseases due to the inability of many therapeutic agents, especially peptides and proteins, to cross blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCB). Thus, an ideal alternative would be nose-to-brain delivery *via* integrated nerve pathways bypassing the BBB and BCB. We designed a novel intranasal delivery strategy of therapeutic peptides to the brain, based on grafting a bioactive amino acid sequence into cyclic peptide odorranalectin (OL, YASPK-*cyclo*[CFRYPNGVLAC]T). OL binds to L-fucose, which is distributed on the olfactory epithelium of nasal mucosa, thereby extending its residence time in the nasal cavity, thus allowing its increased adsorption.

Validating our approach, we successfully synthesized novel opioid-like peptides, DADLE-OL and TIPP-OL, by grafting the sequence of a known mixed  $\mu$  and  $\delta$  agonist DADLE (H-Tyr-D-Ala-Gly-Phe-D-Leu-OH) and  $\delta$  antagonist TIPP (H-Tyr-Tic-Phe-Phe-OH), respectively, into the OL scaffold. Our pilot studies demonstrated that both the peptides can be delivered intranasally to the mouse brain and that these peptides can produce time and dose-dependent effects in the analgesic tail withdrawal test. No impairment in motor coordination in mice was observed in the rotarod test after DADLE-OL treatment, suggesting a possibility for a fewer or absence of the adverse effects commonly associated with opioids such as morphine. To identify additional novel opioid ligands, we prepared a positional scanning combinatorial library of 2,476,099 peptides and screened it for affinity toward  $\mu$ ,  $\delta$  and  $\kappa$  opioid receptors. Results from the screening led to the identification of three series of OL analogues with selectivity for the  $\mu$ ,  $\delta$  and  $\kappa$  opioid receptors. The identified peptides exhibited improved analgesic activity in mice compared to the initial DADLE-OL peptide.

## **MEDI 198**

### **Binary metal-containing nanoparticles for CT imaging and radiosensitization of peritoneal metastatic tumors**

***Raana Kashfi Sadabad***<sup>1</sup>, *raana.kashfi@uconn.edu*, ***Laura Gonzalez-Fajardo***<sup>1</sup>, ***Michael Jay***<sup>2</sup>, ***Xiuling Lu***<sup>1</sup>. (1) *Department of Pharmaceutical Sciences, University of Connecticut, Storrs, Connecticut, United States* (2) *University of North Carolina, Chapel Hill, North Carolina, United States*

One of the limitations of external radiation therapy for metastatic ovarian cancer is delivery of high radiation doses to non-target tissue that can cause significant damage to healthy organs. Image-guided radiotherapy and use of radiosensitizers are effective for localizing, focusing, and delivering external radiation to tumor areas with less damage to the healthy tissues. The current study demonstrates a novel method for synthesizing a family of multifunctional agents composed of two radio-dense elements, gold and tantalum, integrated into a single nanocomposite that can be used for both imaging and radiosensitizing. Dendritic mesoporous silica nanoparticles (dMSNs) with the high surface area were used to integrate these two high atomic number metals in a single nanoplatform. The synthetic approach resulted in stable and monodispersed dMSNs with a uniform distribution of gold nanoparticles on the surface and tantalum

oxide in the core. The rationally designed bimetallic nanosystem exhibits strong x-ray attenuation with high-performance X-ray computed tomography (CT) imaging. The CT numbers, measured in Hounsfield units, for the bimetallic nanosystem, is 2.7 times greater than clinically used iodine-based contrast agents at the same concentration making them promising for a combined CT imaging and radiosensitizing application. Preparation, biodistribution, safety, stability and tumor specificity of the designed nanoparticles are reported to establish their feasibility for improving radiation therapy. Cytotoxicity and histological studies confirmed that the designed bimetallic nanoparticles have good biocompatibility with no toxicity observed. Tumor targeting and accumulation of the bimetallic nanopatform after intraperitoneal administration was demonstrated in a metastatic ovarian cancer mouse model. Micro-CT in conjunction with bioluminescence images showed that the nanoparticles accumulate at the tumor sites. Our work demonstrated that incorporating two radio-dense elements in a single system administrated intraperitoneally provides a new strategy to enhance radiation therapy in metastatic ovarian cancer.

## **MEDI 199**

### **Rapid screening of synergistic combinations of group IB metals and antibiotics for *E. coli* inactivation**

**Otakuye Conroy-Ben<sup>1</sup>**, *otakuye.conroy@asu.edu*, **Diego E. Novoa<sup>2</sup>**, **Shundene Key<sup>1</sup>**, **Michelle Tran<sup>1</sup>**. (1) *Sustainable Engineering and the Built Environment, Arizona State University, Tempe, Arizona, United States* (2) *Civil, Environmental, and Sustainable Engineering, Arizona State University, Mesa, Arizona, United States*

The World Health Organization has listed antimicrobial resistance as one of the top threats facing health today. The over-prescription of antibiotics, use of biocides in commercial products, and misuse of antimicrobials have led to drug-resistant microbes, and stronger pharmaceuticals are often necessary to fight infections. In this work, the results of an extensive screening of biocide combinations to inactivate pathogens is described. Group IB metal ions (Ag, Cu, Au) were mixed with 210 different antibiotics that act on proteins, nucleic acids, cell wall, cell membrane, folate synthesis, among others. Wild-type *E. coli* was exposed to the metal alone, the biocide alone, and the metal mixed with biocide. Relative growth at 16 hours was compared for all three to determine if lethality of the metal-biocide combination was greater than the individual metal or antibiotic. Synergism was observed using the coefficient of drug interaction (CDI) and checkerboard assays. Among the 210 antibiotics tested, trends were observed for various classes mixed with Ag<sup>+</sup>, Cu<sup>2+</sup>, and Au<sup>3+</sup> that are in agreement with published studies. New biocide/metal interactions were also observed that will require additional testing to evaluate mode of action and optimum concentrations. The work demonstrates that this approach for rapid drug screening can be used to study biocide mixtures, and should be used to combat pathogenic survival.

## **MEDI 200**

## **Design and synthesis of metabolically stable endocannabinoid analogs by reversing ester and amide group**

**Lipin Ji**<sup>1</sup>, *l.ji@husky.neu.edu*, Spyros Nikas<sup>1</sup>, Yingpeng Liu<sup>1</sup>, Anisha Korde<sup>1</sup>, Alex Ciesielski<sup>2</sup>, alex straker<sup>2</sup>, Othman Benchama<sup>1</sup>, Amey S. Dhopeshwarkar<sup>2</sup>, Chandrashekhar Honrao<sup>1</sup>, Ken Mackie<sup>2</sup>, Laura M. Bohn<sup>4</sup>, Alexandros Makriyannis<sup>3</sup>. (1) Pharmaceutical Science/ Center for Drug Discovery, Northeastern University, Boston, Massachusetts, United States (2) Psychological and Brain Sciences, Indiana University, Bloomington, Indiana, United States (3) Center for Drug Discovery, Northeastern University, Boston, Massachusetts, United States (4) Molecular Medicine and Neuroscience, The Scripps Research Institute, Jupiter, Florida, United States

CB1 and CB2 receptors are two cannabinoid receptors and belong to the big family of Gi/o-protein-coupled receptors. They are being pursued as potential targets for conditions including pain, inflammation, CNS disorders, and cancer. 2-arachidonoyl glycerol (2-AG) and *N*-arachidonylethanolamine (AEA) are the two most-recognized endogenous ligands for cannabinoid receptors. However, due to their chemical and biochemical instabilities, it is relatively difficult to use endocannabinoids directly to probe its biological role and to explore the bioactivities of related receptors and enzymes. In most tissues, 2-AG and AEA can be metabolized by monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH) respectively. Other enzymes like a brain hydrolase (ABHD6) can also inactivate endocannabinoids. Moreover, recent studies have demonstrated that oxidative enzymes including cyclooxygenase-2 (COX-2), cytochrome P450, and lipoxygenases (LOXs) can transform endocannabinoids into eicosanoid-related bioactive products. Here, 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 and AEA with special emphasis on the ester moiety and the methylene linker. Our design focuses on the reverse ester and amide design approach and the incorporation of steric features at the methylene linker of the endogenous prototype.

### **MEDI 201**

## **Synthesis and structure activity relationship studies of cystargolides based beta-lactones as potent proteasome inhibitors and anti-cancer agents**

**Doleshwar Niroula**<sup>1</sup>, *doleshwar.niroula@student.nmt.edu*, Rodolfo Tello-Aburto<sup>2</sup>. (1) Chemistry, New Mexico Institute of Mining and Technology, Socorro, New Mexico, United States (2) Chemistry, New Mexico Tech, Socorro, New Mexico, United States

The use of proteasome inhibitors (PIs) has been clinically validated strategy for the treatment of certain forms of cancer. Despite the clinical availability of three FDA approved drugs for the treatment of cancer, the development of new compounds with enhanced potency and selectivity with fewer side effects is important. The current research is based on the peptidic  $\beta$  lactone proteasome inhibitors cystargolides A and B

which were used to conduct the SAR studies in order to assess their anticancer potential. We designed and synthesized a group of analogs, and evaluated for proteasome inhibition, for cytotoxicity towards several cancer cell lines, and for their ability to enter whole cells. Driven by X ray crystallography, the structural modification includes the pharmacophoric beta lactone, peptidic composition, and ester moiety of our scaffold. One of the cystargolide analog (5k) with unique side chains exhibited the most promising inhibitory activity for the  $\beta 5$  subunit of human proteasomes ( $IC_{50} = 3.1$  nM) and significant cytotoxicity towards several cancer cell lines. We found that the minor structural modifications have significant effects on the ability of our compounds to inhibit intracellular proteasomes as evidenced by cellular infiltration assays. We identified 5k is a more potent proteasome inhibitor than commercial drug carfilzomib with mid to low nanomolar  $IC_{50}$  measurements and it is cytotoxic against multiple cancer cell lines.

## **MEDI 202**

### **Surface functionalization of polyethylenimine coated iron oxide nanoparticles for dual delivery of doxorubicin and ADAM10 siRNA for prostate cancer treatment**

**Raju Panday**<sup>1</sup>, *raju.panday@hotmail.com*, Ahmed M. Abdalla<sup>1</sup>, Guang Yang<sup>2</sup>. (1) Biomedical Engineering, Huazhong University of Science and Technology, Wuhan, Hubei, China (2) Huazhong University Of Science & Technology, Wuhan, China

We present the surface functionalization of branched polyethylenimine (PEI) coated magnetic nanoparticles for the treatment of prostate cancer. In the present study,  $Fe_3O_4$  nanoparticles prepared via co-precipitation method with citrate as dispersant was coated with PEI. Thus formed PEI- $Fe_3O_4$  nanoparticles were further functionalized with polyethylene glycol (PEG) via free radical reaction between amino groups on the PEI surface and carboxyl groups of PEG-COOH. These nanoparticles were characterized by different chemi-morphological techniques. Well dispersed and easily manipulable sizes were obtained suitable for biomedical purpose. In addition to being smaller in size (10-15 nm), these nanoparticles had good biocompatibility in fairly varying concentration range whereas the PEI- $Fe_3O_4$  nanoparticles showed slight toxicity at concentration of 70  $\mu g/mL$ . Chemotherapeutic drug, doxorubicin and ADAM10 siRNA were co-loaded into the nanoparticles via non-covalent interactions. Drug loading and release were studied and were demonstrated to function synergistically in cytotoxicity analysis against prostate cancer cell line (PC3 cells). In conclusion, PEG functionalized PEI- $Fe_3O_4$  nanoparticles could be further utilized for the dual delivery of anti-cancer drugs in drug resistance tumors.

## **MEDI 203**

### **Design and synthesis of peptidomimetics with attenuated reactivity for the treatment of neurodegenerative diseases**

**Ammar Jastaniah**<sup>1</sup>, *ajasta2@uic.edu*, Rachel Knopp<sup>1</sup>, Irina Gaisina<sup>1</sup>, Marton Siklos<sup>2</sup>, Gregory R. Thatcher<sup>1</sup>. (1) Medicinal Chemistry & Pharmacognosy, University of Illinois

*at Chicago, Chicago, Illinois, United States (2) University of California, San Francisco, San Francisco, California, United States*

Dysregulation of cysteine proteases has been implicated in the progression of CNS diseases, such as Alzheimer's disease. More precisely, it has been posited that the hyperactivation of certain isoforms of cathepsins and calpains, namely calpain-1 and cathepsin B, may initiate neuronal apoptosis in accordance with the "Calpain-Cathepsin hypothesis". Therefore, targeting these enzymes with small molecule inhibitors may present an effective strategy in impeding the progression of the illness. Our early lead oxirane electrophilic compound, epoxysuccinate NYC-438, has been subjected to a battery of *in vitro* and *in vivo* assays. Both NYC-438 and the commercial calpain inhibitor, E-64d, possess significant potency; however, both show limited brain bioavailability and poor selectivity. For these reasons, the objective has been to design and synthesize reversible, selective inhibitors with improved pharmacokinetics. Moreover, we hope to answer whether preferred selective inhibition of one enzyme alone matters. By modifying the early lead NYC-438, a novel series of compounds containing a nitrile warhead were synthesized, some of which showed selective inhibition towards cathepsin K with AJ1-35 and ING-108 being the most potent and selective. In addition, a series of  $\alpha$ -ketoamide compounds were synthesized as selective calpain inhibitors. A few compounds from each of the series were then advanced to two different cell-based assays, both showing positive results: neuroprotection against oxygen-glucose deprivation and increased CREB phosphorylation implicated in synaptic plasticity.

## **MEDI 204**

### **Design, synthesis, and biostudy of bifunctional platinum complexes: Anti-cancer activity through DNA binding and HDAC inhibition**

**Chao Feng**<sup>1</sup>, *c\_feng1@u.pacific.edu*, **Yingbo Huang**<sup>1</sup>, **Dingben Chen**<sup>2</sup>, **Andreas Franz**<sup>3</sup>, **Xin Guo**<sup>1</sup>, **Yi Chen**<sup>4</sup>, **Qinliang Zhao**<sup>1</sup>. (1) *University of the Pacific, Stockton, California, United States* (2) *Taizhou University, Taizhou, China* (3) *University of The Pacific, Stockton, California, United States* (4) *BlueValley Pharmaceutical LLC, Pleasanton, California, United States*

Platinum-based anticancer drugs, such as cisplatin, carboplatin, and oxaliplatin, have been approved for world-wide clinical use for decades. Nearly 50% of all cancer therapies involve the use of them as stand-alone treatments or in combination with other medication. Despite the enormous success, their widespread application and efficacy are hindered by either cross-resistance or toxic side effects, including nephrotoxicity and neurotoxicity. The need to overcome these drawbacks has stimulated research for new Pt-based drugs.

Histone acetyltransferase (HAT) and histone deacetylase (HDAC) are a pair of important enzymes in epigenetic regulation. They work in harmony to acetylate and deacetylate histone lysine residues, which result in a more relaxed or a more condensed chromatin structure, respectively. HDAC has been found to be

overexpressed in some cancer cells, which condenses the chromatin structure of tumor suppressor genes, cell-cycle inhibitor genes and apoptosis inducer genes. Marmion research group has demonstrated that the use of HDAC inhibitors (HDACi) in conjunction with Pt drugs transformed their anti-cancer activity.

We approached the design from a different direction by installing HDACi on the platinum (II) center as a non-leaving group ligand. When the bifunctional drug reaches the cancer cell, a synergistic effect could be maintained as the relaxed chromatin structure makes DNA more susceptible to be attacked by the Pt core. Twelve new HDACi have been synthesized and fully characterized by MS, various nuclear NMR, HPLC analysis, as well as X-ray crystallography. The IC<sub>50</sub> value of HDAC inhibition and cell viability study on HCT-116, A549 and HeLa cell lines were comparable with SAHA and cisplatin. Biostudy of the new Pt complexes with A2780 and A2780cis cancer cell lines are under investigation.

## **MEDI 205**

### **Solvent-free synthesis and activity of new derivatives of hexylarylpiperazines as 5-HT<sub>7</sub> receptors ligands**

*Jolanta M. Jaskowska, jaskowskaj@chemia.pk.edu.pl, Pawel Sliwa, Przemyslaw Zareba, Damian Kulaga, Anna Drabczyk. Cracow University of Technology, Cracow, Poland*

In recent years, a lot of attention of scientists is addressed to the 5-HT<sub>7</sub> receptor due to the fact that it is associated with hopes in the context of treatment of disorders related to learning and cognitive disorder e.g. in Alzheimer's disease [1, 2]. Furthermore 5-HT<sub>7</sub> receptors can play a crucial therapeutic role in treating depression, schizophrenia and insomnia [3, 4].

Based on our previous experiments, we designed and synthesized a new group of 5-HT<sub>7</sub> ligands using the solvent-free method in the presence of microwave radiation, which we have developed in our laboratory. In vitro studies, where we evaluated activity on receptors 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>6</sub>, 5-HT<sub>7</sub> have shown that in the group of obtained ligands there are compounds with high affinity and selectivity for 5-HT<sub>7</sub> receptors.

Molecular modelling study was also performed and results were complementary to the experiment.

## **MEDI 206**

### **Development of a new structural family of microbial choline trimethylamine lyase inhibitors for the treatment and prevention of cardiovascular disease**

*Ashraf Duzan, a.duzan@vikes.csuohio.edu. Molecular medicine, Cleveland state university/ Cleveland Clinic, Westlake, Ohio, United States*

Recent clinical research points to trimethylamine N-oxide (TMAO), a gut microbiota generated metabolite, as a biomarker associated with acute thrombotic event and

cardiovascular disease risks, and a direct causative contributor to these adverse phenotypes. Our goal in this project is to develop novel microbial enzyme inhibitors that alter the biosynthetic pathway of TMAO *in vivo* through the selective potent inhibition of gut microbial choline trimethylamine (TMA) lyase activity, the rate limiting step in TMA and TMAO generation *in vivo*. TMA generation by gut microbiota is predominantly catalyzed by the gut microbial enzyme pair CutC/D, members of the microbial choline utilization (*cut*) gene cluster. 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 the gut microbial community, with high inhibitory potency in multiple *in vitro* assays employing evolutionarily diverse microbial *cutC/D* (primary and secondary screens), polymicrobial communities (tertiary screens), and for inhibitors that pass the above screening assays, progression to *in vivo* studies. We are preparing and assessing inhibitors that can work either through irreversible non-competitive or competitive mechanisms, possess appropriate physico-chemical pharmaceutical properties and have minimal systemic exposure to the host in effort to minimize possibility of side effects. Our leading candidates have excellent enzyme blocking efficiency and display good pharmacokinetic/pharmacodynamics properties.

Figure 1: Structure activity relationship enables to optimization the chemical structure of prospect inhibits. Docking model of TMA lyase microbial enzyme to choline.

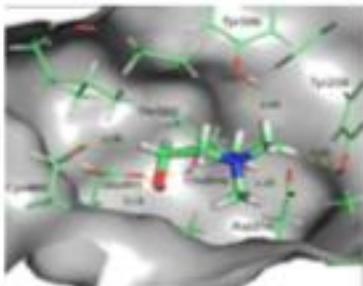


Figure 2: Invitro screening of CC225 on TMA lyase microbial CutC/D P.mirabilis

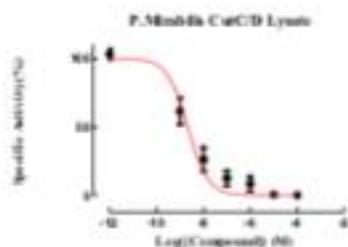
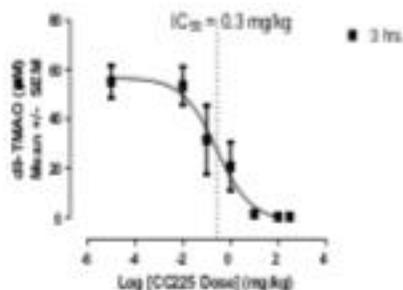


Figure 3: In vivo screening of CC225 on female mice



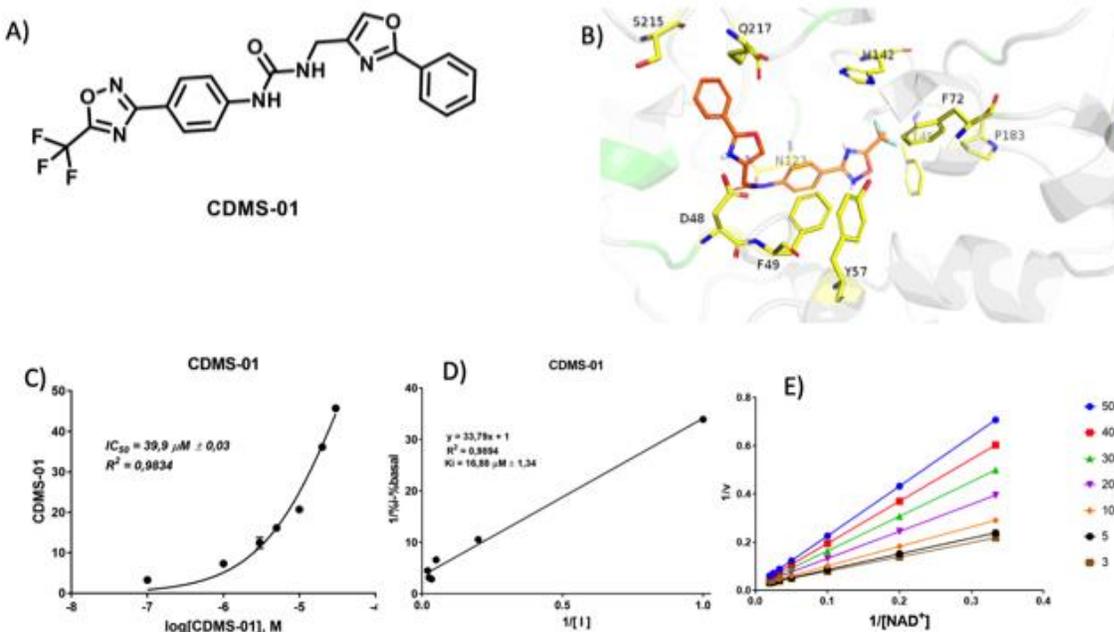
## MEDI 207

### Search of the sirtuin 2 inhibitor as antichagasic candidate by structure-based drug design

**Gustavo H. Trossini**<sup>1</sup>, [trossini@usp.br](mailto:trossini@usp.br), **Glaucio M. Ferreira**<sup>1</sup>, **Vitor M. Almeida**<sup>2</sup>, **Sandro R. Marana**<sup>2</sup>, **Flávio d. Emery**<sup>3</sup>. (1) Farmácia, Faculdade de Ciências Farmacêuticas, São Paulo -SP, Brazil (2) Bioquímica, Instituto de Química, Universidade de São Paulo, São Paulo, São Paulo, Brazil (3) Faculdade de Ciências Farmacêuticas de Ribeirão Preto, USP, Ribeirão Preto, São Paulo, Brazil

Chagas disease, caused by the parasite *Trypanosoma cruzi*, affects between 6 and 8 million people worldwide and It is estimated that 56,000 new cases and about 12,000

annually. The chemotherapy available consists of only two drugs, nifurtimox and benznidazole and it is not effective in chronic phase. Sirtuin 2 (Sir2) enzyme has an important role for *T. cruzi* infection and in cell cycle. This is NAD<sup>+</sup>-dependent enzyme of class III histone deacetylases. The availability of Sir2 genomic sequencing allows us to use SBDD (Structure Based Drug Design) strategies and virtual screening makes it possible to identify and select inhibitors for the chosen target. The model of the *T. cruzi* Sir2 enzyme was constructed by comparative modeling. Molecular dynamics simulation of 200ns was performed to ascertain the stability of the model and the validated was performed by cluster analysis, RMSD and hydrogen bond frequency analyzes with Cofator (NAD<sup>+</sup>). Molecular interaction fields (MIFs) were generated in the GRID program in order to elucidate the regions favorable to the interaction with the enzyme in relation to the physical-chemical properties of Sir2. From the MIFs favorable to Sir2 of *T. cruzi* it was possible to construct two pharmacophoric models, which was based on the interactions of Cofator (NAD<sup>+</sup>) and the catalysis site (Nicotinamide). It was also applied as a Virtual screening filter, using the ZINC<sup>15</sup> and GSK databases. Screening resulted in the selection of 8 inhibitor candidate compounds. Six compounds were obtained and were tested against *T. cruzi* Sir2. After the assay it was possible to evaluate the potency of 4 compounds, the most promising compound being CDMS-01 (IC<sub>50</sub>= 39.9 μM) that will be submitted to molecular optimization processes.



Results of the compound CDMS-01 as sirtuin 2 inhibitor; A) structure; B) docking and major

residues interactions; C) Biological inhibitory assays results and IC<sub>50</sub> calculation; D) Ki calculation; E) Competitive inhibitory mechanism determination

## **MEDI 208**

### **Phytochemical screening, metal concentration determination, and antibacterial evaluation of *Drymaria diandra* plant**

**ashish phuyal**, *apsrh123@gmail.com*. department of chemistry, tribhuvan university, Biratnagar, Province 1 ( प्रदेश नं १ ), Nepal

: *Drymaria diandra* belonging to family Caryophyllaceae exhibits different medicinal properties. So this study is designed to explore the phytochemical constituents, heavy metal concentration and antibacterial activity of *Drymaria diandra* plant. The whole plants were subjected to successive extraction using Soxhlet apparatus with 3 solvents hexane, methanol and methanol-water (1:1) to obtain the respective extracts. AAS method was used for heavy metal concentration test. Agar well diffusion method was used for the antibacterial activity test. Qualitative phytochemical analysis of methanol extracts of *Drymaria diandra* plant showed the presence of alkaloids, carbohydrates, saponins, glycosides, Cardiac glycoside, terpenoids, anthraquinones, flavonoids, proteins, coumarins, glucosides, and steroids. In heavy metal concentration the concentration of Fe (19.64 mg/L) was highest followed by Mn (2.35 mg/L), Zn (1.44 mg/L), Co (0.23 mg/L), Ni (0.09 mg/L). The remaining 4 metals As (<0.005 mg/L), Cd (<0.003 mg/L), Cr (<0.05 mg/L) and Pb (<0.01 mg/L) were nearly below detection limits. Antibacterial activity of methanol extract was higher for *S. aureus* and *E. coli* with 22 mm and 14 mm zone of inhibition respectively and methanol-water extract (1:1) for *P. vulgaris* with the zone of inhibition 17 mm.

## **MEDI 209**

### **Efforts in redesigning the antileukemic drug 6-thiopurine: Decreasing toxic side effects while maintaining efficacy**

**Arnaldo X. Torres Hernandez**<sup>1,2</sup>, *atorreshernandez2@pucpr.edu*, Chamitha J. Weeramange<sup>2</sup>, Prathibha Desman<sup>2</sup>, Anthony Fatino<sup>2</sup>, Olivia Haney<sup>2</sup>, Ryan Rafferty<sup>2</sup>. (1) Chemistry, Pontifical Catholic University of Puerto Rico, Barranquitas, Puerto Rico (2) Chemistry, Kansas State University, Manhattan, Kansas, United States

6-Thiopurine (6TP) is a drug that has been used to treat Acute Lymphocytic Leukemia (ALL) and non-Hodgkin's leukemia since the early 1950s. This drug has the ability to mimic the guanosine nucleotide, which incorporates into the cancer cell's DNA causing its death. Unfortunately, toxic effects have been reported from its use, such as hepatotoxicity, severe vomiting, jaundice, and even death. These side effects come from the enzymatic inhibition of UDP-glucose dehydrogenase (UDPGDH) who is responsible of the solubility and excretion of bilirubin in the body. 6TP metabolites can inhibit UDPGDH causing high concentrations of bilirubin, preventing it from becoming

soluble and excreted. The drug metabolites arrive because 6TP oxidation of carbons two (C2) and eight (C8) by the enzyme xanthine oxidase. 6TP being the lesser inhibitor metabolite and 6-thiouric acid (oxidation in both carbon) the greater inhibitor. Upon discovery of C2/8 oxidation is responsible for enzymatic inhibition, efforts were undertaken for the construction of 6TP analogs, substituted at the C8 position. We looked to measure their inhibition in the UDPGDH enzyme, by avoiding oxidation in hopes to decrease or eliminate 6TP's off-target toxicity while retaining therapeutic efficacy. Installation of groups such as bromine, fluorine, chlorine, deuterium and hydrocarbons were considered for the analogs. Characterization of the synthesized analogs was done by HNMR and CNMR. Half maximal inhibitory concentration (IC<sub>50</sub>) was measure, for synthesized compounds, cultivating ALL cell lines REH for 48 hours using Alamar Blue Assay. Finally, inhibition constant (K<sub>i</sub>) respect to the UDPGDH was calculated. Brominated, chlorinated, and fluorinated 6TP was successfully synthesized with an overall percent yield of 28%, 16%, and 2%, respectively. 6TP showed an IC<sub>50</sub> of 2.94  $\mu\text{m}$  (+/- 0.484) with an K<sub>i</sub> of 288  $\mu\text{m}$ , fluorinated 6TP with 4.71  $\mu\text{m}$  (+/- 1.40) and 215  $\mu\text{m}$ , chlorinated 6TP with 3.95  $\mu\text{m}$  (+/- 1.94) and 163  $\mu\text{m}$ , and brominated 6TP with 9.54  $\mu\text{m}$  (+/- 0.970) and 192  $\mu\text{m}$ . Results have shown that structural modifications can retain cytotoxicity and decrease inhibition towards UDPGDH. It is anticipated that with a decrease in toxicity of new 6TP analogs, an increase in dosage can be administered, resulting in further increase of therapeutic properties of 6TP treatment.

## MEDI 210

### Biological and structural studies of some new Schiff's bases: Computational and experimental approach

**Ataf Ali Altaf**<sup>1</sup>, [atafali\\_ataf@yahoo.com](mailto:atafali_ataf@yahoo.com), Amin Badshah<sup>2</sup>. (1) Department of Chemistry, University of Gujrat, Gujrat, Punjab, Pakistan (2) QAU, Islamabad, Pakistan

Schiff bases found thier importance in various fields such as biological chemistry and chemical catalysis. The current study focused on synthesizing a series of new Schiff base compounds derived from 4-formylbenzoic acid. Structural characterization was carried out by multi-nuclear magnetic resonance (<sup>1</sup>H and <sup>13</sup>C NMR), Fourier transform spectroscopy (FTIR) and mass spectrometry. These artificial compounds were also characterized by density functional theory (DFT). Vibration analysis results based on DFT found in good agreement with experimental structural data. Biological reactions of these compounds were analyzed with seven bacterial strains (*Chromohalobacter israelensis*, *Staphylococcus aureus*, *Chromohalobacter salexigens*, *Shigella Sonnei*, *Neisseria gonorrhoeae*, *Halomonas Halophila* and *Halomonas salina*) and found active to inhibit their growth. Based on the results of the bacterial studies, cholinesterase (AChE) and butylcholinestrace (BCHE) were selected to target their activity. Molecular docking was performed to understand the interaction between synthetic compounds and studied enzymes. We found the linear relationship between the binding energies and the 50% inhibitory concentrations. Pi-stacking and hydrophobic interactions were found to be important to inhibit the activity of target

enzymes. Importantly, these interactions were also found in these compounds during the natural bonding orbital (NBO) analysis using DFT.

## **MEDI 211**

### **Total synthesis of a potent antimicrobial compounds griseoluteins, pelagiomicins and alanylgriseoluteic acid**

**Satish Natha Dighe**, *satish.dighe@qut.edu.au*, Peter Katavic, Trudi Collet. Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia

Antibiotics were considered as “Super Drugs” when first discovered in 20<sup>th</sup> century. Since then, antibiotics have been used as first-line treatment for many bacterial infections. Most of the clinically used antibiotics are synthetic derivatives of natural products. Naturally-occurring phenazines possess broad-spectrum antimicrobial properties. Bacterial species such as *Pseudomonas*, *Streptomyces* and *Pelagibacter*, are the known source of natural phenazines. Among these bacteria, *Streptomyces griseoluteus* and *Pelagibacter variabilis* were reported to produce phenazine antibiotics griseolutein A and pelagiomicin A, B, C respectively. These phenazine derivatives contain common pharmacophore, griseoluteic acid which is also an antimicrobial agent. Recently, *Pantoea agglomerans* was reported to produce alanylgriseoluteic acid which also has potent antimicrobial activity at MIC value  $\leq 0.06\text{--}0.75\ \mu\text{g/mL}$ .

Although griseoluteic acid and its analogues have shown potent antimicrobial properties, only one report is available on their synthesis. We have developed novel synthetic methodology to synthesise griseoluteic acid and its analogues with less number of reaction steps in good yield compared to previously reported synthetic protocol. Condensation of *o*-benzoquinone with 1,2-diaminobenzenes is considered as a useful strategy to synthesise phenazine ring. To achieve total synthesis, we used cheap and easily accessible starting material 2,3,4-trihydroxybenzaldehyde, which is initially converted into *o*-benzoquinone derivative in three simple steps. In next step, *o*-benzoquinone derivative was reacted with 2,3-diamino benzoic acid to obtain griseoluteic acid. Finally, griseolutein A, alanylgriseoluteic acid, pelagiomicin A, B and C were further synthesised from griseoluteic acid in two steps. Therefore, our developed novel synthetic protocol will be useful guide for medicinal chemists to prepare analogues of potent but less explored phenazine class of antibiotics.

## **MEDI 212**

### **Targeting Alzheimer's disease: A virtual screening protocol to discover new central-acting BACE1 inhibitors**

**Judite Coimbra**<sup>1</sup>, *judite.coimbra@student.ff.uc.pt*, Salete J. Baptista<sup>2</sup>, Armanda E. Santos<sup>2</sup>, Paula I. Moreira<sup>2</sup>, Maria M. Silva<sup>1</sup>, Teresa C. Dinis<sup>2</sup>, Jorge A. Salvador<sup>1</sup>. (1) Laboratory of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Coimbra,

Coimbra, Portugal (2) Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal

The most common type of dementia – Alzheimer's disease (AD) – is a serious neurodegenerative disorder that remains without effective pharmacological therapy to prevent the advance of the disease. The neurodegenerative process, which culminates in dementia, might be prevented through innovative disease-modifying approaches. The generation of misfolded amyloid- $\beta$  ( $A\beta$ ) oligomers in the AD brain is indicated in the “Amyloid Cascade Hypothesis” as the main incident underlying neurotoxic events. The  $A\beta$  peptide is produced by sequential Amyloid Precursor Protein (APP) proteolytic cleavage by  $\beta$ - (BACE1) and  $\gamma$ -secretase. Since the processing of APP by BACE1 is the crucial step in the production of  $A\beta$ , this therapeutic target has been explored for AD-modifying intervention over the past years. Thus, the main goal of this research project is the discovery of new small molecules that effectively reach the brain and inhibit BACE1. The project focuses on a reliable multiple-step protocol of virtual screening, which includes: i) a combination of a structure-based (SB) and ligand-based (LB) pharmacophore modeling to screen several druglike compound databases to identify novel anti-BACE1 agents; ii) a subsequent filter to predict their ability to cross the blood-brain barrier (BBB), a pharmacokinetic property required for these drugs; and iii) molecular docking simulations to predict the binding mode and affinity of those molecules, which enable the selection of the best candidates for further biological (*in vitro* and *in vivo*) evaluation. Moreover, while the SB approach is based on receptor-ligand key interactions of BACE1-ligand crystal complexes, the LB strategy captures the essential features of structurally diverse known active compounds that inhibit BACE1. To evaluate the quality of the developed pharmacophore models multiple metrics were calculated. Henceforth, considering simultaneously the structure of the BACE1 enzyme and the properties of the multiple active ligands, the chances of finding new compounds that effectively bind to BACE1 are enhanced.

## **MEDI 213**

### **Leveraging high-throughput experimentation and cutting-edge synthetic chemistries to improve the quality and speed of the drug discovery design cycle**

**Shane W. Krska**, *shane\_krska@merck.com*. RY800-C306, Merck and Co., Inc., Rahway, New Jersey, United States

The chemical complexity and diversity of pharmaceutically active molecules presents a rich opportunity for application of modern catalysis. However, successfully adapting published catalytic methods to complex molecules requires the ability to simultaneously adjust multiple reaction parameters such as solvent, ligand, additives and metal source in a time- and material-sparing manner. To overcome these challenges, scientists at Merck have helped pioneer high-throughput experimentation (HTE) approaches to rapidly identify optimum catalysts and conditions customized for each transformation. Recent advances in HTE miniaturization, automation and analysis have greatly expanded the impact of catalysis in drug discovery. Several case studies will be

discussed that illustrate the diverse ways HTE can enable drug discovery, employing a wide variety of chemistries such as modern cross-coupling and C-H functionalization catalysis.

## **MEDI 214**

### **Acceleration of medicinal chemistry research enabled by high-throughput technologies**

*Ying Wang, wang.ying@abbvie.com. AbbVie Inc, North Chicago, Illinois, United States*

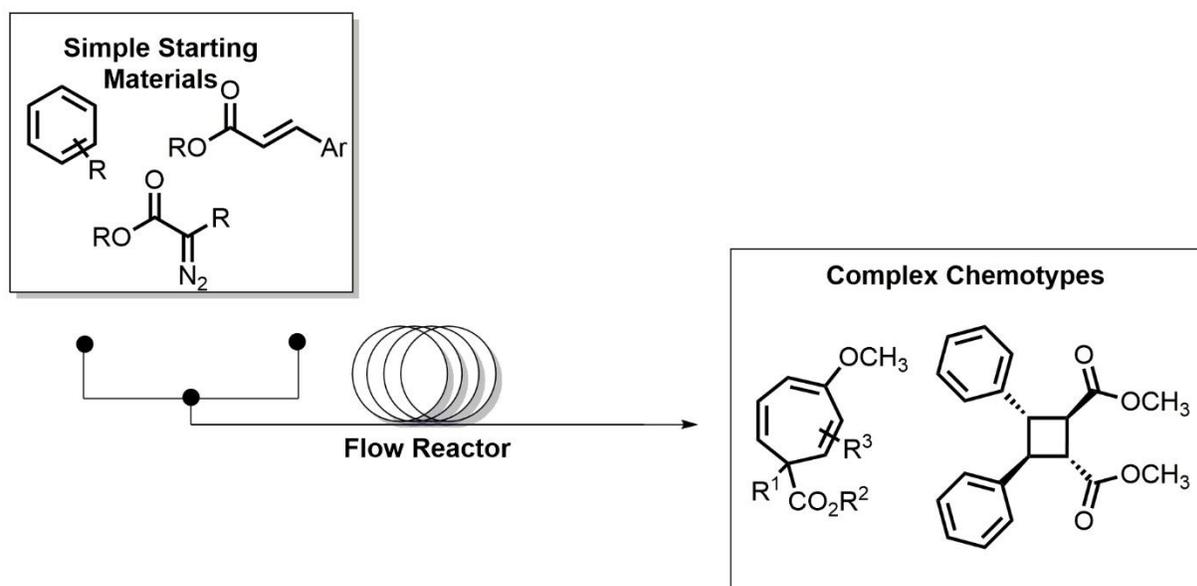
The speed and efficiency of small molecule candidate discovery relies heavily on the hit identification and lead optimization through structure-activity relationship studies. The ability to generate novel bioactive analogs fast and effectively is of utter importance for any medicinal chemistry program. In this context, multiple industry-leading enabling high throughput chemistry technologies will be presented, focusing on the development and implementation of integrated library synthesis systems and micro/nano-mole high throughput reaction screening technologies. The impact of these technologies for the medicinal chemistry programs will also be discussed.

## **MEDI 215**

### **Development of flow reactions to enable synthesis and medicinal chemistry**

*Aaron B. Beeler, beelera@bu.edu, Gabriel Fleming, Reem Telmesani, Alexis L. Courtney, Yann Corre. Chemistry, Boston University, Brookline, Massachusetts, United States*

In the Beeler Research Group, we are developing new technologies and approaches to enable synthesis and medicinal chemistry. The lecture will highlight developments in challenging reactions which can be used to access bioactive small molecules which are critical in our multidisciplinary and collaborative research. A common theme in our lab is the use of flow chemistry to overcome boundaries that limit reactions and to develop efficient reaction processes. Why flow chemistry? Reactions have been carried out in batch vessels for over two centuries and amazingly the tools chemists use have remained largely unchanged. As such, many of the challenges presented by batch reactions are still unsolved. Limitations such as mass transfer, heat transfer, or photon penetration can undermine the potential of a reaction when using traditional batch reactors. However, these limitations are largely mitigated in flow which enables us to reconsider the utility of many transformations for application in synthesis. Ultimately, I hope to demonstrate how flow chemistry provides us a tool for development of new and more efficient reactions that are robust, highly scalable, and provide access to complex and novel chemotypes.



## MEDI 216

### Going faster and leaner: Automated microscale reaction screening in flow

**Paul Richardson**<sup>1</sup>, paul.f.richardson@pfizer.com, Neal Sach<sup>2</sup>, Joseph Tucker<sup>3</sup>, William P. Farrell<sup>4</sup>, Christopher J. Helaf<sup>5</sup>, Damith Perera<sup>6</sup>. (1) Medicine Design, Pfizer, San Diego, California, United States (2) Pfizer Inc, San Diego, California, United States (3) Pfizer, Groton, Connecticut, United States (4) CB2, Pfizer Inc, San Diego, California, United States (5) MS 220-3233, Pfizer Inc, Groton, Connecticut, United States (6) Medicine Design, Pfizer Inc., SAN DIEGO, California, United States

Synthetic chemistry remains a cornerstone of the drug discovery process, and advances in efficiency have the potential to not only strongly influence the identification of new drug candidates, but also expedite their progress to the clinic. We report herein the development of an automated flow-based synthesis platform, designed from commercially available components, that integrates both rapid microgram reaction screening and milligram synthesis into a single modular unit. This system was validated using a medicinal chemistry relevant Suzuki-Miyaura coupling, wherein we demonstrate the ability to explore a diverse range of reaction variables on microgram scale generating LC/MS data points from >1500 reactions in 24 hrs. The system able to holistically examine the full range of cross-coupling electrophiles (e.g. Cl, I, OTf) and nucleophiles (B(OH)<sub>2</sub>, BF<sub>3</sub>K, BPin) totaling over 5500 combinations in a 4 day period. Further, through multiple injections of the same segment, the system was used to directly produce milligram quantities of product in a short time frame. The optimal conditions identified were replicated in traditional flow and batch mode to provide excellent yields of the target product, demonstrating both the broad applicability and wide versatility of this platform to organic synthesis.

## MEDI 217

## Mapping reaction space with machine learning

**Abigail G. Doyle**, *agdoyle@princeton.edu*. Princeton University, Princeton, New Jersey, United States

Due to the multidimensionality of chemical reactivity and structure, vast resources and time are currently expended on the process of “*how to make something*”. Whereas synthetic chemists have an exquisite ability to recognize patterns and generalize trends in a single dimension, extending this intuition to the many interacting dimensions that influence chemical reactivity is difficult. My group is interested in applying modern data science and machine learning tools to enable prediction of reaction performance in many dimensions. In this lecture, I will describe the opportunities and limitations associated with using machine learning tools to facilitate adoption of synthetic methods and gain insight into reaction mechanism.

## MEDI 218

### Current status of drug development for health disparity diseases: Cryptococcal meningitis

**Seth Y. Ablordeppey**, *seth.ablordeppey@famu.edu*. Basic Pharmaceutical Sciences, Florida A&M University, Tallahassee, Florida, United States

Health Disparities research (HDR) is intended to identify the causes of disparities in health and to institute measures to narrow the gaps among the various groups with health conditions and diseases that disproportionately affect parts of the population. Diseases such as cancer, cardiovascular disease and stroke, diabetes, AIDS, opportunistic infections and drug abuse have shown some of the widely known disparities within populations. This symposium is focused on providing therapeutic developments in a variety of disease states. Following a general discussion of the status of HDR, speakers will present therapeutic developments in selected areas of health disparities including AIDS-related OIs, tuberculosis, drug abuse, cancer, prostate cancer specifically and osteoarthritis. Although significant progress has been made in the treatment of HIV/AIDS, the disease remains a cause for concern especially in the developing nations. Worldwide, an estimated 1.8 million individuals became newly infected with HIV in 2016 which amounts to about 5,000 new infections per day. The chronic nature of AIDS and its effect on the immune system has spawned increasing numbers of opportunistic infections including cryptococcal meningitis, one of the deadliest infections. The incidence of cryptococcal meningitis ranges from 0.04 to 12% per year among persons with HIV. And Sub-Saharan Africa has the highest yearly burden with an estimate of 3.2% or about 720,000 cases. Globally, it is estimated that about 957,900 cases of cryptococcal meningitis occur each year, resulting in 624,700 deaths by 3 months after infection. Sub-Saharan Africa accounted for 73% of the estimated cryptococcal meningitis cases in 2014 and cryptococcal meningitis was responsible for 15% of AIDS-related deaths. Current treatment options for cryptococcal meningitis are associated with adverse events which have led to a search of new drugs

as replacements for the existing drugs including Amphotericin B. In this presentation, our efforts in using the natural product Cryptolepine as a lead for drug design will be discussed.

## **MEDI 219**

### **Development of drugs for the treatment of tuberculosis**

**Jason K. Sello**, *jason\_sello@brown.edu*. Chemistry, Brown University, Providence, Rhode Island, United States

*Mycobacterium tuberculosis* (*Mtb*), causative agent of tuberculosis, is the deadliest bacterial pathogen. According to World Health Organization statistics, infections by *Mtb* are among the top 10 causes of death worldwide. In one of the most striking examples of a health disparity, it is well-known that the severity of the tuberculosis pandemic is highly correlated with wealth. The number of cases in high income nations are roughly 10 per 100,000; whereas in some economically countries the burden can exceed 400 per 100,000. Nevertheless, tuberculosis demands attention of all nations because it is highly contagious and *Mtb* is increasingly dangerous via its resistance to drugs. *Mtb* is the focus of drug-development programs and its intracellular proteases have emerged among the hottest drug targets in the past decade. A wealth of genetic data indicate that *Mtb* requires these enzymes for either viability or surviving insults from the immune response. Predictions that these enzymes are “druggable” are validated by a growing number of reports of bioactive small molecules that perturb their catalytic activity. There is cause for optimism in that these molecules could be “first-in-class” drugs that act either as bacteriocidals or suppressors of pathogenicity. This seminar will describe our efforts to gain mechanistic insights into and accelerate the medicinal development of small molecules that perturb the functions of the ClpP peptidase and the 20S proteasome in *Mtb*.

## **MEDI 220**

### **Developing peptides and peptidomimetics as potential treatments for substance abuse**

**Jane V. Aldrich**<sup>1</sup>, *janealdrich@ufl.edu*, Jay P. McLaughlin<sup>2</sup>. (1) Dept. of Medicinal Chemistry, University of Florida, Gainesville, Florida, United States (2) Dept. of Pharmacodynamics, University of Florida, Gainesville, Florida, United States

Substance abuse has become a major health issue in the U.S., especially of opioids, where the number of overdose deaths has skyrocketed in recent years. While there are pharmacological treatments available for opioid abuse there are currently no pharmacological agents for treating abuse of other substances such as cocaine. We have been exploring peptidic ligands, particularly those acting at kappa opioid receptors (KOR), as potential treatments for substance abuse. A major challenge in treating drug abuse is relapse after a period of abstinence. Accordingly, we have been examining

compounds in the mouse conditioned place preference (CPP) assay for their ability to prevent relapse. Stress, which causes activation of KOR via release of endogenous agonist, is a common cause of relapse that can be prevented by pretreatment with KOR antagonists. In contrast, relapse due to exposure to the abused substance can be prevented by KOR agonists. In order to reach their targets in the CNS therapeutics for drug abuse must be brain penetrant. Results will be presented for peptidic ligands, including compounds acting through other opioid receptors, that can prevent drug seeking behavior for cocaine, opioids and ethanol due to stress as well as substance exposure. These compounds prevent drug seeking behavior following systemic administration, including in many cases after oral administration, making them promising lead compounds for potential development to treat substance abuse.

## **MEDI 221**

### **Current approaches to anticancer drug development**

**John K. Buolamwini**, *john.buolamwini@rosalindfranklin.edu*. Rosalind Franklin University of Med Sci, North Chicago, Illinois, United States

Cancer has been undoubtedly the most feared disease not only because it is often relentless in killing its victims, but also because it is very difficult to treat and strikes regardless of age, gender or race. In some sense we could say we are in a golden age of cancer drug discovery as the advances in the studies of cancer biology has unraveled vulnerabilities and identified therapeutic targets that are promoting progress in attacking cancer. Recently these studies have led to the harnessing of the body's immune system as a potent weapon against cancer, whereby immune checkpoint inhibitors such as Keytruda are producing spectacular results against some of the most difficult cancers to treat such as metastatic melanoma. This presentation will highlight some of the new approaches to cancer drug development particular against cancers that largely affect minority communities. The approaches are multi-disciplinary in nature ranging from basic biology, drug design and discovery concepts to clinical translational methodology.



## **MEDI 222**

### **Prostate cancer health disparities in African-American men: Possible targets for race specific drug development**

**Shafiq Khan**, *skhan@cau.edu*. Center for Cancer Research and Therapeutic Development, Clark Atlanta University, Atlanta, Georgia, United States

Prostate cancer is one of the most frequently diagnosed malignancies among men worldwide and remains the second leading cause of cancer related deaths in the United States. According to the American Cancer Society, the estimated new cases of prostate cancer are 164,690 and the deaths from this disease are estimated at 29,430 in the United States in 2018. African-American (AA) men are disproportionately affected by prostate cancer compared to men of other ancestral backgrounds, and AA men are often diagnosed at an earlier age with more advanced and aggressive prostate cancer compared to any other racial/ethnic groups. The overall prostate cancer incidence and mortality rate are remarkably higher in AA men; AA men are 1.6 times more likely to develop prostate cancer, and are ~2.5 times more likely to die from this disease compared to Caucasian American (CA) men. Recent data suggest that the prostate cancer incidence is declining, yet the overall prostate cancer-related mortality continues to rise among AA men. In addition to known risk factors that may play a role in AA men having a higher incidence of more aggressive and advanced prostate cancer, a growing body of evidence now suggests that biological factors such as differences at the genetic and molecular level play crucial roles in racial disparities in prostate cancer incidence and outcome seen in AA men. Recent studies show that molecular factors such as genetic modifications, epigenetic changes, altered microRNAs, and signaling pathways (hormone receptor, growth factor receptor, and inflammation signaling pathways) are associated with prostate cancer racial disparities. Apart from surgery and chemotherapy, hormonal therapy is the most common treatment of choice for advanced

stages of the disease; hormonal therapy is primarily based on the inhibition of androgen production or function. Prostate cancer cells develop resistance to hormonal therapy over time leading to castration resistant disease which ultimately results in mortality. All current treatments are not specific to different ethnic and racial groups. However, recognition of major biological and genetic differences observed in prostate cancer cells between AA men and men of other ethnic backgrounds provides an opportunity to develop specific drugs to target these biological factors in AA men to develop race specific drugs to treat prostate cancer in the population which is most vulnerable to this disease.

## **MEDI 223**

### **New approach to regenerative cartilage tissue engineering using temperature-sensitive therapeutic hydrogels**

*Juana Mendenhall, juana.mendenhall@morehouse.edu. Chemistry , Morehouse College, Atlanta, Georgia, United States*

Injury and diseases that affect articular cartilage present a daunting challenge in orthopedic medicine. During the onset of injury or disease, low oxygen environments decrease healthy cartilage cell growth by limiting extracellular matrix production and creating reactive oxygen species (ROS) such as nitric oxide (NO). Ultimately, this environment reduces the efficacy of traditional biomaterials to cultivate a regenerative scaffold. Our research group has developed a therapeutic injectable hydrogel that provides a regenerative interface for cartilage tissue engineering via a cell-protective mechanism. Using Poly(N-vinylcaprolactam)[PVCL] a smart biomaterial that changes its molecular orientation upon temperature change along with its mechanical properties in conjunction with other natural therapeutic molecules. A variety of therapeutic molecules were functionalized and grafted into a composite hydrogel. We will report the effect of functionalized therapeutic molecule(s) stereochemistry on cellular vitality and ROS concentration which control inflammatory pathways. This hydrogel composite, containing PVCL-hyaluronic acid-therapeutic (PVCL-HA-TH) affords a robust hydrogel with tunable (lower critical solution temperature) [LCST] parameters near physiological temperature. Hydrogels were synthesized using free radical polymerization and cross-linking strategies then studied *in vitro* static cell culture and *in vivo* studies. Using 3D printing, hydrogels were also fabricated to compare the effect of material properties on cell proliferation and metabolism on extra cellular matrix (ECM) proteins. Fetal bovine chondrocytes were harvested and seeded [or 3D bioprinted] into various formulations of PVCL-HA-TH under normoxia (21%) and hypoxia (1%) low oxygen conditions. Our results show that chondrocyte cell viability at 1% O<sub>2</sub> levels remained higher than that of 20% O<sub>2</sub> levels in PVCL-HA for each time point. PVCL-HA hydrogels reached a maximum of 89% on the third day of observance. Higher cell viability was also noted on meHA samples at 1% O<sub>2</sub> levels than at 20% O<sub>2</sub> levels, with the peak value at 74% on the first day of observance. Animal studies were performed for 30 days after injection of therapeutic hydrogels into the defective knee joint confirm higher amounts of chondrocyte cloning within the murine joint. This work shows promise in providing a

cyto-protective biomaterial construct that will begin to regenerate diseased articular cartilage.

## **MEDI 224**

### **Brain-penetrant kinase chemotherapeutics: Learning from CNS space**

*Mary Mader, mader\_mary@lilly.com, Yuan Shi. Discovery Chemistry Research and Technologies, Eli Lilly and Company, Indianapolis, Indiana, United States*

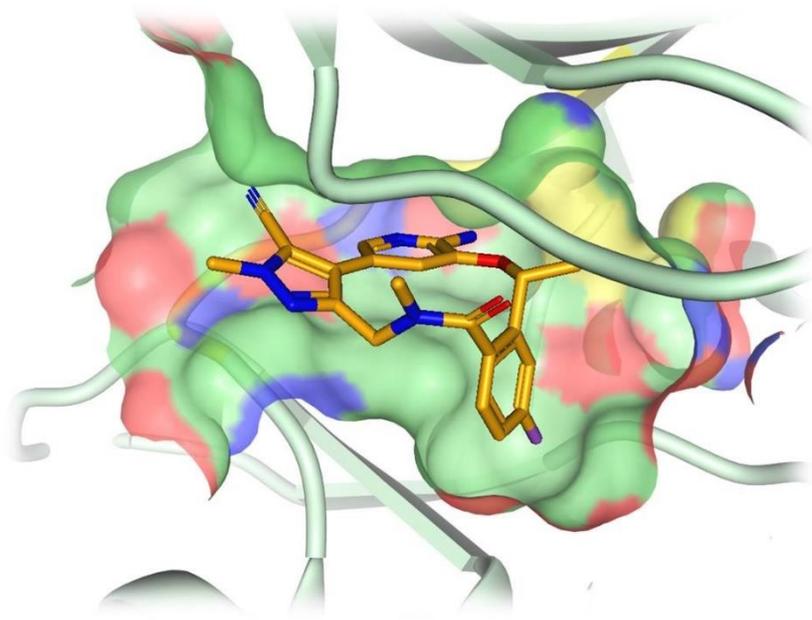
Brain penetrance is significantly impacted by the physicochemical properties of the drugs. Compound properties associated with brain penetrance have been analyzed recently for kinase inhibitors in glioblastoma trials, although many of these examples exploit opportunities identified in clinical development rather than specific compound design strategies. An examination of kinase inhibitors that were optimized specifically for CNS indications could provide insight into preferred property space and lead to greater success in neuro-oncology efforts.

## **MEDI 225**

### **Mechanisms of ALK acquired resistance and the discovery of lorlatinib (PF-06463922), a macrocyclic ALK/ROS1 inhibitor for the treatment of resistant and metastatic NSCLC**

*Ted W. Johnson, ted.w.johnson@pfizer.com. Chemistry, Pfizer, Carlsbad, California, United States*

Insights into ALK acquired resistance were used to define drug design strategies that led to the discovery of lorlatinib (PF-06463922), a novel macrocyclic inhibitor of ALK/ROS1. Structure based drug design, lipophilic efficiency and physicochemical property-based optimization provided inhibitors with overlapping broad spectrum potency, low transporter efflux, and brain penetration. Lorlatinib is in Phase 3 clinical trials for the treatment of patients with ALK-positive non-small cell lung cancer (NSCLC) and was given Breakthrough Therapy status by the FDA in 2016.



Lorlatinib bound to the kinase domain of ALK-L1196M

## **MEDI 226**

### **Discovery of the clinical candidate AZD1390: A high-quality, potent and selective inhibitor of ATM kinase with the ability to cross the blood-brain barrier**

*Kurt Pike, kurt.pike@astrazeneca.com. AstraZeneca, Cambridge, United Kingdom*

Glioblastoma multiforme (GBM) is the most common and lethal form of primary brain tumor and current treatment (surgery followed by fractionated radiotherapy and temozolomide) provides a median survival of just 12-15 months. The poor prognosis associated with GBM is attributed to an extensive infiltration into surrounding brain tissue (thereby limiting the effectiveness of surgical excision), an intrinsic chemo/radioresistance of the tumor and the presence of the blood-brain barrier (BBB) which limits the ability of certain chemotherapies to reach the tumor. Ataxia telangiectasia mutant (ATM) is a serine/threonine protein kinase that plays a crucial role in the cellular DNA damage response signalling activated by DNA double strand breaks (DSB). DSBs are induced by a wide range of chemotherapies, or extrinsically through exposure to ionising radiation and; therefore, ATM inhibition represents an exciting clinical opportunity as a target to hyper-sensitize tumors to chemo/radiotherapy. The optimization of compound properties suitable to allow efficient BBB penetration remains a significant challenge within Medicinal Chemistry and failure to consider these can severely restrict the utility of an agent for CNS disease. Herein, we describe the strategies employed to optimize BBB-penetration, potency and pharmacokinetics that resulted in the identification of AZD1390, a first in class orally available and CNS penetrant ATM inhibitor suitable for the treatment of intracranial malignancies. AZD1390 is an exceptionally potent inhibitor of ATM in cells ( $IC_{50} = 0.78$  nM) with >10,000 fold selectivity over closely related members of the PIKK family of enzymes and excellent

selectivity across a broad panel of kinases. AZD1390 displays excellent oral bioavailability in preclinical species (66% in rat and 74% in dog), is not a substrate for human efflux transporters and has been shown to efficiently cross the BBB in Non-Human Primate PET studies. Profound tumor regressions and increased animal survival (>50 days) have been observed in orthotopic xenograft models of brain cancer following just 2 or 4 days combination treatment of AZD1390 with radiotherapy, compared to radiotherapy treatment alone. These data support the potential of CNS penetrant ATM inhibitors to provide an important new therapeutic agent for the treatment of intracranial malignancies. AZD1390 is currently undergoing early clinical assessment.

## **MEDI 227**

### **Discovery of entrectinib: A novel and potent inhibitor of ALK, ROS1, and Pan-TRKs kinases active in multiple molecularly defined cancer indications**

*Paolo Orsini, paolo.orsini@nervianoms.com. Nerviano Medical Sciences, Nerviano (MI), Italy*

The anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that plays a key role in the development of different tumor types. Even though the oncogenic protein NPM-ALK was originally identified as responsible for a subset of Anaplastic Large Cell Lymphoma (ALCL), its tumorigenic role in subsets of Non-Small Cell Lung Cancer (NSCLC) have been reported to be dependent on activated forms of ALK, the most frequent being the EML4-ALK protein. Later on other oncogenic forms of the strictly related c-ros Oncogene 1 kinase (ROS1) and tropomyosin receptor kinase A (TRKA) have been found to be crucial in the same tumor indication. In addition TRKs fusion proteins have been also identified in subsets of colorectal carcinoma (CRC) and in other tumor types. Despite the remarkable clinical activity of the ALK inhibitor Crizotinib, the emergence of resistance mutations and of brain metastasis often cause patient relapse. The high-throughput screening (HTS) of our corporate compound collection allowed us to identify a 3-aminoindazole derivative endowed with good biochemical potency against ALK ( $IC_{50} = 0.073 \mu M$ ) and good antiproliferative activity on the ALK-dependent ALCL Karpas-299 cell line ( $IC_{50} = 0.253 \mu M$ ). From this starting point a medicinal chemistry effort led to the final candidate compound Entrectinib, that potently inhibits the ALK kinase ( $IC_{50} = 12 nM$ ), and the proliferation of the ALK-dependent Karpas-299 cell line ( $IC_{50} = 31 nM$ ).

Entrectinib is characterized by good oral bioavailability in all animal species, excellent *in vivo* efficacy in ALK-driven tumor models, efficient penetration of the blood-brain barrier (BBB) and good antiproliferative activity on Ba/F3 cell line transfected with different mutated forms of EML4-ALK. Moreover it is a potent inhibitor of the closely related tyrosine kinases ROS1 ( $IC_{50} = 7 nM$ ) and TRKs ( $IC_{50} = 1 - 5 nM$ ), and is highly efficacious in *in vivo* related tumor models. Patients' treatment with Entrectinib resulted in clinically meaningful, deep and durable systemic responses (data recently presented in 19th World Conference on Lung Cancer WCLC 2018 and in the European Society for Medical Oncology Congress ESMO 2018). The molecule is currently undergoing

registration enabling Phase II Clinical Trials for the treatment of selected patients affected by ALK, ROS1-, and TRK-positive tumors.

## **MEDI 228**

### **Discovery of GDC-0084: A BBB penetrating PI3K/mTOR inhibitor**

*Timothy P. Heffron, theffron@gene.com. MS 232A, Genentech, South San Francisco, California, United States*

Aberrant PI3K pathway signaling is observed in a significant majority of patients with the primary brain tumor glioblastoma multiforme (GBM). Additionally, aberrant PI3K pathway signaling is observed in brain metastases.

This presentation will describe the discovery of GDC-0084, a blood-brain barrier penetrating inhibitor of Class I PI3K isoforms and mTOR. Special attention will be given to structural and physicochemical property optimization required to achieve the clinical development candidate. In vivo characterization of GDC-0084 will also be shared.

## **MEDI 229**

### **Drug-target residence time: A misleading concept**

*Rutger Folmer, rutger.folmer@mercachem.com. Medicinal Chemistry, Mercachem, Nijmegen, Netherlands*

Since the importance of drug target residence time was highlighted, over ten years ago, slow binding kinetics has got a lot of attention in drug discovery literature, and within pharmaceutical research. There is a wide-spread believe now amongst medicinal chemists that slow kinetics can give a disconnect between pharmacodynamics and pharmacokinetics. Consequently, chemists actively try to design in slow on-rate into their inhibitors to achieve slow kinetics and the promised benefits. Indeed, many drug discovery scientists believe that long residence time offers something extra that plain potent compounds do not offer.

However, the residence concept as presented in most literature is supported by rather misleading simulations and arguments, and by examples where compounds are taken out of their pharmacokinetic context. Moreover, fast association is typically more desirable than slow, and advantages of long residence time would be partially or completely offset by slow on-rate.

This presentation intends to bring some nuance to the residence time literature by critically examining and discussing some key published simulations and examples, in relation to the claims they were meant to support. I will outline that there are no examples of and only very limited mathematical support for the often-heard claim that long residence time can cause pharmacodynamic effects to outlast pharmacokinetics. It will be argued that optimising both on- and off-rates are important in drug discovery, and if you were to choose only one parameter, good-old potency is still your best bet.

## **MEDI 230**

### ***In vitro* and *in vivo* target life for immucillin transition-state analogs**

**Vern L. Schramm**, *vern.schramm@einstein.yu.edu*. Department of Biochemistry, Albert Einstein College of Medicine, Bronx, New York, United States

Transition-state analogs of human purine nucleoside phosphorylase (PNP) bind with picomolar (pM) dissociation constants. The PNP-inhibitor re-equilibration rates ( $t_{1/2}$  for activity regain) vary from 5 to 24 min for seven Immucillins with dissociation constants of 161 to 2 pM. *In vitro*  $t_{1/2}$  off-rates for DADMe-Immucillin-H by competitive exchange are ~80 min. Treatment of human erythrocytes with DADMe-Immucillin-H, a 19 pM inhibitor, causes rapid inhibition of cellular PNP. Loss of [ $^{14}\text{C}$ ]DADMe-Immucillin-H from erythrocytes during multiple washes is slow, to give a  $t_{1/2}$  of ~100 hr. When the loss of [ $^{14}\text{C}$ ]DADMe-Immucillin-H from erythrocytes is measured in the presence of excess unlabeled DADMe-Immucillin-H, the loss rate increased to a  $t_{1/2}$  of ~80 min, the intrinsic rate. Human volunteers treated with a single oral dose of DADMe-Immucillin-H exhibit complete PNP inhibition and require 59 days to regain 50% of blood PNP activity, corresponding to the erythropoiesis rate. Picomolar transition-state analogues exhibit long lifetimes on their targets in cells because of a high probability of target-recapture relative to loss to the extracellular space.

## **MEDI 231**

### **Kinetic profiling in drug discovery: A case study with EED hit-to-lead program**

**Ying Wang**, *wang.ying@abbvie.com*. AbbVie Inc, North Chicago, Illinois, United States

Extensive kinetic data were collected and analyzed via SPR throughout the hit to lead campaign for the identification of allosteric inhibitor of the PRC2 complex through EED binding. Our investigations had demonstrated the intrinsic complexity in using the kinetic data for prospect design for hit/lead optimization. Correlations with biochemical data and structural information will be presented as well as our perspectives on where we are at on harnessing the power of kinetic profiling in drug discovery.

## **MEDI 232**

### **Importance of binding kinetics on *in vivo* target occupancy**

**Elizabeth de Lange**, *ecmdelange@lacdr.leidenuniv.nl*. Research Division of Systems Biomedicine and Pharmacology, Leiden University, Leiden, Netherlands

For any drug that is administered to patients or being developed, it is essential that the time course of its effects can be predicted to ensure rational drug therapy and drug development. After its administration, the time course of the effect of a drug can be influenced by all processes that constitute the complex system of the human body. Our

research aimed to elucidate how drug-target binding kinetics, in conjunction with plasma pharmacokinetics, tissue distribution kinetics, endogenous ligands competition, kinetics of signal transduction, target turnover, and homeostatic feedback mechanisms, determine the *in vivo* time course of drug action.

This presentation will deal with examples that indicate how and when the association rate constant (*k<sub>on</sub>*) and dissociation rate constant (*k<sub>off</sub>*) value may influence the duration of target occupancy, the selectivity for the therapeutic target compared to a secondary target, and how binding kinetics of drug and endogenous compound determine target occupancy.

It is concluded that the *in vivo* context is important for the contribution of drug-target binding kinetics relative to other processes that govern the *in vivo* time course of drug action.

### **MEDI 233**

#### **Role of free ligand conformations in ligand binding kinetics: AstraZeneca case studies**

**Amber Balazs**, *amber.balazs@astrazeneca.com*. AstraZeneca, Waltham, Massachusetts, United States

Medicinal chemistry has developed a rich tool box for conformational control of small molecules, including: methylation and creation of chirality, macrocyclization, atropisomerism, and the use of stereo-electronic and steric effects. Using free ligand conformational studies in drug design workflows, the first objective is to guide design hypotheses towards ligands that will adopt preferentially the bioactive conformation, eliminating potentially lower energy non-bioactive conformations. Highly stable free ligand molecular conformations that do not mimic the bioactive conformations in solution in fact, lead to ineffective ligand protein collisions and energy penalties on target binding. We showcase how to use simple 1D NMR ligand signatures and biophysical data to guide ligand conformational control designs. Specifically, we will show how we can draw **Structure Kinetics Relationships** when both the protein and the free ligand structural information is available.

### **MEDI 234**

#### **Design of antibiotics for tuberculosis**

**Courtney C. Aldrich**, *aldri015@umn.edu*. Medicinal Chemistry, University of Minnesota, Minneapolis, Minnesota, United States

Tuberculosis (TB) superseded HIV as the leading cause of infectious disease mortality worldwide in 2015 and TB shows no indication of relinquishing this notorious distinction. The obligate pathogen *Mycobacterium tuberculosis* (*Mtb*) has evolved over millennia to

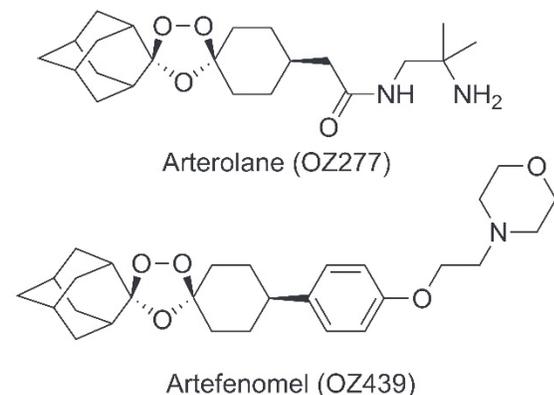
evade and co-opt host immune responses to establish a persistent infection. Consequently, antimicrobial therapy for even the simplest drug-susceptible TB involves prolonged treatment for six to nine months employing a combination regimen of four drugs: isoniazid, rifampicin, ethambutol, and pyrazinamide. Drug-resistant TB (DR-TB) or co-morbidity with the chronic diseases diabetes and HIV, further complicates the management of TB. Motivated by the need to combat DR-TB, shorten the treatment duration, and improve adherence, researchers have sought to identify vulnerable metabolic pathways for drug development. We will describe our efforts to design small-molecules targeting several critical biochemical pathways in iron acquisition and cell wall biogenesis as well as the design of antibiotics that overcome resistance through rationale design.

## MEDI 235

### Award Address (ACS Award for Creative Invention sponsored by the ACS Corporation Associates). Antimalarial ozonides

**Jonathan L. Vennerstrom**, *jvenners@unmc.edu*. Univ Nebraska Med Ctr 986025, Omaha, Nebraska, United States

The discovery of the endoperoxide sesquiterpene lactone artemisinin in 1979 initiated a new era in malaria chemotherapy. The peroxide bond in artemisinin is essential for activity, suggesting a chemistry-driven mechanism of action. The semisynthetic artemisinins are important antimalarial drugs because they rapidly reduce parasite burden and have good therapeutic indices, but their short half-lives require three-day treatment regimens in combination with longer-acting antimalarials to maximize cure rates. With this in view, many synthetic peroxide antimalarials have been prepared. Yet, identification of synthetic peroxides that are easily synthesized, inexpensive, and with good biopharmaceutical properties has been surprisingly difficult. In this talk, we highlight the discovery of the antimalarial ozonides (1,2,4-trioxolanes) arterolane (OZ277) and artefenomel (OZ439). The former was registered in India as a combination product with piperazine (Synriam) and the latter is in Phase IIb trials.



## MEDI 236

### Modulating host proteostasis to restrict viral adaptation

**Matthew Shoulders**, *mshoulde@mit.edu*. Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States

Progress in understanding the roles of the human proteostasis network in evolution at the host-pathogen interface will be presented. For example, we discovered that the biophysical consequences of host chaperone depletion very strongly reduce the ability of influenza to escape innate immune system factors. Key mutations that helped drive the pathogenicity of the 1918 Spanish Flu rely on host chaperones for their fitness. The connections drawn between host proteostasis and viral evolution have potentially important implications for issues including viral host-switching, vaccine development, and the design of improved antiviral therapeutic strategies.

## MEDI 237

### Small-molecule modulation of HSP60/10 chaperonin systems: A therapeutic strategy over 100 years in the making?

*Mckayla Stevens*<sup>1</sup>, *Sanofar Abdeen*<sup>1</sup>, *Anne-Marie Ray*<sup>1</sup>, *Alex Washburn*<sup>1</sup>, *Siddhi Chitre*<sup>1</sup>, *Jared Sivinski*<sup>2</sup>, *Yangshin Park*<sup>1</sup>, *Quyên Hoang*<sup>1</sup>, *Eli Chapman*<sup>2</sup>, **Steven Johnson**<sup>1</sup>, *johnstm@iu.edu*. (1) Indiana University School of Medicine, Indianapolis, Indiana, United States (2) The University of Arizona, College of Pharmacy, Tucson, Arizona, United States

The over-arching theme of our research is to determine whether or not small molecule modulation of HSP60/10 chaperonin systems is a viable therapeutic strategy for a number of indications. Our initial studies have focused on targeting the chaperonin systems of infectious organisms as an antibiotic strategy. While we recently reported promising results for two inhibitor series that are cytotoxic to *Trypanosoma brucei* parasites and *Staphylococcus aureus* bacteria, a concern for this strategy is the potential for deleterious effects against the human HSP60/10 homolog. Helping to alleviate this concern, we found that closantel, rafoxanide, and suramin are actually potent inhibitors of human HSP60/10, yet they are used therapeutically as anthelmintics in veterinary medicine (closantel and rafoxanide) and as a first-line treatment for *T. brucei* infections in humans for over 100 years (suramin). These unexpected findings prompted us to investigate whether other drugs may also inhibit HSP60/10 chaperonin systems. In a recent screen, we discovered a surprisingly high hit rate (2-3%) from a library of ~3,900 known drugs, natural products, and bioactive compounds. Confirmatory screening revealed that hits were nearly equipotent against the *Escherichia coli* chaperonin system, called GroEL/ES, and human HSP60/10. While our accumulating results support the notion that inhibiting human HSP60/10 *in vitro* may not be dire to the clinical development of chaperonin-targeting antibiotics, they raise some intriguing questions. For instance, have researchers unknowingly been

developing chaperonin-targeting therapeutics over the past couple centuries? Has nature developed a similar strategy of targeting chaperonins as a defense mechanism, or for other purposes? What contribution does targeting HSP60/10 chaperonin systems make to the bioactivities of these drugs and natural products? Our current and future studies are geared towards elucidating the mechanisms of action of chaperonin inhibitors to help shine light on such mysteries.

## **MEDI 238**

### **Targeting protein-protein interactions to treat misfolding diseases**

**Jason E. Gestwicki**, *jason.gestwicki@ucsf.edu*. *Pharmaceutical Chemistry, University of California at San Francisco, Moss Beach, California, United States*

Many inherited protein misfolding diseases, such as cataract and cystic fibrosis, are caused by mutations that destabilize the target protein. One approach to potentially treat these diseases is to identify “correctors” that bind to the mutant and restore its lost stability. In addition, such molecules can be useful probes for understanding the molecular origins of the folding defect. Our group is working to create high throughput differential scanning fluorimetry (HT-DSF) methods to rapidly identify potential correctors. In our first model, we screened a cataract-associated mutation in alpha-crystallin by HT-DSF to identify molecules that limit misfolding and aggregation. After a medicinal chemistry campaign, we found that the best molecules bound to the native, dimeric state of the alpha-crystallin and that it did not bind to the misfolded or amyloid structures. In turn, this compound partially reversed aggregation of this target in vitro and in multiple animal models. From a mechanistic perspective, we used these compounds revealed the reversible aggregation of alpha-crystallin, which is unusual amongst the amyloid-prone proteins. Inspired by this concept, we have been building next-generation HT-DSF approaches that improve sensitivity, scope and scale.

## **MEDI 239**

### **Award Address (E. B. Hershberg Award for Important Discoveries in Medicinally Active Substances sponsored by the Merck Research Laboratories). Adapting the chemistry and/or biology of proteostasis to ameliorate aggregation-associated degenerative diseases**

**Jeffery W. Kelly**, *jkelly@scripps.edu*. *BCC 265, Scripps Rsrch Inst, La Jolla, California, United States*

The cellular protein homeostasis, or proteostasis network, regulates proteome function by controlling ribosomal protein synthesis, chaperone and chaperonin mediated protein folding, protein trafficking, proteasome and lysosomal protein degradation and related processes. Stress responsive signaling pathways match proteostasis network capacity with demand in each subcellular compartment to maintain or alter cellular homeostasis. The beginning of the seminar will focus on how the proteostasis network can be

adapted pharmacologically through stress responsive signaling pathway activators to alleviate gain-of-toxic-function diseases, including light chain amyloidosis and the transthyretin amyloidoses, where excessive secretion of misfolding and aggregation of proteins leads to a degenerative phenotypes. We will also cover our efforts towards the discovery of autophagy activators for ameliorating proteinopathies. Autophagy activators are envisioned to be generally useful for ameliorating multiple neurodegenerative diseases based on human genetic evidence. These strategies will be contrasted with high affinity small molecule binding to the normally folded structural ensemble of an aggregation-prone protein inside and/or outside of the cell to stabilize the native state, lowering the population of misfolded, misassembly competent states that lead to aggregates, including amyloid fibrils. Our progress towards discovering transthyretin kinetic stabilizers will be covered, as will the clinical efficacy of tafamidis, a transthyretin kinetic stabilizer approved for use in 37 countries for the amelioration of polyneuropathy. The recently completed transthyretin phase 3 tafamidis cardiomyopathy clinical trial (0 vs 20 mg vs 80 mg QD, 441 patients) met its primary endpoint, ( $P=0.0006$ ) demonstrating a statistically significant reduction in the combination of all-cause mortality and frequency of cardiovascular-related hospitalization in the intent-to-treat population at 30 months. That dramatically slowing the process of aggregation slows neurodegeneration and cardiomyopathy provides strong evidence for the amyloid hypothesis, the notion that the process of transthyretin aggregation causes post-mitotic tissue destruction.

## **MEDI 240**

### **Ras proteins in normal cells and in human disease**

**Frank P. McCormick**<sup>1,2</sup>, [frank.mccormick@ucsf.edu](mailto:frank.mccormick@ucsf.edu). (1) UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States (2) Frederick National Laboratory for Cancer Research, Frederick, Maryland, United States

The KRAS protein is frequently mutated in human cancer, leading to oncogenic forms that contribute directly to more than one million deaths per year. Currently, no drugs are available that target KRAS directly or work effectively on KRAS cancers, such as pancreatic cancer and lung adenocarcinoma. The KRAS protein consists of a highly conserved G-domain and C-terminal region that targets KRAS to the plasma membrane. The G-domain does not contain active sites that are available for small-molecule based therapeutic approaches. The C-terminal region is thought to be unstructured and, again, not suitable for traditional medicinal chemistry approaches. Nevertheless, progress is being made on finding compounds that bind and inactivate this major oncoprotein. Compounds that bind covalently to the G12C mutation in KRAS are already undergoing clinical trials. Compounds that bind to KRAS directly, identified using NMR-based fragment screening and Second Harmonic Generation have been reported. We have identified compounds that bind covalently to the C185 residues of KRAS 4B, the site of prenylation. These compounds prevent KRAS processing and inhibit proliferation on KRAS-dependent cells in culture. They bind to a novel pocket that is formed when the C-terminal binds to the G-domain. Compounds bind non-covalently

to this pocket and then react covalently and irreversibly with C-185 through electrophilic attack. The existence of this pocket was predicted using Molecular Dynamic simulations and by in silico docking and confirmed using NMR and SAXS (Small Angle XRAY Scattering). We have also identified compounds that bind covalently to residue H95 on KRAS, an amino acid that is unique to KRAS relative to other members of the RAS family. These specific binders offer the opportunity of targeting KRAS for degradation or disrupting the proteins' function. Progress in developing these approaches will be discussed.

## **MEDI 241**

### **Small-molecule inhibitors of mutant RAS-effector protein interactions derived using an intracellular antibody fragment**

**Terry Rabbits**<sup>1,2</sup>, *terence.rabbits@imm.ox.ac.uk*. (1) Weatherall Institute of Molecular Medicine, Oxford, United Kingdom (2) Molecular Haematology, University of Oxford, Oxford, United Kingdom

Mutation in RAS family members is among the most frequent in human cancer and the mutant RAS proteins are tumour-specific proteins for therapy. We have previously selected an intracellular antibody fragment that binds to mutant forms of KRAS, NRAS and HRAS. We have used the intracellular antibody fragment macrodrug to demonstrate that blocking RAS-effector interaction-dependent signal transduction prevents tumour initiation and overt tumour growth in mouse preclinical models. By employing the binding of the anti-RAS intracellular antibody fragment to KRAS as a starting point, we have derived compounds that bind to RAS, using the fragment as a competitor, in a small molecule library screen. We have identified compounds that bind RAS where the antibody binds and used X-ray crystallography structure-based design to increase the potency of a chemical series that interacts with RAS inside cells, prevent RAS-effector PPI and inhibits endogenous RAS-dependent signaling. In addition, we have developed a new macrodrug that has the potential to be used to screen for KRAS-specific chemical series using similar competition approaches. Our results demonstrate a general approach for developing compounds for any target molecule using intracellular antibody fragments or from other form of macrodrug.

## **MEDI 242**

### **Discovery of small-molecule inhibitors of GTP bound KRAS<sup>G12C</sup>**

**Adrian L. Gill**, *15adrian.gill@gmail.com*. Chemistry Dept, Revolution Medicines, Redwood City, California, United States

KRAS<sup>G12C</sup> is a common driver oncogene of non-small cell lung cancer where it is estimated to exist in ~12% of lung carcinomas. Although small molecules targeting GDP bound, inactive KRAS<sup>G12C</sup> have shown efficacy in KRAS<sup>G12C</sup> preclinical models, we envisioned that directly targeting the active GTP-bound form of KRAS<sup>G12C</sup> would be the

preferred route of pharmacological inhibition of KRAS<sup>G12C</sup> with therapeutic advantages.

We have identified proprietary ‘beyond rule of five’ small molecule compounds that selectively and covalently inhibit GTP bound KRAS<sup>G12C</sup>. Mechanistically inspired by natural products such as sanglifehrin, our inhibitors first bind to a presenter protein cyclophilin A (CYPA) to form a binary complex. This binary complex then recognizes and binds to GTP bound KRAS<sup>G12C</sup> forming a ternary complex that inhibits downstream signaling.

Structure-based drug design efforts led to the discovery of potent and highly selective covalent inhibitors of GTP bound KRAS<sup>G12C</sup> that disrupt the KRAS<sup>G12C</sup> RAF interaction in biochemical assays. The ternary binding interactions were further characterized in  $k_{inact}/K_i$  analysis. These compounds demonstrate KRAS<sup>G12C</sup> and CYPA dependent cellular pERK inhibition and anti-proliferation effects that correlate well with their biochemical potencies. High selectivity in the cellular setting was confirmed by cysteinome profiling.

Importantly, the cellular pharmacology of GTP-KRAS<sup>G12C</sup> inhibitors is differentiated from GDP-KRAS<sup>G12C</sup> targeting compounds (e.g. ARS-1620) as the cellular activity of ARS-1620 is significantly attenuated by growth factor treatment to mimic the tumor microenvironment. Under the same conditions, the activity of GTP-KRAS<sup>G12C</sup> inhibitors is not affected.

To our knowledge, these are the first examples of mutant-selective KRAS inhibitors that target the GTP bound KRAS<sup>G12C</sup>. We are currently optimizing the drug-like properties of these covalent inhibitors and evaluating their activity in *in vivo* models.

## **MEDI 243**

### **Use of chemotype evolution to discover novel, potent, irreversible inhibitors of the oncogenic G12C mutant form of KRAS**

**Daniel A. Erlanson**<sup>1</sup>, [erlanson@gmail.com](mailto:erlanson@gmail.com), Tara Arvedson<sup>2</sup>, Victor Cee<sup>2</sup>, Ray Fucini<sup>1</sup>, Stig Hansen<sup>1</sup>, Jeff Iwig<sup>1</sup>, Joon Won Jeong<sup>1</sup>, John McCarter<sup>2</sup>, Sudi Sabet<sup>1</sup>, Andrew Sawayama<sup>1</sup>, Steven Sethofer<sup>1</sup>. (1) Carmot Therapeutics, Inc., Berkeley, California, United States (2) Amgen, Thousand Oaks, California, United States

Discovering innovative drugs depends on the ability to search vast chemical diversity efficiently. Carmot’s discovery technology, Chemotype Evolution, provides rapid access to chemical space relevant to a target of interest. Chemotype Evolution can swiftly and iteratively generate and screen libraries of small molecules or small molecule-peptide hybrids to produce drug leads.

The process starts by designing an anchor molecule or “bait”. The bait can be derived from known inhibitors, substrates, co-factors, peptides, hits from a fragment screen, or pharmaceutically acceptable “warheads”. In addition to its target-interacting

components, the bait contains a reactive functionality such that it can be linked individually with members of Carmot's 16,000+ fragment collection, which has been custom-built for the technology over several years focusing on diversity, lead-likeness, low molecular weight, and lipophilicity.

The linked molecules (each consisting of a bait and a fragment) constitute a custom library biased towards the target. This customized library is screened to detect binding or modulation of target activity in biochemical or cell-based assays. Chemotype Evolution does not screen pools of compounds; all compounds are synthesized and tested individually.

Hits identified from a first iteration screen can be fed into a medicinal chemistry program or converted into new baits and used in a second iteration screen to identify more potent molecules. Alternatively, fragment hits can be repurposed as baits to identify fragments that replace the initial anchor molecule. This process can be repeated as many times as desired. Chemotype Evolution is highly efficient, with tens of thousands of molecules screened per iteration, and does not require protein structural information.

This presentation will demonstrate how Chemotype Evolution, medicinal chemistry, and structure-based drug design were combined to discover novel irreversible small molecule inhibitors of the oncogenic G12C mutant form of KRAS that show potent biochemical and cell-based activity.

## **MEDI 244**

### **Structure-based drug discovery of MRTX1257: A selective, covalent KRAS G12C inhibitor with oral activity in animal models of cancer**

**Matthew A. Marx**<sup>1</sup>, [matt@marxpharma.com](mailto:matt@marxpharma.com), **Brian R. Baer**<sup>2</sup>, **Joshua K. Ballard**<sup>2</sup>, **James F. Blake**<sup>2</sup>, **Karyn Bouhana**<sup>2</sup>, **David Briere**<sup>1</sup>, **Laurence E. Burgess**<sup>3</sup>, **Michael Burkhard**<sup>2</sup>, **Harrah Chiang**<sup>1</sup>, **Mark J. Chicarelli**<sup>2</sup>, **James G. Christensen**<sup>1</sup>, **John P. Fischer**<sup>2</sup>, **Jill Hallin**<sup>1</sup>, **Macedonio J. Mejia**<sup>2</sup>, **Peter Olson**<sup>1</sup>, **Pavel Savechenkov**<sup>2</sup>, **Niranjan Sudhakar**<sup>1</sup>, **Tony P. Tang**<sup>2</sup>, **Guy P. Vigers**<sup>2</sup>, **Jay B. Fell**. (1) Mirati Therapeutics, San Diego, California, United States (2) Array BioPharma Inc., Boulder, Colorado, United States (3) Array Biopharma Inc, Boulder, Colorado, United States

The ability to effectively target mutated KRAS has remained elusive despite decades of research. By solving a highly informative set of ligand-complexed co-crystal structures coupled with iterative structure-based drug design, substituted tetrahydropyridopyrimidines were identified as selective, covalent inhibitors of mutant KRAS G12C. Key molecular interactions with the protein were optimized, with the potency of lead compounds evaluated by (a) mass spectrometric quantification of modified KRAS protein with and without treatment of test compounds, and (b) measurement of phospho-ERK in a whole-cell assay using H358 cells after incubation with test compounds for 3 hours. These efforts identified MRTX1257 as a potent and selective inhibitor of mutant KRAS G12C activity. This lead compound was utilized as a

research tool to aid in a deeper understanding of therapeutic susceptibility and KRAS dependence. MRTX1257 makes a covalent bond with the codon 12 cysteine and binds in the “Switch-2” pocket of KRAS, stabilizing the protein in the inactive, GDP-bound state. MRTX1257 contains a cyanomethyl group that displaces a water found near Gly10 in co-crystal structures of less potent analogs and contains an 8-methylnaphthyl group that fills a hydrophobic pocket resulting in enhanced potency compared with unsubstituted naphthyl analogs. MRTX1257 demonstrated rapid, irreversible modification of GDP-bound recombinant KRAS G12C and suppressed ERK phosphorylation with an  $IC_{50} = 1$  nM in the H358 cell line. In proteomics studies designed to assess global protein modification, MRTX1257 was shown to be highly selective for the targeted Cys12 of KRAS G12C versus other surface-exposed cysteine residues in NCI-H358 cells. Finally, at a 30mg/kg PO dose, MRTX1257 exhibited 31% bioavailability in mouse, demonstrated near complete inhibition of KRAS signaling in tumor tissue, and complete durable tumor regression in MIA PaCa-2 xenografts. The discovery of the tetrahydropyridopyrimidine series, the structure-based optimization to MRTX1257 and its preclinical potency, selectivity, ADME and efficacy profile will be presented.

## **MEDI 245**

### **Utility of acidic and basic compounds in medicinal chemistry**

**Patrick Walters**<sup>2</sup>, [wpwalters@gmail.com](mailto:wpwalters@gmail.com), Paul Charifson<sup>1</sup>. (1) Golden Road Consulting, Framingham, Massachusetts, United States (2) Relay Therapeutics, Cambridge, Massachusetts, United States

Attenuating charge can be a powerful tool when optimizing a drug candidate. The addition or removal of ionic groups can impact a wide range of properties including selectivity, solubility, hERG activity, and permeability. More than two-thirds of all existing drugs can be considered to be weak electrolytes and most drugs are estimated to be 60-90% ionized at physiological pH. The availability of public databases like ChEMBL and DrugBank enables us to evaluate the impact of ionization state on a range of physical properties and biological activities. This presentation will provide an updated overview of the impact of acidic and basic compounds in medicinal chemistry.

## **MEDI 246**

### **Toxicity arising from amine-containing drugs: Where do we draw the line?**

**Amit S. Kalgutkar**, [amit.kalgutkar@pfizer.com](mailto:amit.kalgutkar@pfizer.com). Medicine Design, Pfizer Worldwide Research and Development, Cambridge, Massachusetts, United States

Aliphatic/aromatic amine-containing drugs cover a broad range of marketed therapeutics and possess a wide spectrum of physicochemical properties. Retrospective analyses of their disposition characteristics in animals and human suggest that inclusion of basic amine centers in small molecule investigational drugs can confer several

pharmacokinetic benefits including enhanced oral absorption (due to increased aqueous solubility of corresponding salt forms) and long elimination half-lives (due to increased steady state distribution volumes). On the other hand, certain amine-containing drugs have gained dubious notoriety with respect to their off-target pharmacology (e.g., hERG channel blockade leading to cardiac arrhythmia) and preclinical toxicology, which in turn, is governed by their lipophilicity and basicity. Furthermore, there are several reports associating amine-containing drugs (and drug candidates) with metabolism-driven genotoxicity, drug-drug interactions, and even idiosyncratic adverse drug reactions. The lecture will summarize the current state-of-the-art on the facts and myths associating this otherwise attractive functionality with undesirable toxicological consequences, which has also led to its characterization as a "structural alert" in some cases.

## **MEDI 247**

### **Use of a pH-dependent conformational switching mechanism to enable the discovery of potent, selective and orally bioavailable CCR2 antagonists**

*Michael Yang, Zili Xiao, Robert J. Cherney, Andrew J. Tebben, Douglas G. Batt, Gregory D. Brown, Jing Chen, Mary E. Cvijic, Marta Dabros, John V. Duncia, Michael A. Galella, Daniel S. Gardner, Purnima Khandelwal, Soo S. Ko, Mary F. Malley, Ruowei Mo, Jian Pang, Anne V. Rose, Joseph B. Santella, Hong Shi, Anurag Srivastava, Sarah C. Traeger, Ragini Vuppugalla, Bei Wang, Songmei Xu, Rulin Zhao, Joel C. Barrish, Sandhya Mandlekar, Qihong Zhao, **Percy H. Carter**, percy.carter@bms.com. Bristol Myers Squibb, Princeton, New Jersey, United States*

The search for CC Chemokine Receptor-2 (CCR2) antagonists has been complicated by challenges in balancing molecular properties. Our own studies in a series of trisubstituted cyclohexyl compounds confirmed this trend, and largely led to molecules that exhibited either poor oral bioavailability or poor ion channel selectivity. Our attempts to address this problem through simple modification of physicochemical properties failed. Ultimately, we were able to advance the series through the installation of a protonation-dependent conformational switching mechanism. Subsequent optimization enabled the identification of orally bioavailable CCR2 antagonists with good oral bioavailability and high ion channel selectivity. We will discuss these efforts in the context of the discovery of two molecules that advanced to human clinical studies.

## **MEDI 248**

### **Carboxylic acids and their isosteres**

*Donna M. Huryn, huryn@pitt.edu. University of Pittsburgh, Allentown, New Jersey, United States*

Carboxylic acids are one of the most prevalent functional groups among fragments that bind to drug targets. This observation is not surprising given that they can participate in

various intermolecular interactions such as ionic, H-bonding and polar interactions. Despite their capacity to bind, and their typically excellent solubility, carboxylic acids can suffer from certain limitations, including poor passive permeability, and rapid metabolism. Therefore, medicinal chemists often replace this functional group with a carboxylic acid bioisostere with the intention of maintaining the desirable properties of the acid, but improving on its liabilities. We recently published the synthesis of and an extensive data set on a diverse set of carboxylic acid bioisosteres installed on an identical backbone. Specifically reported were experimental data on these isosteres' pKa, permeability, solubility, lipophilicity and plasma protein binding. The design of this study was meant to isolate the contribution of the bioisosteric fragment to these properties. This data set should be useful when medicinal chemists aim to replace an essential carboxylic acid within a larger scaffold, but require specific properties (e.g. pKa, lipophilicity) to be maintained or improved. The use and application of this data set will be presented, including 1) using computational chemistry to enhance and extend our understanding of carboxylic acid bioisosteres and 2) applying the data set to a drug discovery project aimed at identifying novel agents to treat acute kidney injury

## **MEDI 249**

### **Design and evaluation of surrogate structures of the carboxylic acid and other acidic functional groups as possible candidates for isosteric replacements**

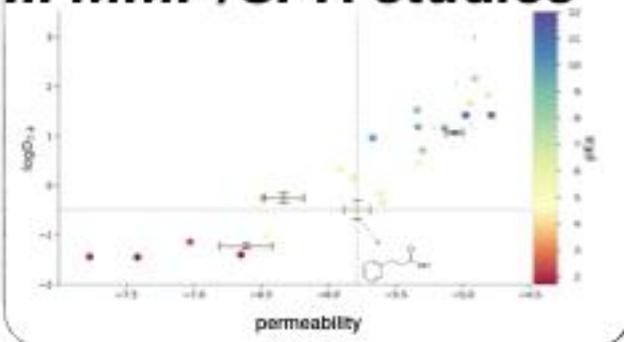
**Carlo Ballatore**, *cballatore@ucsd.edu*. Skaggs School of Pharmacy and Pharmaceutical Sciences, University Of California San Diego, La Jolla, California, United States

The replacement of the carboxylic acid moiety of a biologically active compound with a surrogate structure is a strategy frequently used in medicinal chemistry to identify new analogs with potentially improved pharmacokinetics and/or pharmacodynamics. Like all isosteric replacements, the success of this strategy is invariably context dependent and no individual bio-isostere can be considered optimal under all circumstances. Carboxylic acid bio-isosteres are typically designed to mimic the carboxylic acid functional group; however, it is the differentiation in structure and properties relative to the parent carboxylic acid compound that is ultimately critical to the success of this strategy. Although numerous carboxylic acid bio-isosteres have been described and successfully deployed in drug design, the identification of alternative surrogates that could complement the existing set with tunable/different properties remains a promising area of research in medicinal chemistry. A schematic of a possible general strategy for the evaluation of novel bio-isosteres is highlighted below. To illustrate this process, candidate bio-isosteres derived from the cyclopentane-1,3-dione scaffold and substituted four-membered ring heterocycles, such as oxetane and thietane, will be discussed.

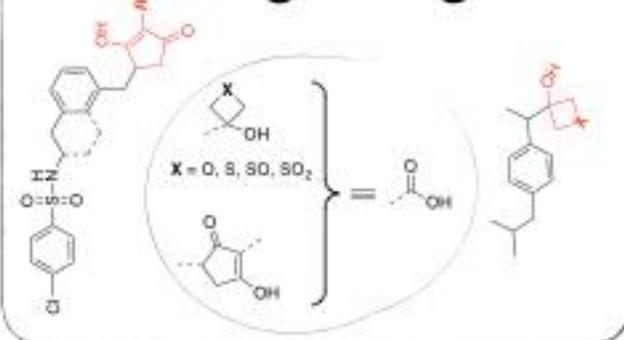
## I. Design of Surrogate Structures

- Rational, hypothesis driven
- Computational screenings

## II. MMP/SPR studies



## III. Drug Design



MEDI 250

Challenges with zwitterions: Discovery of zwitterionic CCR3 antagonist clinical candidates

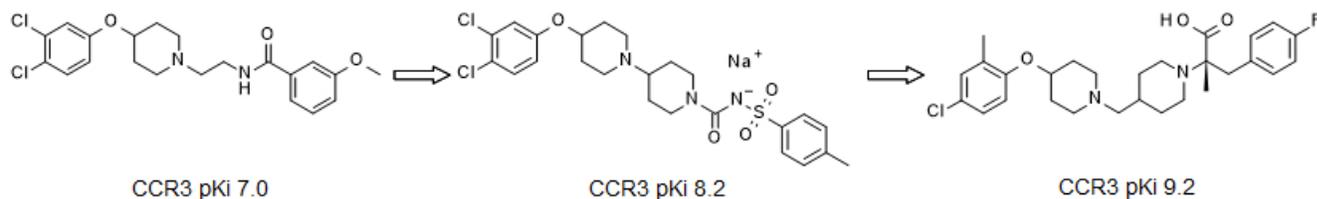
*Matthew W. Perry, matthew.perry@astrazeneca.com. RIA, AstraZeneca Gothenburg, Gothenburg, Sweden*

Asthma is a chronic respiratory condition that has been estimated to affect more than 350 million people worldwide with a sharp increase over recent years. Despite the availability of multiple medications asthma continues to represent a burden on the lives of many patients.

The CCR3 receptor is a seven transmembrane, G-protein-coupled receptor, which belongs to the CC chemokine family. In humans the receptor is expressed on eosinophils, basophils, airway epithelia, airway smooth muscle, dendritic cells, mucosal mast cells and Th2 cells. These cell types are believed to play a key role in the pathophysiology of asthma. Chemokine activation of the CCR3 receptor leads to chemotaxis and activation of cells. The CCR3 receptor is activated by a range of endogenous chemokines, which include eotaxin-1 (CCL11), eotaxin-2 (CCL24) eotaxin-3 (CCL26), MCP-4 (CCL13) and RANTES (CCL5). Levels of these chemokines are raised in allergic diseases such as asthma (atopic and non-atopic), allergic rhinitis and atopic dermatitis. As such antagonists of CCR3 are an attractive target for an oral treatment for asthma and other allergic diseases.

In this presentation I will describe the identification and optimisation of a series of phenoxy piperidine based CCR3 antagonists. In the course of this work we encountered many challenges, the first major one of which involved activity at the hERG potassium channel and which we solved by moving from a basic subseries to a zwitterionic one. The clinical results obtained with the first compound will be described.

The first identified compound suffered from variable bioavailability related to low solubility and we engaged in a process of scaffold-hopping to identify a subseries with improved physicochemical properties that had reproducibly high bioavailability and long *in vivo* half-life. Optimisation of the substituents around the molecule leading to the identification of the final clinical candidate will be described. Despite the excellent performance in *in vivo* models, this last compound and analogues suffered from reproductive toxicity issues that ultimately lead to closure of the programme. The relationship between the physicochemical properties and the observed toxicity will be discussed.



## MEDI 251

### ***In vitro* selection assays: On-DNA medicinal chemistry optimization of peptidomimetic ligands to chromodomains**

**Casey J. Krusemark**<sup>1</sup>, [ckrusema@purdue.edu](mailto:ckrusema@purdue.edu), **Sijie Wang**<sup>1</sup>, **Kyle Denton**<sup>2</sup>. (1) Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette,

*Indiana, United States (2) X-Chem Pharmaceuticals, Waltham, Massachusetts, United States*

In vitro selection assays of encoded libraries allow for a collective querying of function for many molecules simultaneously. This approach has several advantages over assays employed in traditional small molecule screening, including much improved throughput and dramatically lower cost. We present an evaluation of in vitro selection assays with regard to their application to discovery from DNA-encoded libraries (DELs). We explored both traditional as well as crosslinking-based selections to the chromodomains of the CBX family. We present a quantitative evaluation of selection assay robustness using DNA-linked ligands of known affinity. Statistical analysis of assays indicated low DNA tag bias and adequate robustness for both ligand discovery and determination of quantitative structure activity relationships. Implementation of optimal assays were employed with iterative "design, build, test" cycles of DNA-encoded libraries, which were assayed in parallel against all members of the CBX family. We present progress with isoform selective ligands in cellular assays, particularly with inhibition of growth of select cancer cell lines.

## **MEDI 252**

### **Development of novel transformations and structural templates to fuel medicinal chemistry discovery and optimization**

*Jennifer E. Golden, jennifer.golden@wisc.edu. Pharmaceutical Sciences, University of Wisconsin-Madison, Waunakee, Wisconsin, United States*

The identification and advancement of early hit compounds to promising leads and beyond in drug discovery depends on a synergy among synthetic chemistry development, medicinal chemistry optimization and biology expertise. Our group has focused on deriving unique, drug-like structural architecture that can be leveraged to study intricate cellular pathways and discover new therapeutic opportunities. The methodologies pioneered in our lab have been used to assemble a proprietary compound library that is rigorously maintained, tracked and assessed across diverse assay platforms in partnership with a network of skilled biologists representing virology, parasitology, bacteriology, cancer mechanisms, and metabolic and neurologic diseases. Early results emerging from the screening of some of these new scaffolds will be discussed, and a mature project will be highlighted that demonstrates the pivotal role that synthetic chemistry has played in defining a pharmacophore and engineering a modified scaffold worthy of preclinical evaluation.

## **MEDI 253**

### **Allosteric targeting of the Parkinson's-related protein LRRK2**

*Eileen J. Kennedy, ekennedy@uga.edu. Pharmaceutical and Biomedical Sciences, University of Georgia, Athens, Georgia, United States*

Parkinson's disease (PD) is a neurodegenerative disorder affecting more than five million people worldwide and only palliative treatment currently exists for the disease. Mutations in Leucine-rich repeat kinase 2 (LRRK2) are the most frequent cause of late-onset and idiopathic PD. LRRK2 belongs to the group of Roc proteins, which are characterized by the presence of a Ras-like G-domain (Roc), a C-terminal of Roc domain (COR), a kinase and several protein-protein interaction domains. LRRK2 has a complex activation mechanism, involving intra-molecular signaling, dimerization and protein-protein interactions. Significantly, several PD mutations in LRRK2 have been linked to decreased GTPase activity and increased kinase activity. However, it is not well understood how LRRK2 activity is regulated and how mutations in nearly every domain of the protein can alter the protein activity and function. Further, although mutations in LRRK2 are the most frequent cause of late-onset and idiopathic PD, each of the different but commonly occurring PD mutations in LRRK2 likely trigger different defects in LRRK2 function. As a strategy to investigate LRRK2 regulation and function, we sought to develop hydrocarbon-constrained peptides to disrupt LRRK2 dimerization. These dimerization disruptors were found to be cell permeable and could significantly inhibit LRRK2 dimerization and kinase activity in cells. Further, unlike many LRRK2 kinase inhibitors, these allosteric compounds do not induce altered localization of LRRK2 in cells. The inhibitors may serve as an effective strategy to downregulate LRRK2 kinase function in cells and also serve as templates for therapeutic agents for PD or assist in target validation.

## **MEDI 254**

### **Molecule-driven discovery for the identification of therapeutic leads**

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

The development of innovative synthetic strategies for the assembly of natural products enables the systematic evaluation of a molecules' biological function and can serve to generate novel chemical probes and therapeutic lead molecules. Given the dire need for novel scaffolds to fight the growing threat of antimicrobial resistance, the ability to access scaffolds with antibacterial activity and achieve deep-seated, pin-point modifications to their structures is critical. Herein, our efforts to utilize marine natural products as scaffolds for infectious disease drug discovery will be discussed, highlighted by our efforts on the lipoxazolidinones.

## **MEDI 255**

### **Caspase-2 inhibitors for the treatment of tauopathy-related cognitive decline**

*Kathryn M. Nelson<sup>1</sup>, kmnelson@umn.edu, Jessica Strasser<sup>1</sup>, Gurpreet Singh<sup>1</sup>, Benjamin Smith<sup>2</sup>, Karen Ashe<sup>2</sup>, Michael A. Walters<sup>3</sup>. (1) Medicinal Chemistry, University of Minnesota, Minneapolis, Minnesota, United States (2) Neurology, University of*

*Minnesota, Minneapolis, Minnesota, United States (3) Medicinal Chemistry, The University of Minnesota, Minneapolis, Minnesota, United States*

Academic drug discovery presents both opportunities and challenges beyond those encountered in an industrial setting. The same standards for safety and selectivity are required for any compound moving towards the clinic. Yet, many academic groups have a focused skill set that does not allow the multidisciplinary evaluation of lead compounds. The use of collaborations and contract laboratories becomes a must. In contrast to these challenges, academic groups have the ability to follow-up on active molecules that might be passed over in an industrial setting, and to explore nuances of chemical matter that can help inform decisions later in development. These obstacles and advantages also apply to the development of probes for target engagement and validation.

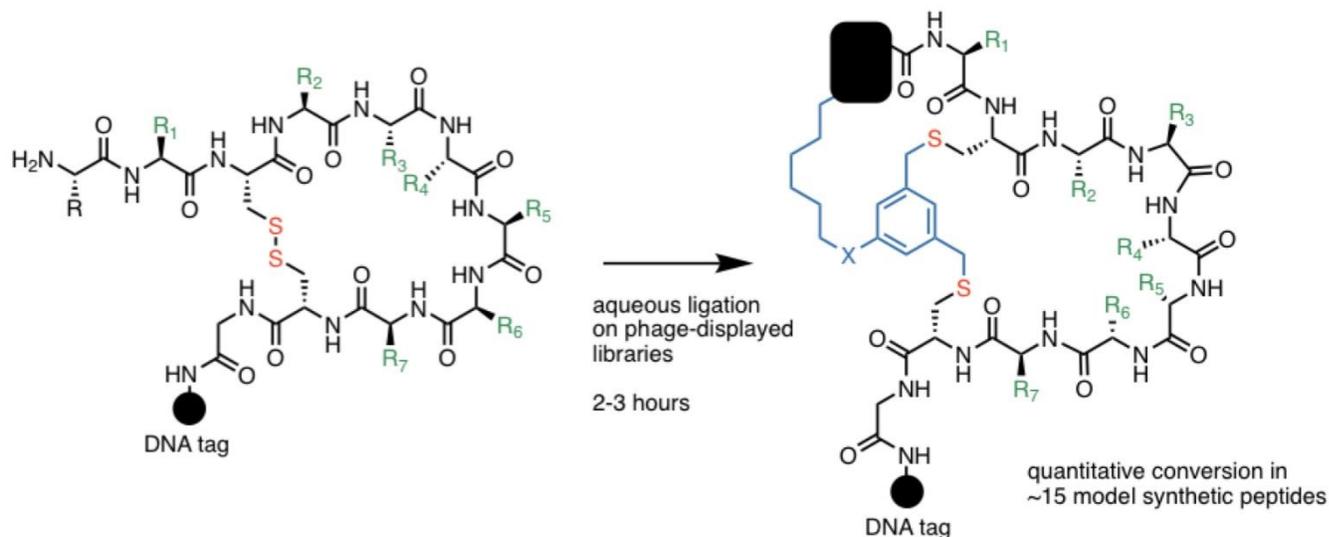
With this in mind, our collaborative work has revealed caspase-2 as a potential new target for the treatment of tauopathy-related cognitive decline. We have embarked on multiple routes toward lead chemical matter for the development of selective probes and inhibitors: substrate mimics, high-throughput screening campaigns, fragment screening campaigns, and structure-based drug design. Quality control and assay development/validation have been critical to project success. Details of our successes, failures, and learning experiences on these routes will be presented.

## **MEDI 256**

### **Novel genetically encoded cyclic and bicyclic architectures: Towards *de novo* discovery of bioavailable drugs**

*Ratmir Derda, ratmir@ualberta.ca. Chemistry, University of Alberta, Edmonton, Alberta, Canada*

The talk will describe genetically-encoded (GE) platform for discovery of macrocyclic and macrobicyclic peptides synthesized by aqueous late-stage functionalization of readily-available libraries of peptides displayed on phage. The structure of these chemical post-translational modifications can be encoded in the genome of phage using silent encoding technology. The resulting phage displayed libraries of "unnatural" macro(bi)cyclic peptides could be used to target either proteins or cells and tissues; the latter targets are difficult to address with DNA/RNA or bead-based libraries. Expanded chemical space offers value-added properties such as stability to aggressive protease environment and incorporation of unnatural chemotypes that are known to increase bioavailability.



## MEDI 257

### Discovery of AB680: A potent and selective CD73 inhibitor for cancer immunotherapy

**Kenneth V. Lawson**, [kvlawson@chem.ucla.edu](mailto:kvlawson@chem.ucla.edu), Jarek Kalisiak, Erick Lindsey, Eric Newcomb, Ehesan U. Sharif, Dillon Miles, Jenna Jeffrey, Manmohan Reddy Leleti, Ada Chen, Lixia Jin, Joanne Tan, Uli Schindler, Steve Young, Juan Jaen, Jay Powers. Arcus Biosciences, Inc., Hayward, California, United States

Extracellular adenosine (ADO) is present in high concentrations in the tumor microenvironment (TME) and exerts profound immunosuppressive effects on a variety of tumor-infiltrating leukocytes. Intra-tumoral generation of ADO depends on the sequential catabolism of ATP by two ecto-nucleotidases, CD39 (ATP→AMP) and CD73 (AMP→ADO). Inhibition of CD73 eliminates a major pathway of ADO production in the TME and can reverse ADO-mediated immune suppression. We will describe the evolution of a concise series of potent and selective CD73 inhibitors optimized via interrogation of structure activity relationships (SAR) and structure-based drug design. From this series, AB680 was identified as a highly potent, reversible and selective inhibitor of both soluble and cell-bound CD73 ( $IC_{50} < 0.01$  nM on human CD8<sup>+</sup> T cells). X-ray crystallography of hCD73-AB680 co-crystals confirms that AB680 binds to the closed form of the enzyme at its active site and identifies specific inter-molecular interactions responsible for the approximately 1,000,000-fold greater affinity of AB680 relative to the enzyme's substrate, AMP. AB680 potentially reverses AMP and ADO-mediated suppression of human immune cell function *in vitro* and has demonstrated antitumor activity in xenograft mouse models. The high potency of AB680 is complemented by excellent pharmacokinetic properties. AB680 has demonstrated very low clearance and long half-lives across preclinical species, resulting in a PK profile

suitable for long-acting parenteral administration. AB680 is currently being evaluated in Phase 1 clinical trials.

## **MEDI 258**

### **Identification and characterization of LHC165, a TLR7 agonist designed for localized intratumoral therapies**

**German Cortez**<sup>1</sup>, [acortez@gnf.org](mailto:acortez@gnf.org), **Steven Bender**<sup>1</sup>, **Jonathan Deane**<sup>1</sup>, **Nora Eifler**<sup>2</sup>, **Shailaja Kasibhatla**<sup>2</sup>, **Chun Li**<sup>2</sup>, **Shifeng Pan**<sup>3</sup>, **Nehal Parikh**<sup>2</sup>, **Tom Wu**<sup>2</sup>. (1) *Discovery Chemistry, Genomics Institute of the Novartis Research Foundation, San Diego, California, United States* (2) *Novartis Pharma AG, Basel, Switzerland* (3) *GNF, San Diego, California, United States*

Checkpoint inhibition has transformed immunotherapy by alleviating T cell exhaustion in a subset of patients. However, an important component of effective immune targeting to expand the benefit of immune response requires engagement of both innate and adaptive responses. Our understanding of safe and effective engagement of the innate immune system is evolving, with multiple preclinical and clinical agents targeting pathways such as the Toll-like Receptors. Here we disclose the structure and preclinical activity of LHC165, a benzonaphthyridine TLR7 agonist that is adsorbed to aluminum hydroxide. The interaction between LHC165 and aluminum hydroxide allows for a slow release from the injection site resulting in improved efficacy in mouse models compared with free LHC165. This localization allows for immune activation at the site of the tumor and also results in lower systemic exposure and cytokine induction. Intratumoral studies in syngeneic preclinical studies show single agent activity and a benefit when dosed in combination with checkpoint blockade. LHC165 as a single agent and in combination with PDR001 is currently enrolling patients with advanced malignancies in CLHC165X2101.

## **MEDI 259**

### **Discovery of VNRX-7145: A broad-spectrum orally bioavailable beta-lactamase inhibitor (BLI) for highly resistant bacterial infections ("superbugs")**

**Christopher J. Burns**, [burns@venatorx.com](mailto:burns@venatorx.com), **Robert Trout**, **Allison Zulli**, **Eugen Mesaros**, **Randy Jackson**, **Steven Boyd**, **Bln Liu**, **Lisa McLaughlin**, **Cassandra Chatwin**, **Jodie Hamrick**, **Denis Daigle**, **Daniel Pevear**. *VenatoRx Pharmaceuticals, Malvern, Pennsylvania, United States*

A major mechanism of gram-negative bacterial resistance is the growing evolution and production of beta-lactamase enzymes that catalytically inactivate the superfamily of beta-lactam antibiotics. The recent spread of carbapenem-inactivating "superbugs" is causing increased global alarm due to the high mortality associated with corresponding infections. While intravenous agents have advanced against such resistant bacteria, there are no orally bioavailable counterparts to allow hospital step-down and outpatient

treatment. To address this medical need, an iterative program of medicinal chemistry and biochemical/microbiological profiling was used to identify an orally bioavailable broad spectrum beta-lactamase inhibitor, VNRX-7145, which is currently in clinical development. The combination of VNRX-7145 with a known orally bioavailable beta-lactam antibiotic has been shown *in vitro* and *in vivo* to rescue the latter's activity against key carbapenem-resistant enterobacteriaceae. This presentation will explore the medicinal chemistry optimization to VNRX-7145 from less active, non-bioavailable lead compounds.

## **MEDI 260**

### **Discovery of TAK-981, a first-in-class inhibitor of Sumo Activating Enzyme (SAE) in phase 1 clinical trials**

**Steven P. Langston**, *steve.langston@takeda.com*, Dylan England, Xingyue He, Dennis Huszar, Paul D. Greenspan. *Takeda Pharmaceuticals International Co., Cambridge, Massachusetts, United States*

SUMOylation is a reversible post translational modification that regulates protein function through covalent attachment of a SUMO (Small Ubiquitin like Modifier) protein. The SUMOylation cascade is analogous to the ubiquitination cascade and involves activation of a SUMO protein through an ATP-dependent process catalyzed by Sumo Activating Enzyme (SAE). Here we describe the identification of TAK-981, a mechanism-based inhibitor of SAE which forms a SUMO-TAK-981 adduct as the inhibitory species, within the catalytic site. Optimization of selectivity against related enzymes, as well as enhancement of mean residence time of the adduct, were critical to identification of compounds with potent cellular pathway inhibition and ultimately a prolonged pharmacodynamic effect in tumor models, culminating in the identification of the clinical molecule TAK-981.

In preclinical studies with TAK-981, we have found immune cells to be particularly responsive to SUMO pathway inhibition. *In vivo* treatment with TAK-981 in animal models was shown to promote an antitumor immune response characterized by induction of a Type I interferon response in immune cells. Inhibition of SUMOylation through TAK-981 may represent a novel, mechanistically unique, opportunity within the immune-oncology arena.

## **MEDI 261**

### **Exploring cryptic pockets formation in targets of pharmaceutical interest with enhanced sampling simulations**

**Francesco Luigi Gervasio**, *f.l.gervasio@ucl.ac.uk*. *Chemistry, University College London, London, London, United Kingdom*

“Cryptic” pockets are sites that are not visible on unliganded target proteins’ structures and only become apparent when a drug bind. They might offer a valid alternative to

classical substrate-competitive sites in otherwise “undruggable” targets, but their hidden nature makes it difficult to use standard structure-based or computer-aided drug discovery approaches. What is more, the molecular mechanism by which cryptic sites are formed is still debated. Here, we investigate the nature of the cryptic sites harboured by seven diverse, pharmacologically relevant targets and compare the performance of different enhanced sampling approaches, including our recently-developed SWISH. Sampling water interfaces through scaled Hamiltonians (or SWISH) is a Hamiltonian-replica-exchange-based method that improves the sampling of hydrophobic cavities by scaling the interactions between water molecules and protein atoms. Our simulations, whose cumulative sampling time was more than 200  $\mu$ s, help in clarifying the molecular mechanism of pocket formation and provide a solid basis for the choice of an efficient computational method. The induced-fit mechanism plays an important role in the opening of all the cryptic sites studied. Of the enhanced sampling methods tested, the combination of SWISH with small probes was the most efficient in exploring the cryptic sites.

## **MEDI 262**

### **Identifying and exploiting protein shape-shifting**

*Gregory Bowman, g.bowman@wustl.edu. Washington University School of Medicine, St. Louis, Missouri, United States*

Allosteric drugs are of increasing interest but many proteins are thought to lack druggable allosteric sites. Identifying cryptic allosteric sites in ‘undruggable’ proteins could provide a means to target them. However, such sites are often only discovered in tandem with the identification of a small molecule that binds and stabilizes the open form of the pocket. Here, I will introduce a pipeline that integrates atomically-detailed computer simulations and biochemical experiments to identify and target cryptic allosteric sites. First, Markov state models (MSMs) and adaptive sampling are used to identify cryptic pockets. Promising pockets are then experimentally tested with a thiol labeling assay. Next, a virtual screening method that accounts for protein conformational heterogeneity, called Boltzmann docking, is used to identify small molecules that are likely to bind structures of a cryptic pocket from our computational model. Finally, these compounds are tested experimentally. As a proof of principle, we have applied this pipeline to a classic target involved in antibiotic resistance, called  $\beta$ -lactamase, that is particularly pertinent because it has historically been viewed as an extremely rigid protein. However, we have found multiple cryptic allosteric sites in this system, and identified both allosteric inhibitors and activators. These results suggest application of this pipeline to proteins that are known to be more dynamic is likely to be highly fruitful.

## **MEDI 263**

### **Development of drug design methods and applications in first-in-class drug discovery**

**Jian Zhang**, *jzhang.dr@gmail.com*. School of Medicine, Shanghai Jiaotong University, Shanghai, China

Drug design method has been widely used to rationally create drug candidates, specially the combination of drug design, medicinal chemistry, and pharmacological evaluation helped more than 20 drugs reach the global market. However, more than 60% potential targets are still orphan due to their undruggable features. To make these targets druggable, we developed a series of drug design methods including recognition of protein-protein interaction, identification of allosteric site and allosteric drug screening to overcome the inaccessibility of the targets in the drug discovery. Inspired by the advantage of the methods, novel activators/inhibitors were discovered by our group in several drug targets and used to address the challenges of finely-tuned biological regulation and human disorder treatment and medicine, for example APC-Asef interaction inhibitor. The binding of APC to its receptor Asef relieves the negative intramolecular regulation of Asef and leads to aberrant migration in human colorectal cancer. Due to its crucial role in metastatic dissemination, the interaction between APC and Asef is an attractive target for anti-colorectal cancer therapy. Using an interface-induced method, we rationally designed a series of peptidomimetics that act as potent inhibitors of the APC interface. Crystal structures, biochemical, and cellular assays revealed that the peptidomimetics in the APC pocket inhibited colorectal cell migration by disrupting APC-Asef interaction. This work demonstrated the feasibility of using the APC-Asef interaction as a target to regulate colorectal cancer migration and provided the first class of protein-protein interaction inhibitors available for the development of APC-Asef signaling cancer therapeutics.

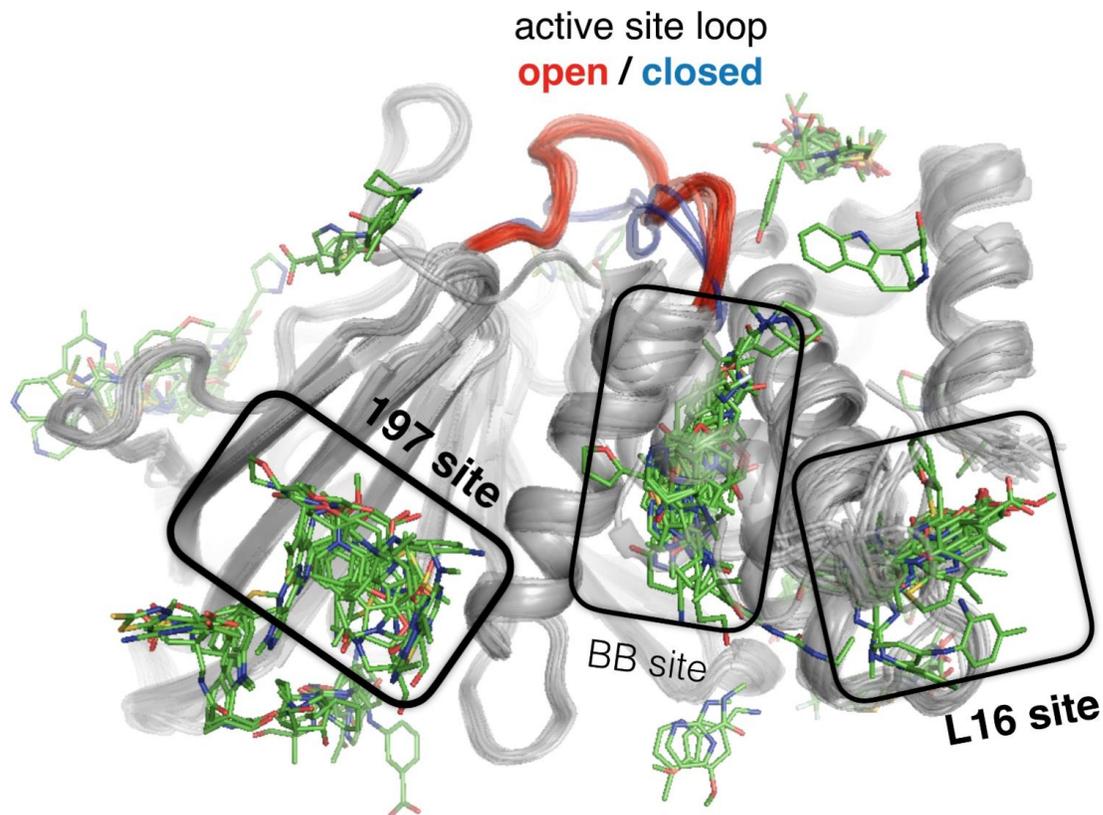
## **MEDI 264**

### **Remote control of a dynamic enzyme by leveraging small-molecule fragments**

*Tamar Skaist, Syeda M. Azeem, Daniel A. Keedy, daniel.keedy@gmail.com*. Structural Biology Initiative, CUNY Advanced Science Research Center, New York, New York, United States

Protein structures are fundamentally dynamic. Transitions between conformations are important for many biological processes, including allostery, in which a signal at one site in a protein effects a change elsewhere in the protein to regulate its function. Although allosteric inhibition is attractive from the therapeutic perspective, the inherent conformational heterogeneity involved makes it difficult to structurally reveal allosteric binding sites, much less target them with small molecules. The archetypal protein tyrosine phosphatase, PTP1B, exemplifies the challenges and opportunities associated with allosteric inhibition. It is a highly validated drug target and is known as the Achilles' heel of diabetes -- but its active site is highly charged and conserved among PTPs, raising limitations for active-site inhibitors. This has led some to refer to PTP1B as "undruggable". Recent work using multitemperature X-ray crystallography and multiconformer modeling revealed a surprisingly extensive allosteric network in PTP1B, including two previously untargeted allosteric sites. This work also used high-throughput

cocrystal structure determination to resolve in atomic detail 110 small-molecule fragments bound to PTP1B, including dozens in the new allosteric sites. However, the challenge remains to leverage these low-affinity, low-molecular-weight fragments into more potent allosteric modulators. Currently we are developing methods to exploit multiple experimentally resolved protein conformations and constellations of small-molecule fragment poses in flexible allosteric sites to enable "remote control" of PTP1B. Our work also has more general implications for understanding the mechanisms linking protein conformational heterogeneity to biological function.



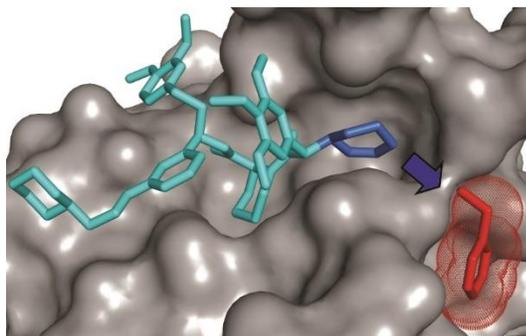
**MEDI 265**

**Selective FKBP51 inhibitors enabled by transient pocket binding**

**Felix Hausch**, [hausch@drugdiscovery.chemie.tu-darmstadt.de](mailto:hausch@drugdiscovery.chemie.tu-darmstadt.de). Technical University Darmstadt, Darmstadt, Germany

The FK506-binding protein 51 (FKBP51) plays a key role in human stress biology and contributes to major depression, obesity and chronic pain. Drug discovery for FKBP51 has been hampered by lack of selectivity against the highly homologous functional counter-player FKBP52. Here, we present the discovery of SAFit2, the first potent and highly selective inhibitor of FKBP51. SAFit2 achieves selectivity for FKBP51 by an unanticipated induced-fit mechanism that is much less favorable for FKBP52. By using this ligand we demonstrate that selective inhibition of FKBP51 enhances neurite

elongation in neuronal cultures and improves neuroendocrine feedback and stress-coping behavior in mice. Furthermore, SAFit2 ameliorated inflammatory pain-induced disabilities and diet-induced obesity. Our findings show how high selectivity can be achieved in the conserved class of FKBP proteins by exploiting differences in conformational dynamics. The resulting ligands allowed to validate FKBP51 inhibition as a novel pharmacological treatment option for depression, obesity and chronic pain.

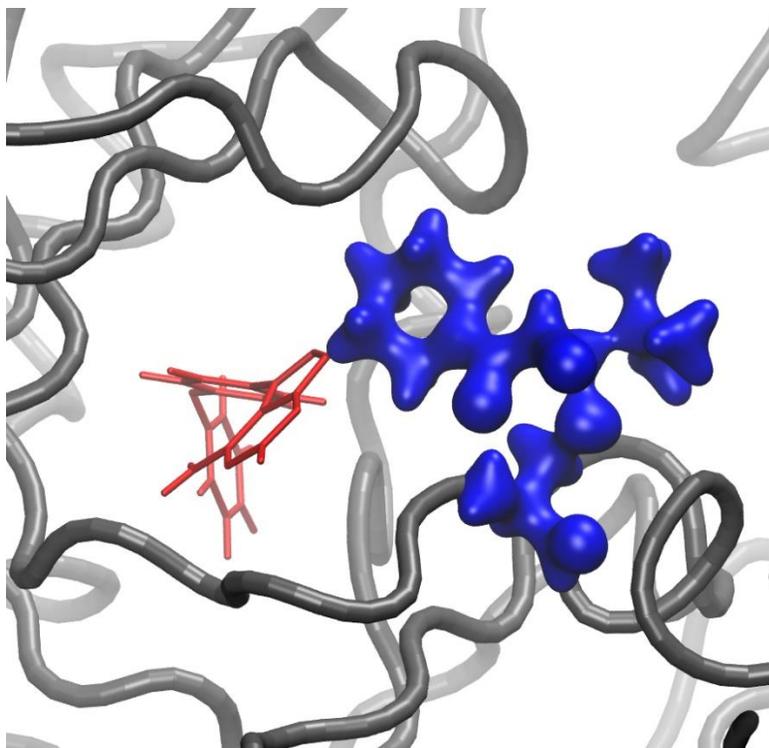


## MEDI 266

### Targeted covalent inhibition: Review of the field and recent advances

**Christopher N. Rowley**, [cnrowley@gmail.com](mailto:cnrowley@gmail.com). Dept of Chemistry, Memorial University of Newfoundland, St. Johns, Canada

Covalent modifier drugs have experienced a resurgence of interest with new models for their development. The chemical reaction barriers required for dissociation and association can result in exceptionally high residence times that can be tuned by varying the substituents of the “warhead” functional group of the inhibitor. Targeted Covalent Inhibitors (TCIs) achieve high selectivity and efficacy by optimizing both the non-covalent and covalent interactions with their targets. By targeting non-conserved cysteine residues in the active site for covalent-modification, high selectivity has been achieved in the highly-conserved kinase family. More recently, development of TCIs has extended beyond cysteine residues, targeting residues like lysine, tyrosine, and methionine. This talk will summarize recent advances in the field, including new computational and experimental methods for discovering covalent modifier drugs.



## MEDI 267

### Novel, boronic-acid-based, covalent lysine inhibitors

**Thomas A. McTeague**, [tamcteague@gmail.com](mailto:tamcteague@gmail.com), Neil Grimster, Alex Hird, Qibin Su. Medicinal Chemistry, Oncology, IMED Biotech Unit, AstraZeneca, Boston, Massachusetts, United States

Due to its prevalence and the nucleophilicity of its  $\epsilon$ -amino side chain, lysine represents an attractive target for covalent modification. Under physiological conditions, however, solvent exposed  $\epsilon$ -amino groups exist almost entirely in the protonated form, and are thereby rendered essentially non-nucleophilic. Furthermore, in the context of covalent inhibition, lysine's ubiquity presents a significant challenge in achieving modification site selectivity. Despite these obstacles, boronic acid carbonyls have been shown to act as reversible covalent binders of lysine residues through the formation of an imine adduct stabilized by the adjacent boronic acid. In application to the inhibition of the anti-apoptotic protein Mcl-1, these warheads, when incorporated into the scaffold of a known binder of Mcl-1, conferred an increase in both biochemical and cellular potency as well as affected their pharmacokinetic properties. Starting from a simple warhead, we sought to explore how the steric and electronic properties of these boronic acid carbonyls influence their reactivity, selectivity, and binding profiles with Mcl-1. These insights were then applied to explore the generality of boronic acid carbonyls as covalent binding motifs to target lysine residues in other proteins of interest beyond Mcl-1.

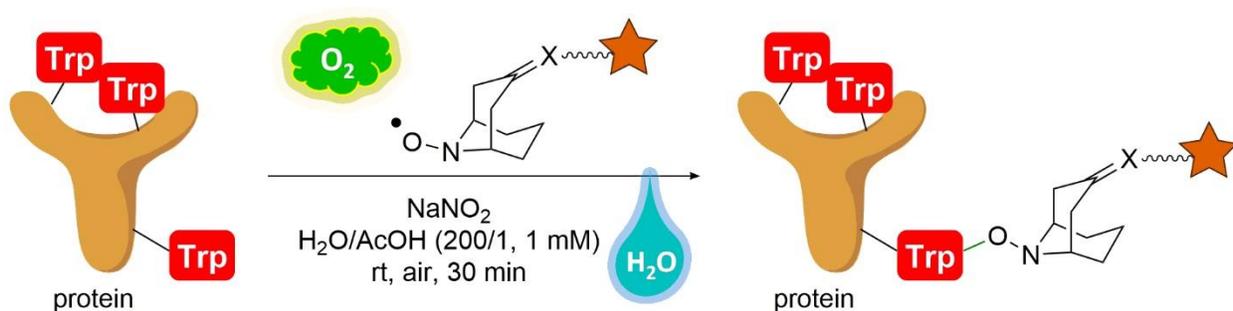
## MEDI 268

## Transition-metal-free, tryptophan-selective bioconjugation of proteins

**Motomu Kanai**, [kanai@mol.f.u-tokyo.ac.jp](mailto:kanai@mol.f.u-tokyo.ac.jp). Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan

Our long-term research goal is developing synthetic catalysts or reagents that surrogate enzymes, and using the synthetic catalysis in our body as a new paradigm of medicine (catalysis medicine). This research direction will in turn contribute to green synthesis of functional molecules, including drugs, in test tubes or larger-scale artificial reaction vessels. To do so requires powerful catalysts or reagents, which can functionalize stable, multifunctional molecules ranging from small molecules to biomacromolecules, under mild conditions and protecting group-free settings with synthetically-valuable selectivity (e.g. chemo-, target-, site-, and residue-selectivity).

Protein bioconjugation is a fascinating and very important target for methodology development along such direction. We are especially interested in protein modifications through modulating the redox states. We developed a tryptophan-selective bioconjugation of proteins using an organo-radical, keto-ABNO. I will discuss and update the strength and application of the method in my presentation.



## MEDI 269

### Mapping of immunomodulatory receptor protein interactions via photocatalytic-based proximity labeling of the cell surface

**Olugbeminiyi Fadeyi**, [olugbeminiyi.fadeyi@merck.com](mailto:olugbeminiyi.fadeyi@merck.com). Exploratory Science Center, Merck, Cambridge, Massachusetts, United States

Protein proximity labeling is a powerful technique for the unbiased assessment of protein-protein interactions or bystander proteins with effector function. A number of enzyme-based strategies have been developed over the last 10 years that either generate a reactive labeling species in proximity to the protein of interest, or physically "stamp" neighboring proteins. The success of these approaches has led to the consideration of other chemical-based methods that are smaller in size, can be temporally controlled, and/or can avoid harsh treatment conditions. One notable example is the use of photocatalytic-based transformations whereby protein residues

are labeled in the presence of visible light and a photocatalyst to alter protein activity and/or probe cellular function. To this end, we have successfully developed a visible light-activated tyrosine labeling strategy for temporally-controlled membrane protein proximity labeling. This talk will describe the successful demonstration of this novel labeling technology on different cell types and protein targets with the end goal of identifying proteins with effector function.

## **MEDI 270**

### **Protein functionalization platform based on selective reactions at methionine residues**

**Matthew Gaunt**, *mjg32@cam.ac.uk. Chemistry, University of Cambridge, Cambridge, United Kingdom*

Nature displays a remarkable ability to carry out site-selective post-translational modification of proteins, therefore enabling a dramatic increase in their functional diversity. Inspired by this, chemical tools have evolved for the synthetic manipulation of protein structure and function, and have become essential to the continued advancement of chemical biology, molecular biology and medicine. However, the number of chemical transformations suitable for effective protein functionalization is limited because the stringent demands inherent to biological systems preclude the applicability of many potential processes. Put simply, these chemical transformations often need to be selective at a single site on a protein, proceed with very fast reaction rates, operate under biologically ambient conditions and should provide homogeneous products with near perfect conversion. While many elegant bioconjugation methods exist at cysteine and lysine, we reasoned that a method targeting a less explored amino acid would significantly expand the protein functionalization toolbox. This presentation will detail the development of a multifaceted-approach to protein functionalization based on chemoselective labelling at methionine residues. By exploiting the unique electrophilic reactivity of a bespoke hypervalent iodine reagent, one can target the S-Me group in the side-chain of methionine. The bioconjugation reaction is fast, selective, operates at low  $\mu\text{M}$  concentrations and is complementary to existing bioconjugation strategies. Moreover, the new reaction produces a protein conjugate that is, itself, a high energy intermediate with reactive properties that can serve as a platform for the development of secondary, visible-light mediated bioorthogonal protein functionalization processes. Taken together, the merger of these approaches provides a versatile platform for the development of distinct transformations that can deliver versatile, information-rich protein conjugates directly from the native biomacromolecules.

## **MEDI 271**

### **Discovery of AMG 510, a first-in-human covalent inhibitor of KRAS<sup>G12C</sup> for the treatment of solid tumors**

**Victor Cee**, *victor.cee@amgen.com*. Medicinal Chemistry, Amgen, Thousand Oaks, California, United States

The *RAS* gene family encodes the small GTPase proteins NRAS, HRAS, and KRAS. *KRAS* is one of the most frequently mutated oncogenes in human cancer, with *KRAS*<sub>p.G12D</sub>, *p.G12V*, and *p.G12C* constituting the major mutational subtypes across lung, colon, and pancreatic cancers. Despite over three decades of research, indirect approaches targeting *KRAS* mutant cancers have largely failed to show clinical benefit, and direct approaches have been limited by the apparent 'undruggable' nature of *KRAS*. The cysteine at position 12 of *KRAS*<sup>G12C</sup> has emerged as a unique vulnerability that can be directly targeted with covalent inhibitors, and a small number of tool molecules have been disclosed. Our approach to *KRAS*<sup>G12C</sup> inhibitors involved iterative electrophile library design and screening campaigns. In one series, co-crystal structures of improved molecules revealed that a side-chain motion exposed a shallow groove that was occupied by ligand atoms. To further enhance potency and drug-like properties, scaffold hopping was employed, leading to a new series characterized by an *N*-aryl quinazolin-2(1H)-one core. Extensive optimization of this series was conducted, and a highly potent, selective, and well-tolerated covalent inhibitor of *KRAS*<sup>G12C</sup> was identified and nominated for clinical development as AMG 510. In preclinical *KRAS*<sup>G12C</sup> tumor models, AMG 510 rapidly binds irreversibly to *KRAS*<sup>G12C</sup> and provides a long duration of mitogen activated protein kinase (MAPK) pathway suppression, and when dosed orally once daily as a single agent is capable of inducing tumor regression. AMG 510 can also be combined safely and effectively with chemotherapy, targeted therapy, and immunotherapy in preclinical models. AMG 510 is, to the best of our knowledge, the first direct *KRAS*<sup>G12C</sup> therapeutic to reach human clinical testing, and is currently in a Phase I clinical trial evaluating safety, tolerability, PK, and efficacy in subjects with solid tumors with the *KRAS*<sub>p.G12C</sub> mutation (NCT03600883).

## **MEDI 272**

### **Discovery of ABBV-951 to enable continuous subcutaneous infusion of levodopa for the treatment of Parkinson's disease**

**Philip Kym**<sup>6</sup>, *phil.r.kym@abbvie.com*, **Eric A. Voight**<sup>1</sup>, **Russell Klix**<sup>2</sup>, **Peter Mayer**<sup>3</sup>, **Brian Enright**<sup>4</sup>, **Xiaochun Lou**<sup>3</sup>, **Teodora Moldovan**<sup>3</sup>, **Deanne Stolarik**<sup>5</sup>, **Mark A. Matulenko**<sup>1</sup>, **Alexander Hutters**<sup>2</sup>, **Jianguo Ji**<sup>2</sup>, **Maurizio Facheris**<sup>6</sup>, **Matthew Rosebraugh**<sup>7</sup>, **Janet Benesh**<sup>8</sup>. (1) Medicinal Chemistry, AbbVie, North Chicago, Illinois, United States (2) Process Research Department, AbbVie, North Chicago, Illinois, United States (3) Formulation Sciences, AbbVie, North Chicago, Illinois, United States (4) Preclinical Safety, AbbVie, North Chicago, Illinois, United States (5) DMPK, AbbVie, North Chicago, Illinois, United States (6) Neuroscience Development, AbbVie, North Chicago, Illinois, United States (7) Clinical Pharmacokinetics, AbbVie, North Chicago, Illinois, United States (8) Asset Leadership, AbbVie, North Chicago, Illinois, United States

In patients with advanced Parkinson's disease (APD), the efficacy of oral treatment options is significantly limited by the short oral absorption window and short half-life of levodopa (LD) in plasma. In addition, the tolerance of many patients to variability in dopamine levels in the brain decreases as the disease progresses and the therapeutic window narrows. The high variability in LD plasma levels with oral treatment leads to increasing motor complications over time, such as sudden "Off" time, peak exposure dyskinesia, and wearing-off, leading to significant unmet medical need in this patient population. ABBV-951 has been identified as a highly water soluble prodrug that enables the delivery of stable levels of LD through continuous subcutaneous infusion (CSCI). Preclinical proof of concept to achieve stable levels of > 5 mg/mL systemic levodopa in rats, dogs, and pigs via CSCI has been demonstrated with favorable tolerability. The combined PK characteristics and safety in preclinical species supported the further characterization of ABBV-951 in humans. The discovery of ABBV-951 and FIH data will be presented.

## **MEDI 273**

### **Structure guided discovery of S64315 (MIK665): a potent and selective MCL1 inhibitor**

*Andras Kotschy<sup>1</sup>, andras.kotschy@servier.com, Zoltan Szlavik<sup>1</sup>, Olivier Geneste<sup>2</sup>, James Murray<sup>3</sup>, James Davidson<sup>3</sup>, Roderick E. Hubbard<sup>3</sup>, Mike Wood<sup>3</sup>, Marton Csekei<sup>1</sup>, Attila Paczal<sup>1</sup>, Zoltan B. Szabo<sup>1</sup>, Szabolcs Sipos<sup>1</sup>, Agnes Proszenyak<sup>1</sup>, Balazs Balint<sup>1</sup>, Ana L. Maragno<sup>2</sup>, Didier Demarles<sup>4</sup>, Gaetane Le Toumelin-Braizat<sup>2</sup>, Maia Chanrion<sup>2</sup>, Alain Bruno<sup>2</sup>, Audrey Claperon<sup>2</sup>, Allan Surgenor<sup>3</sup>, Pawel Dokurno<sup>3</sup>, Natalia Matassova<sup>3</sup>, Ijen Chen<sup>3</sup>, Ben J. Davis<sup>3</sup>, Heather Simmonite<sup>3</sup>, Aurelie Studeny<sup>2</sup>, Gaelle Lysiak-Auvity<sup>2</sup>, Anne-Marie Girard<sup>2</sup>, Fabienne Grave<sup>2</sup>, Ghislaine Guascon<sup>2</sup>, Nicolas Cauquiel<sup>2</sup>, Frederic Colland<sup>2</sup>, John A. Hickman<sup>2</sup>. (1) Sevier Research Institute of Medicinal Chemistry, Budapest, Hungary (2) Oncology R&D Unit, Institut de Recherches Servier, Croissy Sur Seine, France (3) Vernalis (R&D) Ltd., Cambridge, United Kingdom (4) Technology Servier, Orleans, France*

MCL1 is highly expressed in a variety of human cancers (including those of hematopoietic, lymphoid and solid tumor origin) and is exploited by cancer cells to evade cell death and develop resistance to diverse chemotherapeutic agents. The function of MCL1 is to sequester pro-apoptotic BH3 domain containing members of the BCL2 family. Inhibition of these protein-protein interactions with small molecules has been difficult to achieve until recently. We have used fragment-based, structure-guided methods to develop MCL1 inhibitors, resulting in the clinical candidate S64315 (also named MIK665).

The presentation describes how we overcame the hurdles of this process, from establishing structural support and understanding its limitations, through choosing the appropriate pharmacological tools to assess our leads, to addressing the drug-likeness of our potential candidates.

## **MEDI 274**

## **Discovery of PF-06882961: A potent, orally bioavailable small molecule agonist of the GLP-1 receptor**

**David J. Edmonds**, *david.edmonds@pfizer.com*, David A. Griffith, Scott W. Bagley, Clare Buckeridge, Edward L. Conn, John M. Curto, David R. Derksen, Heather Eng, Mark E. Flanagan, Jean-Philippe Fortin, Matthew C. Griffor, Margaret V. Jackson, Amit S. Kalgutkar, Joseph B. Kuzmiski, Margaret S. Landis, Daniel J. Lettiere, Chris Limberakis, Spiros Liras, Paula M. Loria, Alan M. Mathiowetz, David W. Piotrowski, David Price, Lucy Stevens, Timothy P. Rolph, Roger B. Ruggeri, Aditi R. Saxena, Andrew H. Smith, David A. Tess, Liuqing Wei. Pfizer Worldwide R&D, Cambridge, Massachusetts, United States

Glucagon-like peptide-1 (GLP-1) receptor agonists comprise a growing class of agents that deliver unprecedented efficacy in diabetes. Members of the class are also approved or under development for obesity, and the class shows further promise for the treatment of non-alcoholic steatohepatitis (NASH). GLP-1 is a 30 amino acid peptide hormone that activates the GLP-1 receptor, a class B GPCR that is particularly challenging to stimulate with small molecules. To date, all approved agents are large peptide drugs that are administered by injection, negatively impacting both the patient experience and uptake of these highly effective medicines. We will report on a program to identify an oral, small molecule GLP-1 receptor agonist for the treatment of diabetes. An innovative hit identification strategy provided weak leads that were progressed through structure-activity exploration to achieve drug-like potency and ADME attributes, ultimately leading to the identification of PF-06882961 as a clinical candidate.

### **MEDI 275**

#### **Chemical biology impacting drug discovery**

**Christopher Am Ende**, *Christopher.amEnde@pfizer.com*. Pfizer Inc. , Mystic, Connecticut, United States

This presentation will describe the application of chemical biology probes towards the understanding of target engagement, selectivity/off-target identification and binding site ID across multiple drug discovery projects. A series of vignettes will be presented which include the use of clickable photoaffinity probes to identify off-targets of BACE inhibitors, evaluation of a series of cleavable linkers to aid in the binding site identification of gamma secretase inhibitors and profiling covalent adduct stability of irreversible MAGL inhibitors. Additional emphasis will be focused on the use of chemical biology monomer sets to support the rapid assembly of new probe compounds, as well as the development of new tools and technologies to further enable chemical biology in drug discovery.

### **MEDI 276**

## **Biological activity of ferrocenyl derivatives: Study of the effect of different core moieties and substituents on anticancer and antioxidant activity**

**Sara M. Delgado-Rivera**<sup>1</sup>, *saramdr2@gmail.com*, **Sebastian A. Henriquez Lopez**<sup>2</sup>, **Giovanny E. Pérez-Ortiz**<sup>1</sup>, **Abel Baerga-Ortiz**<sup>3</sup>, **Ingrid Montes-Gonzalez**<sup>1</sup>, **Dalice M. Pinero Cruz**<sup>4</sup>. (1) Chemistry, University of Puerto Rico - Río Piedras Campus, Las Piedras, Puerto Rico, United States (2) Chemistry, University of Puerto Rico at Rio Piedras, Bayamón, Puerto Rico (3) Biochemistry Dept, University of Puerto Rico-Medical Science Campus, San Juan, Puerto Rico, United States (4) Chemistry, University of Puerto Rico, Río Piedras Campus, San Juan, Puerto Rico, United States

In our research group we synthesized a variety of ferrocenyl compounds with different cores: chalcone, stilbene, and ethyne. We also prepared these compounds with different substituents in the phenyl group like amino, nitro, methoxy, fluorine, methylpyridinium, and others. These derivatives have been synthesized with simple and well known synthetic methodologies like Claisen-Schmidt and Heck reactions with moderate to good yields (35%- 99%). Our research interest is also focused on the biological applications of these compounds. For this reason, we study the biological activities of our compounds against some cancer cell lines such as MDA-MB-231, PC-3, HeLa, among others; and the cytotoxicity of the compounds against normal cells (MCR-5). Also, the radical scavenging properties of the compounds were explored by de DPPH assay to know their potential as antioxidants. Our aim with these studies is to establish some trends of different ferrocenyl cores and substituents with the biological activity results and apply these findings in the design of new drugs containing ferrocenyl moiety. The long-term goal is, after more advanced biological tests and studies, to develop better active compounds to treat cancer disease. The biological assays results and the trends showed by our compounds will be presented.

### **MEDI 277**

## **Structure-activity relationship of non-electrophilic naphthalene and isoquinoline based inhibitors of the KEAP1-NRF2 protein-protein interaction**

**Phillip Lazzara**<sup>1</sup>, *plazzara@uic.edu*, **Benjamin Richardson**<sup>1</sup>, **Brian David**<sup>1</sup>, **Haranatha R. Pottet**<sup>2</sup>, **Katherine Dye**<sup>4</sup>, **Sekhar Reddy**<sup>2</sup>, **Terry W. Moore**<sup>3</sup>. (1) Medicinal Chemistry and Pharmacognosy, University of Illinois Chicago, Chicago, Illinois, United States (2) Pediatrics, University of Illinois Chicago, Chicago, Illinois, United States (3) Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Chicago, Illinois, United States (4) UICentre for Drug Discovery, University of Illinois Chicago, Chicago, Illinois, United States

Chronic oxidative stress is implicated in a number of disease states such as multiple sclerosis, chronic wound healing, and chronic kidney disease. Upregulation of the cellular response to oxidative stress is promoted by a key transcription factor, Nuclear factor erythroid 2-related factor 2 (NRF2). A cysteine-rich sensor protein, Kelch-like ECH-associated protein 1 (KEAP1), represses NRF2's activity in the absence of

oxidative or electrophilic stressors by sequestering NRF2 and polyubiquitinating it, marking it for proteasomal degradation. Reaction of an electrophilic stressor with one of the cysteines on KEAP1 induces a conformational change in the KEAP1 structure that, most likely, does not allow for NRF2 ubiquitination. This allows for NRF2 to build up in the cytoplasm, translocate into the nucleus, and promote the transcription of detoxifying enzymes such as glutathione S-transferases (GST), NADPH:quinone oxidoreductase 1 (NQO1), and heme oxygenase 1 (HO1). Current therapies that target the KEAP1/NRF2 interaction are electrophilic in nature and behave as an electrophilic stressor to stimulate NRF2's transcriptional ability; however, electrophilic compounds may be prone to off-target effects that obscure their mechanism of action. Therefore, synthesis and optimization of a selective non-electrophilic inhibitor of the KEAP1-NRF2 interaction would be beneficial to understand the role of NRF2 in chronic inflammatory diseases. The work in our lab has focused on evaluating the structure activity relationship (SAR) of a known non-electrophilic inhibitor based on a 1,4-diaminonaphthalene scaffold, which we have modified to an isoquinoline. The work herein explores what portions of the compound's side arms are critical for binding to KEAP1 and address key issues of metabolic stability and solubility. Furthermore, cell-based assays have been conducted to evaluate the ability of our inhibitors to upregulate NRF2 target genes in keratinocytes. Lastly, we evaluated a subset of these compounds for their efficacy in expediting wound closure in diabetic mice.

## **MEDI 278**

### **Evolution-guided design of phosphatase inhibitors**

*Michael Hjortness<sup>1</sup>, Laura Riccardi<sup>2</sup>, Akarawin Hongdusit<sup>1</sup>, Alex Ruppe<sup>1</sup>, Edward Kim<sup>1</sup>, Mengxia Zhao<sup>3</sup>, Peter Zwart<sup>4</sup>, Banumathi Sankaran<sup>4</sup>, Haribabu Arthanari<sup>5</sup>, Marcelo Sousa<sup>6</sup>, Marco Devivo<sup>2</sup>, **Jerome M. Fox<sup>1</sup>**, [jerome.fox@colorado.edu](mailto:jerome.fox@colorado.edu). (1) Chemical and Biological Engineering, University of Colorado, Boulder, Boulder, Colorado, United States (2) Molecular Modeling and Drug Discovery Lab, Istituto Italiano di tecnologia, Genova, Italy (3) Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts, United States (4) Lawrence Berkeley National Laboratory, Berkeley, California, United States (5) Harvard Medical School, Boston, Massachusetts, United States (6) Biochemistry, University of Colorado, Boulder, Boulder, Colorado, United States*

The design of inhibitors that bind tightly and selectively to proteins represents a longstanding challenge of applied biophysics. This study uses a broad set of experimental and computational analyses of protein tyrosine phosphatase 1B (PTP1B), an important regulator of cell signaling and an elusive drug target, to show how natural evolutionary constraints on the structures of biomolecules can guide efforts in inhibitor design. Results suggest that abietic acid, a plant-derived secondary metabolite, can inhibit PTP1B by stabilizing its catalytically essential WPD loop in an inactive conformation, and they show that minor, evolutionarily accessible changes in the structures of abietane-type diterpenoids can significantly improve potency. A multidisciplinary evolutionary analysis, in turn, indicates that protein tyrosine

phosphatases share a conserved allosteric network that makes them susceptible to inhibitors that bind to poorly conserved regions. The diterpenoids and allosteric sites identified in this study provide new starting points for building inhibitors of PTPs—a class of enzymes that has long eluded drug design. The central findings support the notion that the evolutionary trajectories of secondary metabolites enable an efficient sampling of molecular structures likely to bind proteins, and they provide rigorous evidence that patterns of residue-residue coevolution within protein families can reveal sets of functionally conserved, yet structurally distinct allosteric sites.

## **MEDI 279**

### **Chemical tools to probe the function of TRIM33**

**Amy Scorah**<sup>1</sup>, amy.scorah@chem.ox.ac.uk, Larissa See<sup>1</sup>, Joseph Bluck<sup>1</sup>, Jessica Reynolds<sup>1</sup>, William McCoull<sup>2</sup>, Stuart J. Conway<sup>1</sup>. (1) Department of Chemistry, University of Oxford, Oxford, United Kingdom (2) AstraZeneca, Cambridge, United Kingdom

Tripartite motif-containing (TRIM) protein 33 possesses a tandem bromodomain and PHD finger at its C-terminus, and is involved in the PARP-dependent DNA damage repair pathway. The development of TRIM33 bromodomain ligands will help validate the concept that TRIM33 inhibitors will be synthetically lethal in situations where DNA damage is increased, similar to PARP inhibitors.

Based on a TRIM33 AlphaScreen™, a bromodomain ligand possessing a benzimidazolone core as the acetyl-lysine mimic (TRIM33 $\alpha$  IC<sub>50</sub> = 4.22  $\mu$ M; TRIM33 $\beta$  IC<sub>50</sub> = 10.6  $\mu$ M) was identified. This project has explored a diverse range of related analogues, using docking and molecular dynamics to guide design. A combination of AlphaScreen™ and WaterLOGSY NMR experiments have been used to evaluate binding. Extensive investigation has led to a deeper understanding of the key structural features of the TRIM33 bromodomain binding pocket and has resulted in the development of a ligand (TRIM33 $\alpha$  IC<sub>50</sub> = 2.48  $\mu$ M; TRIM33 $\beta$  IC<sub>50</sub> = 7.08  $\mu$ M) which is selective over close relative TRIM24, and also BRD4.

This project also explores targeted protein degradation of TRIM33 using proteolysis-targeting chimeras (PROTACs) to unveil the function of the whole protein. The TRIM33 bromodomain ligands will be linked to an E3 ubiquitin ligase warhead to recruit TRIM33 to the E3 ligase cereblon. The synthesis of the TRIM33 ligand and E3 ligase binding moiety with appropriate functional handles allows diversification of the linker to enable rapid optimisation.

The development of ligands for the bromodomain of TRIM33 in parallel with PROTACs for TRIM33 will highlight the differences between inhibition of the bromodomain and degradation of the whole protein, and thus reveal the relevance of TRIM33 and its bromodomain in disease.

## MEDI 280

### Effects of phosphate linker modifications on 2',3'-cyclic dinucleotide STING agonists

**Shawn P. Walsh**<sup>1</sup>, *shawn\_walsh@merck.com*, Michael D. Altman<sup>2</sup>, Brian M. Andresen<sup>3</sup>, Wonsuk Chang<sup>1</sup>, Anthony Donofrio<sup>3</sup>, Timothy J. Henderson<sup>3</sup>, James P. Jewell<sup>3</sup>, Chip Lesburg<sup>4</sup>, Jongwon Lim<sup>3</sup>, Hong Liu<sup>1</sup>, Min Lu<sup>3</sup>, Ryan Otte<sup>3</sup>, Jeremy Presland<sup>5</sup>, Dietrich Steinhuebel<sup>6</sup>, Brandon Taoka<sup>1</sup>, Quang Truong<sup>1</sup>, Wen-Lian Wu<sup>1</sup>, Samantha Perera<sup>5</sup>, Saso Cemerski<sup>7</sup>, Wes Trotter<sup>3</sup>, Jared Cumming<sup>1</sup>. (1) Department of Medicinal Chemistry, Merck & Co., Inc., Kenilworth, New Jersey, United States (2) Department of Computational Modeling & Informatics, Merck & Co., Inc, Boston, Massachusetts, United States (3) Department of Medicinal Chemistry, Merck & Co., Inc., Boston, Massachusetts, United States (4) Department of Structural Chemistry, Merck & Co., Inc., Boston, Massachusetts, United States (5) Department of Pharmacology, Merck & Co., Inc., Boston, Massachusetts, United States (6) Department of Discovery Process Chemistry, Merck & Co., Inc., Boston, Massachusetts, United States (7) Department of Immunology and Oncology, Merck & Co., Inc., Boston, Massachusetts, United States

In recent years, immuno-oncology therapies have emerged as attractive alternatives and / or supplements to traditional methods of cancer treatment. While checkpoint inhibitors and other immune therapies have enjoyed clinical success and improved patient outcomes, even gaining approval as front line therapy in some cases, opportunities for further progress remain. One such strategy with the potential to provide synergy with existing immunotherapies is activation of the innate immune system. To that end, activation of the Stimulator of Interferon Genes (STING) pathway by endogenous or synthetic STING agonists results in a cascade response ultimately resulting in STING-dependent activation of innate immune response and enhanced anti-tumor efficacy in pre-clinical murine models. To identify STING agonists suitable for development as novel therapeutics, our group started with the endogenous ligand for STING, cyclic guanosine monophosphate–adenosine monophosphate (2',3'-cGAMP) and embarked on a systematic investigation of SAR around modifications to that cyclic dinucleotide (CDN), including to the nucleobase, ribose, ribose substituents, phosphate linkers, and combinations thereof. A number of synthetic analogues from our group and others employ thiophosphates for both of the CDN linkages, which are well tolerated but their synthesis can produce up to four diastereomers owing to the chirality at the phosphorous center. This presentation will focus on exploration of combinations and permutations of phosphate, thiophosphate, and dithiophosphate linkages to reduce stereochemical complexity and streamline synthesis. We will report on the activity, stability, and *in vivo* efficacy of these novel STING agonists.

## MEDI 281

### 2NDEP highlights allosteric activation of the $\alpha 7$ nicotinic acetylcholine receptor

*Alican Gulsevin<sup>1</sup>, Clare Stokes<sup>2</sup>, Roger L. Papke<sup>2</sup>, **Marta Quadri<sup>1,2</sup>**, marta.quadri@chem.ufl.edu, Nicole Horenstein<sup>1</sup>. (1) Department of Chemistry PO Box 117200, University of Florida, Gainesville, Florida, United States (2) Department of Pharmacology and Therapeutics PO Box 100267, University of Florida, Gainesville, Florida, United States*

Activation of the  $\alpha 7$  nicotinic acetylcholine receptor typically occurs upon binding of agonists at the receptor orthosteric binding site and is characterized by intrinsically low open probability. Positive allosteric modulators (PAMs) reverse this limitation by binding in the transmembrane domain, which promotes prolonged receptor activity. While PAM effects are linked to the presence of an orthosteric agonist, ago-PAMs are able to evoke  $\alpha 7$  ion channel currents in the absence of orthosteric ligands via a direct allosteric activation (DAA) site in the extracellular domain. At present, allosteric agonists displaying DAA but not PAM activity have been not reported. We here identify 1,1-diethyl-4-(naphthalene-2-yl)piperazin-1-ium (2NDEP) as the first  $\alpha 7$  allosteric agonist that selectively activates  $\alpha 7$  via DAA with no intrinsic PAM component, as confirmed by the requirement of PAM co-application. Despite being formerly reported as an  $\alpha 7$  partial agonist potentiated by type II PAM co-application, our present investigation highlighted favorable docking and MMPBSA binding energies at the  $\alpha 7$  DAA site for 2NDEP. We therefore hypothesized that part of the PAM-potentiated responses observed for 2NDEP are ascribable to the coupling between the PAM with the DAA site rather than the orthosteric site. To verify this hypothesis, we tested 2NDEP on the  $\alpha 7$  Y93C and C190A mutants, which are known to be insensitive to orthosteric agonists but effectively activated by ago-PAMs like GAT107. 2NDEP acted as an antagonist of GAT107 on Y93C, and as an allosteric agonist of C190A when co-applied with the type II PAM PNU-120596. Moreover, co-application with the DAA site-selective antagonist 4-(2,3,5,6-tetramethylphenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide (2,3,5,6MP-TQS) nearly abolished the 2NDEP allosteric activity. These results were consistent with involvement of the DAA site and were further investigated in computational analyses. Overall, our findings reveal a novel mode for  $\alpha 7$  agonist activation via the DAA site and offer new structural insights to develop purely allosteric  $\alpha 7$  ligands.

## **MEDI 282**

### **Discovery of selective FactorD inhibitors targeting the alternative complement pathway**

***Rajeshri G. Karki<sup>1</sup>**, rajeshri.karki@novartis.com, James J. Powers<sup>1</sup>, David Belanger<sup>1</sup>, Donglei Liu<sup>1</sup>, Nan Ji<sup>1</sup>, Keith Jendza<sup>1</sup>, Christine Gelin<sup>1</sup>, Stefanie Flohr<sup>2</sup>, Edwidge Lorthiois<sup>2</sup>, Anna Vulpetti<sup>2</sup>, Aengus Mac Sweeney<sup>2</sup>, Karen Anderson<sup>3</sup>, Muneto Mogi<sup>1</sup>, Nello Mainolfi<sup>1</sup>. (1) Global Discovery Chemistry, Novartis Institutes for Biomedical Research, Cambridge, Massachusetts, United States (2) Novartis Pharma AG, Basel, Switzerland (3) Novartis Institutes for Biomedical Research, Cambridge, Massachusetts, United States*

Complement Factor D (FactorD), a highly specific S1 serine protease plays a central role in the amplification of the alternative complement pathway (AP) of the innate immune system. Dysregulation of AP activity predisposes individuals to diverse disorders such as age-related macular degeneration, atypical hemolytic uremic syndrome, membranoproliferative glomerulonephritis type II and paroxysmal nocturnal hemoglobinuria. In our quest to find low molecular weight FactorD inhibitors, a large number of chemically tractable starting points was generated through computational virtual screening, high throughput screening and fragment based screening methods. We embarked on an iterative cycle of rational structure-based design, synthesis and data driven validation of our hypothesis. This approach culminated in the discovery of an orally bioavailable, selective FactorD inhibitor with sustained oral and ocular efficacy in animal models expressing human FactorD.

## **MEDI 283**

### **Multi-parameter optimization of isoform-selective dual Nav1.6/1.2 antagonists to balance CNS penetration with PK and *in vivo* efficacy in mouse models for epilepsy**

**Christoph M. Dehnhardt**<sup>1</sup>, *cdehnhardt@xenon-pharma.com*, **Kristen Buford**<sup>1</sup>, **Jean-Christophe Andrez**<sup>1</sup>, **Mike E. Grimwood**<sup>1</sup>, **Alla Zenova**<sup>2</sup>, **Matt Taron**<sup>1</sup>, **Wei Gong**<sup>1</sup>, **Shannon Decker**<sup>2</sup>, **Sultan Chowdhury**<sup>1</sup>, **Christopher Higgs**<sup>3</sup>, **Parisa Tar**<sup>2</sup>, **Rainbow Kwan**<sup>2</sup>, **Luis Sojo**<sup>2</sup>, **Robert J. Devita**<sup>4</sup>, **Charles Coher**<sup>2</sup>, **James P Johnson**<sup>2</sup>, **Steven Wesolowski**<sup>1</sup>, **James Empfield**<sup>2</sup>, **Thilo Focken**<sup>1</sup>. (1) Chemistry, Xenon Pharmaceuticals, Burnaby, British Columbia, Canada (2) Xenon Pharmaceuticals, Vancouver, British Columbia, Canada (3) Schrodinger Inc, New York, New York, United States (4) Icahn School of Medicine at Mt. Sinai, Westfield, New Jersey, United States

Non-selective blockers of voltage-gated sodium channels (Nav) are the standard treatment option for many epileptic disorders despite their often dose limiting side-effects. Adult Central Nervous System (CNS) neurons primarily express three sodium channel isoforms: Nav1.1, Nav1.2, and Nav1.6. Nav1.1 is the dominant isoform in inhibitory interneurons, whereas Nav1.2 and Nav1.6 are responsible for initiation and propagation of signaling in excitatory glutamergic neurons. An imbalance in the excitatory/inhibitory neurons caused by abnormal expression or function of Nav's contributes to the pathophysiology of epilepsy. It is believed that block of Nav1.1 is counter-productive since genetic loss-of-function of this channel leads to seizures. On the other hand, block of Nav's expressed in excitatory neurons, in particular Nav1.6, can be linked to anticonvulsant activity.

In this talk, we discuss the multi-parameter optimization and *in vivo* studies of brain penetrant selective dual Nav1.6/1.2 inhibitors with high selectivity over Nav1.1 and good CNS exposure. Besides balancing potency, microsomal stability, and brain exposure, we strived to minimize DDI risk by reducing PXR. Furthermore, using small molecule X-ray crystal structures in conjunction with molecular modeling guided compound design to optimize potency and CNS exposure. We also report on the ability of these novel

inhibitors to prevent seizures in the highly validated maximal electroshock seizure (MES) test in mice.

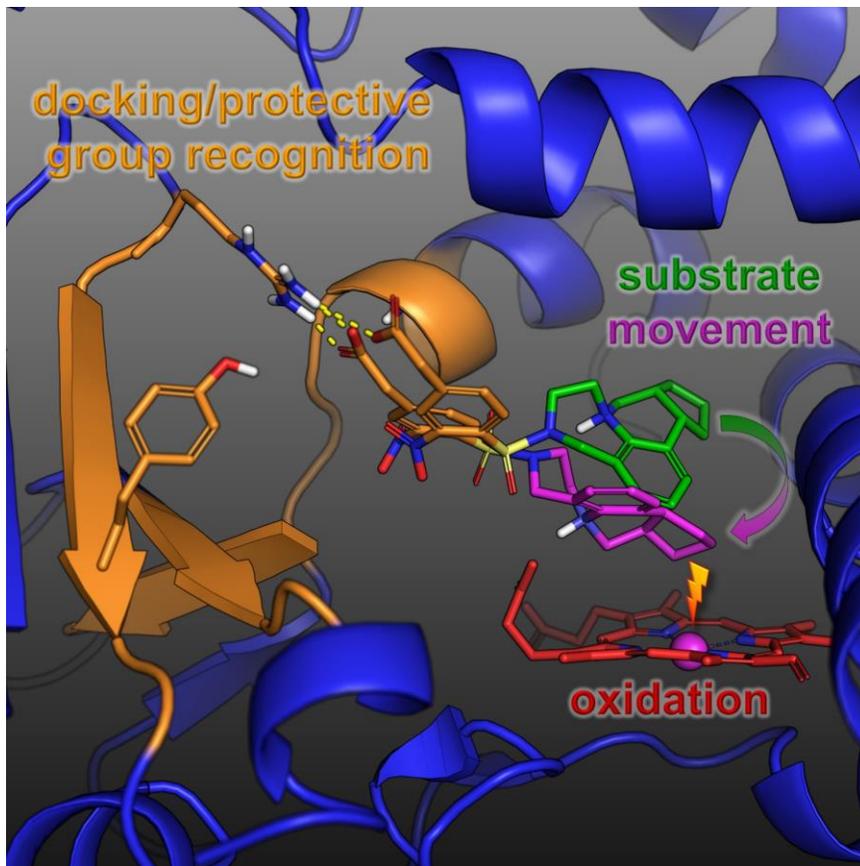
## **MEDI 284**

### **Enzymatic late-stage oxidation of lead compounds with solubilizing biomimetic docking/protecting groups**

*Udo E. Lange, udo.lange@abbvie.com. Neuroscience Research, AbbVie Deutschland GmbH&Co. KG, Ludwigshafen, Germany*

Late stage functionalization of lead compounds is of high interest in drug discovery since it offers an easy access to metabolites and derivatives of a lead compound without the need to redesign an often long multistep synthesis. Owing to their high degree of chemoselectivity biocatalytic transformations and enzymatic oxidations in particular are potentially very powerful since they could allow the synthesis of less lipophilic derivatives of a lead compound.

It will be presented how the concept of docking/protecting groups could be used in a biomimetic fashion helping to steer the regioselectivity of a P450BM3-mediated oxidation. A novel set of docking/protecting groups was designed that can be cleaved under very mild conditions and address the often problematic aqueous solubility of the substrates. Vabicaserin was used as tool compound containing typical groups such as basic, aliphatic and aromatic moieties. The results were rationalized with the help of in silico docking and molecular dynamic studies (Chemistry – A European Journal in press).



## MEDI 285

### Development and characterization of LHC165, a TLR7 agonist designed for localized intratumoral injection

*Nora Eifler, nora.eifler@novartis.com. Novartis Pharma AG, Basel, Switzerland*

LHC165 is a Toll-like receptor 7 (TLR-7) agonist, developed as a suspension for IT administration. Here, we present the technical development and characterization of a novel sustained release formulation for administration into the tumor tissue. An early and common understanding of the Target Product Profile (TPP) with the clinical team helped identify the desired product attributes for Clinical Manufacturing and Control. Salt and polymorph screening was performed to ensure sufficient solubility and fast dissolution enabled a focused formulation screening. As intratumoral injection is a novel route of administration, testing syringeability at extreme needle length and gauge as well as dose accuracy confirmation according to Ph. Eur. Guidelines are vital to ensuring a robust dosing strategy in the clinic. Innovative experiments using pork meat syringeability testing with statistical rigor resulted in an efficient and effective early product development approach.

LHC165 as a single agent and in combination with PDR001 is currently enrolling patients with advanced malignancies in CLHC165X2101.

## MEDI 286

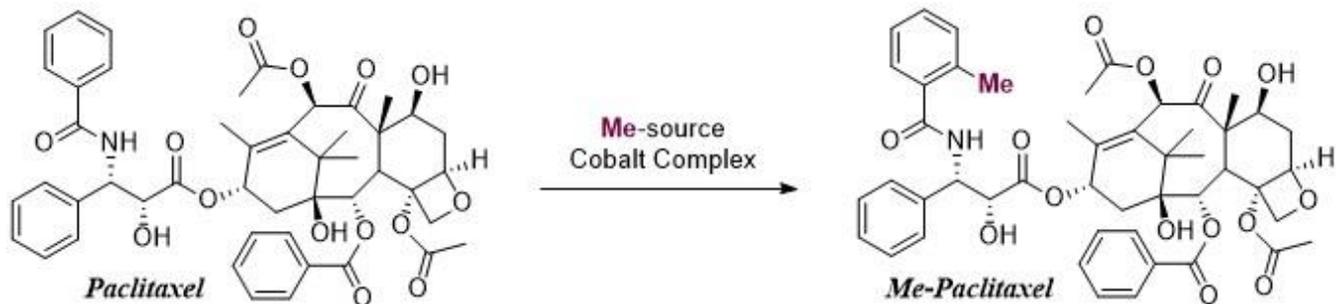
### Versatile C-H methylation reaction for late-stage functionalization

**Stig D. Friis**<sup>1</sup>, [sfriis@mit.edu](mailto:sfriis@mit.edu), **Lutz Ackermann**<sup>2</sup>, **Magnus J. Johansson**<sup>3</sup>. (1) Medicinal Chemistry, CVRM, IMED Biotech Unit, AstraZeneca, Gothenburg, Sweden (2) IOBC, Georg-August University, Goettingen, Germany

Changing a hydrogen for a methyl can have profound effects on both the biological stability and the binding affinity of a lead compound. As a consequence, medicinal chemists are on a constant lookout for that “magic methyl” which will, for example, rigidify their molecule to provide a boost in potency, at a very low cost in terms of lipophilicity and molecular weight.

The medicinal chemistry interest in changing a C-H for a C-Me is in sharp contrast to the available synthetic method that enables this transformation, especially if one wants to modify an advanced intermediate or complex lead compound. Most current chemistry for late stage C-H methylation either rely on activated C-H bonds and/or require multiple synthetic steps, making this small molecular change far from trivial.

In our efforts to address this synthetic challenge, we have developed and cobalt catalyzed C-H methylation protocol that uses a benign transmetallating reagent, which renders this chemistry mild and tolerant to a wide variety of functional groups. To facilitate C-H activation, the reaction relies on a broad selection of directing groups commonly found in biologically active compounds. All these features enable this chemistry to perform late stage C-H methylation on a diverse selection of unprotected biologically active compounds under a mild and uniform set of conditions.



## MEDI 287

**Enzyme target pre-clinical (in)validation: The value of rational exploration of the unknown, and how application of target engagement principles can address key pharmacology questions**

**Timothy B. Durham**, [durhamti@lilly.com](mailto:durhamti@lilly.com). Eli Lilly Company, Indianapolis, Indiana, United States

Frequently medicinal chemists are tasked with helping to identify tool molecules to provide pharmacological (in)validation of targets of interest. In many of these cases, tool molecules are not known and must be discovered or created. At Eli Lilly Research Laboratories, we have found value in using a rational approach to explore the unknown at the intersection of drug-like chemical diversity space and the target enzyme. Our experience has shown that when a ligand identification strategy uses mechanistically balanced, biologically relevant in vitro assays, non-essential activities are avoided and unexpected, valuable opportunities can arise. By focusing on the most important questions and using principles of Target Engagement, we have been able to move quickly from ligand identification to pharmacological proof of concept experiments, facilitating target (in)validation.

## **MEDI 288**

### **Promoting illiteracy: Development of chemical probes for epigenetic reader domains to explore untapped targets**

*Lindsey I. James, ingerman@email.unc.edu. Center for Integrative Chemical Biology and Drug Discovery, UNC Chapel Hill, Chapel Hill, North Carolina, United States*

As the fundamental determinant of cell fate and identity, the epigenome plays a central role in differentiation, development, and disease. Our understanding of epigenetic regulation is in its infancy and chemical biology is poised to play a central role in advancing scientific knowledge and assessing therapeutic opportunities in the field. Specifically, the creation of small molecule high-quality chemical probes that modulate the epigenome are a critical step in assessing preclinical target validity, while providing the potential for an immediate transition to a drug discovery effort.

Chromatin reader proteins functionally bind or interpret histone post-translational modifications to recruit protein complexes that mediate access to the underlying DNA. Considering the abundant disease associations with reader proteins that recognize methyl-lysine (Kme), ranging from cancer to neurodegeneration to viral latency, Kme reader chemical probes have the potential to establish a new class of therapeutics. The underlying mechanisms linking many of these proteins to disease remain to be defined and pharmacologic targeting is critical in determining their suitability for therapeutic intervention. We apply a target-class strategy to Kme reader antagonist development and generate focused chemical libraries and in vitro and cellular assays to discover probes for this family.

We have pioneered the development of inhibitors for Kme reader proteins, reporting the first chemical probe for a protein within this family (L3MBTL3). More recently we developed a peptidomimetic cellular probe targeting the chromodomains of Polycomb Repressive Complex 1 (PRC1), as the centrality of PRC activity in cancer establishes a pressing need for chemical probes that help to validate PRC components for therapeutic intervention. We are currently developing improved PRC1 chromodomain inhibitors and utilizing these tools to better understand Polycomb biology, while also

exploring inhibitors for other chromodomains and families of Kme reader proteins for various biological and disease relevant applications. We hope that such novel probes will serve as invaluable reagents in validating understudied epigenetic targets with therapeutic potential for drug discovery programs, and similarly invalidating those targets that may have otherwise been pursued for good reason, yet ultimately consume massive amounts of time and resources with little productive outcome.

## **MEDI 289**

### **Lessons learnt from the discovery of CDK8/19 protein kinase inhibitors: From phenotypic screen to selective chemical probes**

*Paul A. Clarke, paul.clarke@icr.ac.uk. CR UK Cancer Therapeutics Unit, Institute of Cancer Research, London, United Kingdom*

WNT signalling is a major regulator of mammalian development and tumorigenesis through control of cellular functions such as proliferation and differentiation. Many canonical WNT pathway mutations occur in tumours at or upstream of b-catenin; thus, if signalling is blocked at or below b-catenin, an inhibitor should be active against multiple tumours driven by WNT-activating mutations. With this in mind, we employed a cell-based screen to identify small molecules that block WNT signalling at or downstream of b-catenin. With no prior knowledge of the molecular target we used hypothesis-driven medicinal chemistry optimization to progress a series of 3,4,5-trisubstituted pyridines to a potent orally bioavailable small-molecule WNT-pathway inhibitor with *in vivo* activity. Knowledge of the potency and structure-activity relationships gained during the series optimisation allowed us to use a chemo-proteomics strategy to find the molecular target. We identified the mediator-associated kinases CDK8/19, that were confirmed as targets by biophysical approaches including SPR and X-ray crystallography. We used phospho-proteomics to identify robust target engagement biomarkers, microarray gene expression profiling to demonstrate regulation of specific transcription factors and super-enhancer activity, and CRISPR gene knockout to show that CDK8 inhibition was the predominant driver of tumour cell responses. We subsequently discovered and optimised an additional chemically-distinct series that identified a 3-methyl-1H-pyrazolo[3,4-b]pyridine. Having two potent and selective exemplars from structurally differentiated chemical series in hand, we were well positioned to investigate whether dual CDK8/19 modulation had a sufficient therapeutic window that would justify the clinical development of these compounds. We established that both series had antiproliferative and antitumor activity in WNT-dependent models, but tolerability studies found severe multi-organ toxicity and no therapeutic window. In light of these observations the clinical development of these series was halted. In this presentation I will give an overview of the target ID, validation and our learnings. Our data showed CDK8/19 inhibitors elicit multiple effects beyond WNT-signalling, suggest caution in progressing them to the clinic and that although targeting pleiotropic mechanisms may have the potential to overcome or prevent resistance, they come with an increased potential for toxic liabilities.

## MEDI 290

### Small molecules from phenotypic screens: Looking for “a” target?

**Samarjit Patnaik**, [samarjitpatnaik@gmail.com](mailto:samarjitpatnaik@gmail.com). DPI, National Center for Advancing Translational Sciences, Rockville, Maryland, United States

The Division of Preclinical Innovation at the National Center for Advancing Translational Sciences, NIH, often engages in phenotypic screening campaigns followed by medicinal chemistry to discover small molecules that reverse disease phenotypes in cell-based assays. This often catalyzes follow up efforts to deconvolute the small molecule's biological target leading to its mechanism of action. Case studies from collaborative projects will be presented with an introduction to the screening paradigm and the approaches that led to the discovery of possible valid targets for the active small molecule.

## MEDI 291

### Discovery of a novel kinetoplastid inhibitor for the treatment of human African Trypanosomiasis

**Jan Jiricek**, [jan.jiricek@novartis.com](mailto:jan.jiricek@novartis.com), Srinivasa Rao, Suresh B Lakshminarayana, Christopher Sarko, Natasha Aziz, Feng Gu, Thierry Diagana. Novartis Institute for Tropical Diseases, Emeryville, California, United States

Human African Trypanosomiasis (HAT) is a parasitic disease caused by *Trypanosoma brucei gambiense* and *T. b. rhodesiense*. It is endemic to sub-saharan Africa. Initially the parasite resides in hemolymphatic region, later spreading to central nervous system causing neurologic and sleep disorders. Current anti-trypanosomal therapies suffer from problems of toxicity, inadequate efficacy and need advanced clinical settings to treat patients. Recent research efforts have yielded 2 oral clinical candidates with potential to cure HAT, but fexinidazole has high pill burden (10 days dosing 1.8g for 4 days + 1.2 g for 6 days) and acoziborole has long half-life (~112 days). Hence there is a need for safer, short-course, more efficacious and 'easy to use' oral drugs against HAT.

A cell based HTS with *Trypanosoma brucei brucei* (*Tbb*) identified various hit series of which 30 entered hit evaluation, seven series progressed to hit to lead optimization and two series advanced to lead optimization. During the hit to lead selection process, biological advanced profiling, including *in vivo* efficacy testing in the blood stage disease model in mice, identified disease relevant scaffolds. *In silico* parameters guided the design towards brain penetrant CNS-efficacy candidates. It is noteworthy that a stringent cutoff in MW, cLogP, PSA to enhance the hit-list with brain penetrable hits indeed yielded CNS-penetrable series for further evaluation, however they were biologically inferior and lacked *in-vivo* efficacy.

The frontrunner scaffold was optimized and a brain penetrable ( $K_p/K_{p,uu} \sim 0.7/0.3$ ), highly efficacious preclinical candidate emerged, with no serious *in vitro* safety profiling flags. A two week rat toxicity study revealed accumulation of Sphingosine-1-phosphate in

spleen and kidneys and a NOAEL could not be established. Analysis of *Tbb* metabolomic data of different compounds of the lead series led to the hypothesis that the observed adverse events were not mechanistically related to the mode of action of the series, which remains unknown. Core changes and further lead optimization with an early toxicological 1 day rat model for the S1-P accumulation identified a novel preclinical candidate with improved brain penetration ( $K_p/K_{p,uu} \sim 0.7/1.4$ ) and single dose potential in the CNS disease model, fitting the target product profile.

## **MEDI 292**

### **SMYD3 target (in)validation from a medicinal chemistry perspective**

**Beth A. Knapp-Reed**, *bknappreed@yahoo.com*. Medicinal Chemistry, GlaxoSmithKline, Collegeville, Pennsylvania, United States

Smyd3 is a SET-domain containing lysine methyltransferase that methylates both histone and non-histone proteins. Smyd3 methylation at MEKK2 lysine 260 (K260) has been reported to disrupt the interaction of MEKK2 with the inhibitory PP2A phosphatase, resulting in elevated phospho-ERK1/2 and phospho-ERK5. Additionally, Smyd3 is overexpressed in several tumor cell lines including colorectal carcinoma, breast cancer cells, and hepatocellular carcinoma. Lowering Smyd3 expression through treatment with small interfering RNA duplexes results in significantly suppressed growth in several cancer cell lines, suggesting that Smyd3 plays an important role in tumor proliferation. A three-pronged screening approach which included an HTS campaign, ELT screen, and a fragment screen, followed by lead optimization delivered multiple chemical series for key target validation studies. Several compounds exhibited excellent potency in the biochemical and cellular assays and demonstrated target engagement, however, failed to show anti-proliferative activity or changes in downstream pERK signaling.

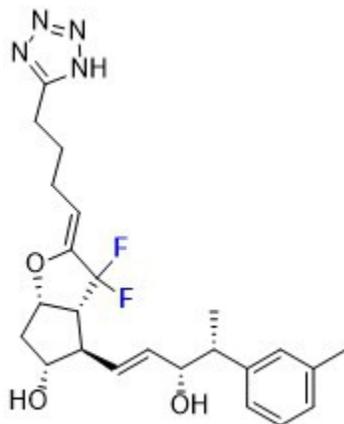
## **MEDI 293**

### **Discovery of KAG-308: A potent and orally available EP4 agonist for the treatment of inflammatory bowel disease**

**Yuichiro Ishibashi**<sup>1</sup>, *y.ishibashi0808@gmail.com*, **Yasushi Matsumura**<sup>1</sup>, **Yoshihide Miyake**<sup>2</sup>. (1) AGC inc., Yokohama, Kanagawa, Japan (2) Kaken Pharmaceutical Co.,Ltd., Bunkyo-ku, Tokyo, Japan

A new EP4 receptor agonist, KAG-308 was designed and synthesized efficiently by the route using one-step difluorination of Corey lactone derivative and the subsequent stereoselective Wittig reaction. It showed a high and selective affinity for human EP4 receptor. KAG-308 is orally available because of its high chemical and metabolical stability. Orally administered KAG-308 prevented the symptoms in the DSS-induced acute colitis model in mouse, and also demonstrated a therapeutic effects on relapse in the chronic model and promoted induction of remission. KAG-308, an orally available

EP4 agonist, is a promising drug for induction and maintenance of remission in inflammatory bowel disease in clinical studies. The synthesis and pharmacological activities for the compounds will be described herein.



KAG-308

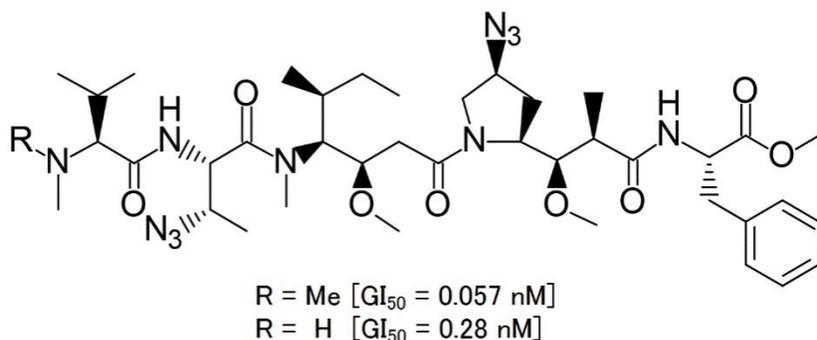
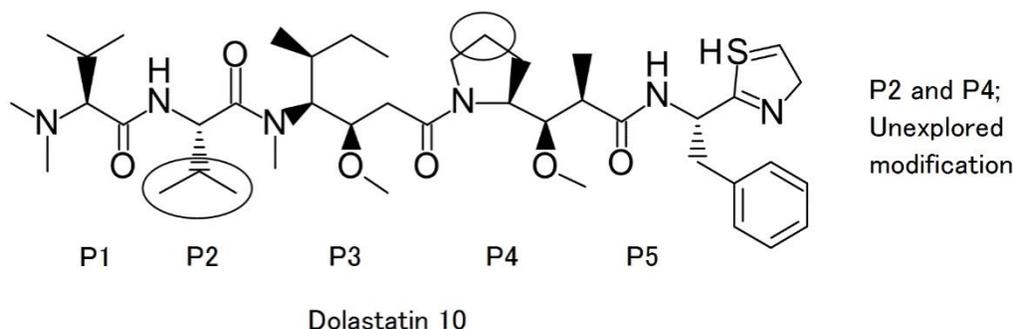
## MEDI 294

### Synthesis and evaluation of linear and macrocyclic dolastatin 10 analogues containing heteroatoms on the amino acid side chains

**Michinori Akaiwa**<sup>1,2</sup>, [michinori.akaiwa@agensys.com](mailto:michinori.akaiwa@agensys.com), **Tioga Martin**<sup>1,3</sup>, **Brian A. Mendelsohn**<sup>1,4</sup>. (1) Agensys Inc., Santa Monica, California, United States (2) Institute for Drug Discovery Research, Astellas Pharma Inc., Tsukuba, Ibaraki, Japan (3) Asilomar Bio, Inc., Emeryville, California, United States (4) Ajinomoto Althea, Inc., San Diego, California, United States

Due to their potent cytotoxic activity, members of the auristatin family (synthetic analogues of the natural occurring dolastatin 10) have remained a target of significant research, most notably in the context of antibody drug conjugate (ADC) payloads. Typically, modifications of the backbone scaffold of dolastatin 10 have focused on variations of the N-terminal (P1) and C-terminal (P5) subunits. Scant attention has been paid thus far to the P2 and the P4 subunit in the scientific literature. In this presentation we discuss the introduction of heteroatoms to the P2 and/or P4 side chain; resulting in potent cytotoxic activity seen in vitro.

Another highly active compound in this study contained azide functional groups in both the P2 and P4 subunits and required dolavaline as the P1 subunit and a phenylalanine as the P5 subunit. Furthermore, these two azide groups served not only as modifiers of cytotoxicity, but also as handles for linker attachment or as a tether for use in the synthesis of a macrocyclic analogue.



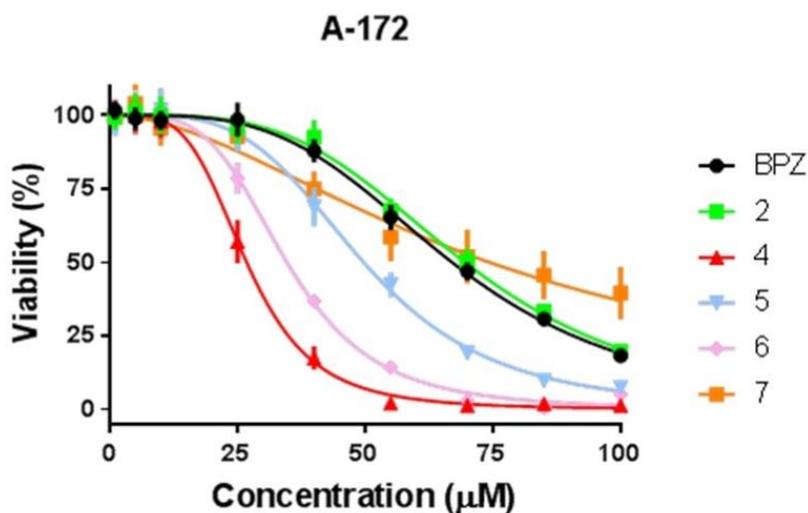
## MEDI 295

### Design, synthesis, and biological evaluation of bisphenol Z derivatives

*Lea M. Stitzlein, stitzleins@findlay.edu, Christopher T. Stang, Laura R. Inbody, Ryan A. Schneider, Richard W. Dudley. Pharmaceutical Sciences, The University of Findlay, Findlay, Ohio, United States*

Bisphenol substitutes have been employed to circumvent the pleiotropic effects of bisphenol A. Despite varying structures of bisphenols, modulation of various cellular processes continue to occur. In an attempt to explore and repurpose the bisphenol scaffold, several derivatives of bisphenol Z (BPZ) with varying degrees of hydrophilic and hydrophobic character were synthesized and investigated for proliferative effects in A-172 glioblastoma cells. A fluorescent (dansylated) BPZ analog was also synthesized to help determine cellular localization of such molecules. Derivatives were synthesized in one or two steps to contain a polar or non-polar bulky head group. Derivatives with the highest degree of lipophilicity demonstrated anti-proliferative activity as measured by the XTT assay. Hydrophilic derivatives were devoid of any activity (proliferative or anti-proliferative). The dansylated BPZ derivative showed predominantly cytosolic distribution and was excluded from the nucleus. Synthesis of additional derivatives are

planned which impart lipophilicity in a compact manner as well as the synthesis of several aromatic-substituted derivatives.



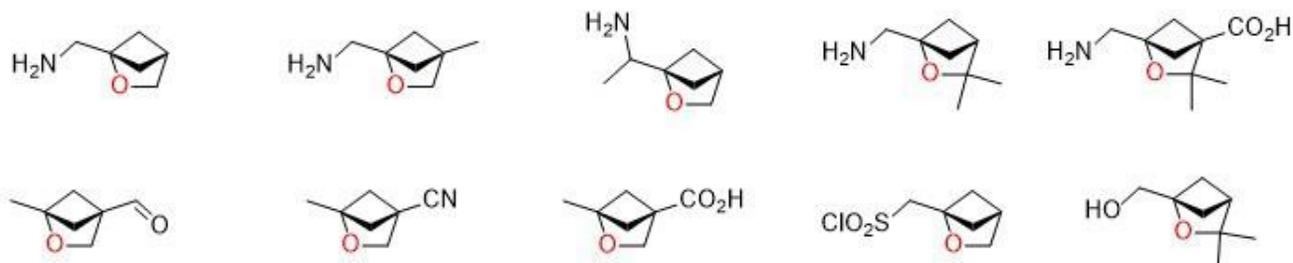
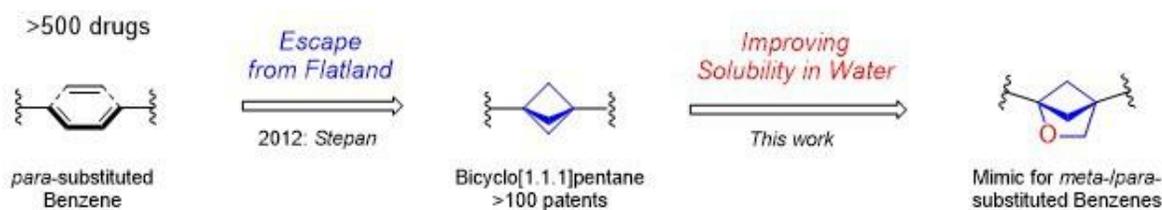
**Figure 1.** Concentration response curves of A-172 glioblastoma cells following 24-hour incubation with indicated BPZ derivatives. Derivative **4**, palmitoylated derivative and **6**, isopropyl derivative, were the most active and most lipophilic. Results are presented as percent of vehicle control (DMSO). Data points are representative of mean  $\pm$  SEM of three independent experiments ran in quadruplicate.

## MEDI 296

### Saturated bioisosteres of benzene with improved solubility

*Pavel Mykhailiuk, Pavel.Mykhailiuk@gmail.com, Vadym Levterov, Oleksandr O. Stepaniuk. Chemistry, Enamine Ltd, Kiev, Ukraine*

“Escape the Flatland” concept has already gained considerable attention in medicinal chemistry. Scientists are looking more and more now for 3D-shaped saturated building blocks. In this context, conformationally rigid bicyclic tetrahydrofurans are intrinsically promising for drug discovery. In continuation of our ongoing program towards novel building blocks for drug discovery, herein we have designed and synthesized a library of saturated mimics of the benzene ring with improved solubility in water.



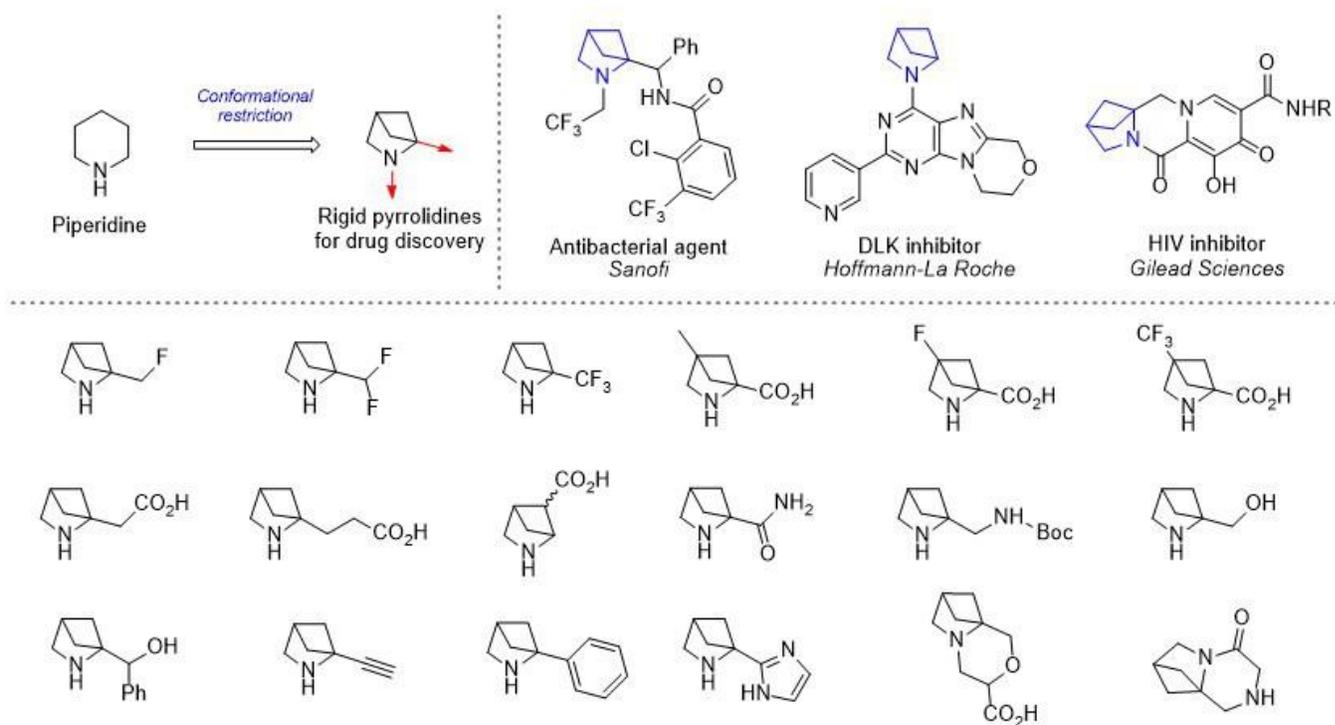
## MEDI 297

### Conformationally restricted pyrrolidines for drug discovery

**Pavel Mykhailiuk**, [Pavel.Mykhailiuk@gmail.com](mailto:Pavel.Mykhailiuk@gmail.com), Vadym Levterov, Artem Cherepakha. Chemistry, Enamine Ltd, Kiev, Ukraine

“Conformational restriction” concept has already gained a considerable attention in medicinal chemistry. Scientists are looking more and more now for 3D-shaped saturated building blocks. In this context, intrinsically conformationally rigid bicyclic amines seem to be promising for drug discovery.

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]-cyclization. Details of the synthesis and application of the obtained compounds will be discussed.



## MEDI 298

### Synthesis and evaluation of thalassotalic acid A and analogs

Joseph Schulz, **James Patrone**, [jpatrone@rollins.edu](mailto:jpatrone@rollins.edu). Chemistry, Rollins College, Winter Park, Florida, United States

Thalassotalic Acids A-C are a family of N-acyldehydrotyrosine derivatives that were recently isolated from the marine bacterium *Thalassotalea* sp. PP2-459 and identified as modest inhibitors ( $IC_{50} = 130, 470, \text{ and } 280 \mu\text{M}$ , respectively) of the melanogenesis enzyme tyrosinase. Due to their tyrosinase inhibition, these molecules have the potential be used in a variety of ways including as skin whitening agents for dermatological disorders or as agricultural preservatives for fruits and vegetables. In order to explore the possibility of optimizing these molecules as tyrosinase inhibitors, a three-step modular synthesis was devised and executed. Thalassotalic Acids A-C and unnatural analogs were synthesized and evaluated as inhibitors of tyrosinase to begin an SAR study.

## MEDI 299

### Synthesis of prodrugs from a quinazoline derivative to optimize its behavior against cancer cells

**Lourdes C. Arenas Corona**, [lourdesarenas\\_226@hotmail.com](mailto:lourdesarenas_226@hotmail.com), Francisco Hernández Luis. Universidad Nacional Autónoma de México, Mexico City, Mexico City, Mexico

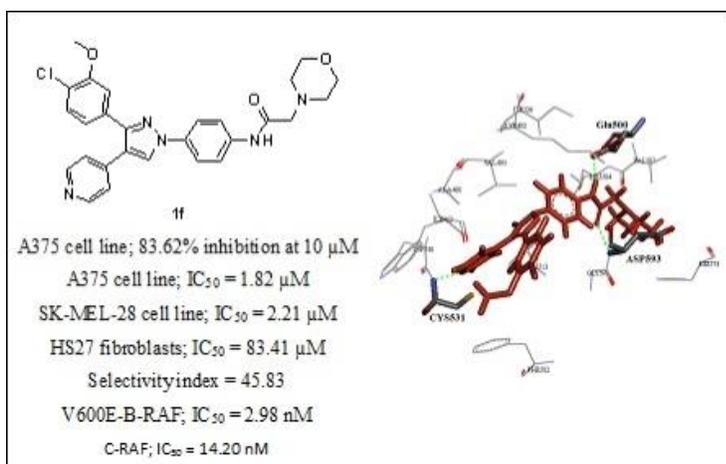
Cancer continues to be one of the main public health problems since it is the second cause of death in the world. At present, chemotherapy is considered conventional therapy for several illnesses of this group; however, it still has certain limitations, such as the low selectivity of action towards the cancer cells and the low susceptibility, which they develop to drugs for clinical use. Due to the aforementioned drawbacks, we are still looking for compounds that can act through different mechanisms of action and at different levels of carcinogenic processes. Currently, there are reports that the modification of the redox status of cancer cells can lead them to death. From this premise we have looked for molecules that affect the functioning of Xanthine oxidase (XO) in order to modify the cellular redox balance, taking advantage of the fact that this enzyme is over-expressed and that it is one of the sources of reactive oxygen species (ROS) in malignant cells. It has been observed that some derivatives of N-(2,4-diaminoquinazolin-6-yl) carboxamides show inhibitory activity against XO. One of them, the so-called **MLB13**, stood out for its inhibitory action and antioxidant potential; however, it presented problems of low aqueous solubility, which limited its evaluation in cultures of different malignant cell lines. For this reason, the objective of this work is to carry out the synthesis of **MLB13** by means of an alternate synthesis route to subsequently be able to synthesize some of its prodrugs of amino acid esters and thus being able to increase its aqueous solubility and antioxidant potential.

## **MEDI 300**

### **Design and synthesis of a novel series of highly potent RAF kinase-inhibiting triarylpyrazole derivatives with potential antiproliferative activity against melanoma**

*Mohammed El-Gamal<sup>1</sup>, drmelgamal2002@gmail.com, Mohammad Ashrafuddin Khan<sup>2</sup>, Hamadeh Tarazi<sup>1</sup>, Hong Seok Choi<sup>3</sup>, Chang-Hyun Oh<sup>2</sup>. (1) Medicinal Chemistry, University of Sharjah, College of Pharmacy, Sharjah, United Arab Emirates (2) Korea Institute of Science and Technology, Seoul, Korea (the Republic of) (3) College of Pharmacy, Chosun University, Gwangju, Republic of Korea, Gwangju, Korea (the Republic of)*

Inhibition of V600E-B-RAF kinase represents a potential avenue for melanoma treatment. In this work, a novel series of 1,3,4-triarylpyrazoles possessing amide linker were designed, synthesized, and evaluated for RAF kinase inhibition. Compounds **1d** and **1f** were more potent than Sorafenib against A375 melanoma cell line, and their selectivity indexes towards A375 than HS27 fibroblasts were 25.43 and 45.83, respectively. Compound **1f** was more potent against the melanoma cell lines with B-RAF V600E mutation than melanoma cells with NRAS mutation and normal skin epithelial cells. Compounds **1d** and **1f** showed strong potency and selectivity against V600E-B-RAF kinase with IC<sub>50</sub> values of 3.80 nM and 2.98 nM, respectively. Molecular docking studies revealed their binding mode. As a result, potent and selective V600E-B-RAF anti-melanoma agents were discovered.

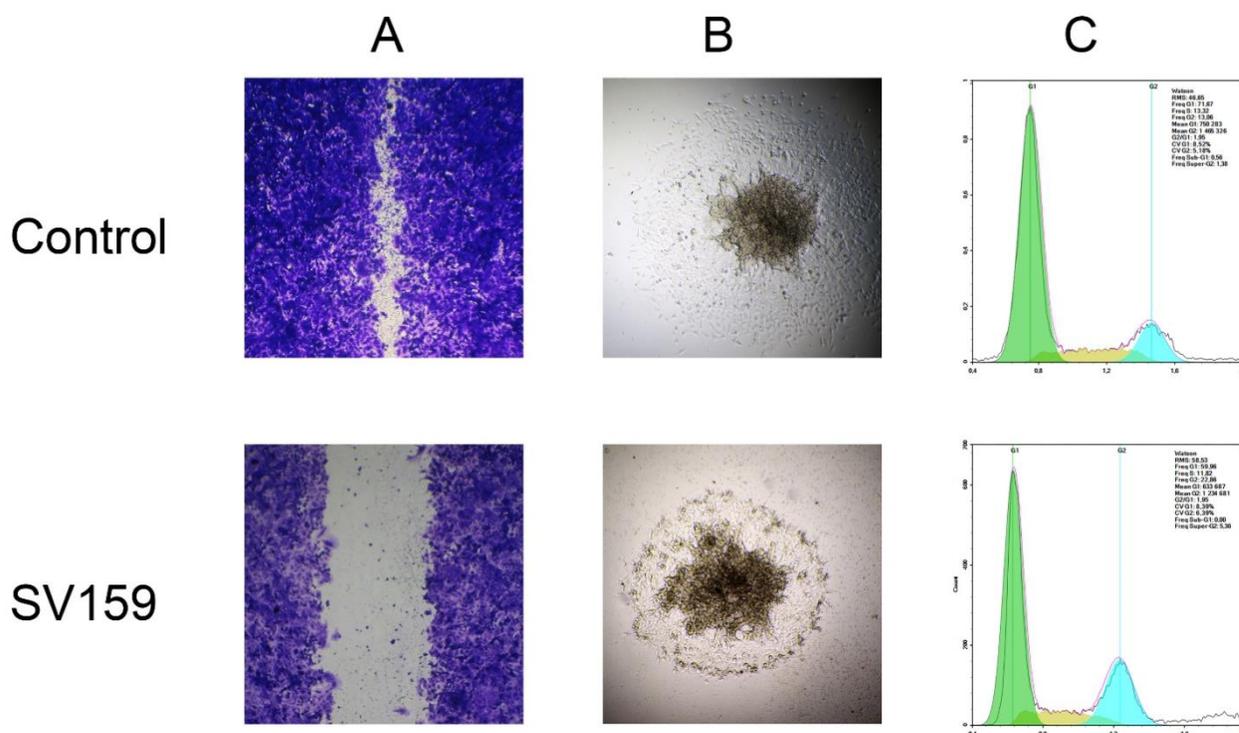


## MEDI 301

### Design, synthesis, and evaluation of biological properties of new 5-cyanopyrimidine-based compounds

**Alexander S. Bunev**<sup>1</sup>, *a.s.bunev@gmail.com*, **Dmitriy Khochenkov**<sup>1,2</sup>, **Yuliya Khochenkova**<sup>2</sup>, **Evgeniya Stepanova**<sup>2</sup>. (1) Medicinal Chemistry Center, Togliatti State University, Togliatti, Samara Region, Russian Federation (2) Laboratory of biomarkers and tumor angiogenesis mechanisms, N.N. Blokhin National medical research center for oncology, Moscow, Russian Federation

The synthesis of the studied compounds was carried out on the basis of products of three-component cyclization of S-alkylisothiuronium salts, malondinitrile (or ethylcyanoacetate) and an aromatic aldehyde under basic catalysis. The resulting 5-cyanopyrimidine derivatives were further subjected to direct oxidation under the action of oxone, or transformed into 4-amino-5- derivatives cyanopyrimidine followed by oxidation. The synthesized compounds showed high cytotoxic activity against a broad spectrum of tumor lines: A549, A431, MCF-7, HCT-116 ( $\text{IC}_{50}$ =0.3–35  $\mu\text{M}$ ). In the study of selected hit-compounds, a pronounced reducing of the migration activity of A549 lung cancer cells was established by the method of wound healing and A549 cell spheroid migration assay after 48 hours of cultivation with compounds (Fig.1 A,B). To study the mechanism of inhibition of cell migration, we performed a cell cycle analysis. According to the obtained data, the derivatives of 5-cyanopyrimidines synthesized by us cause the G2/M cell cycle arrest during cultivation with A549 cell lines in non-cytotoxic concentration (Fig.1C). Consequently, the derivatives obtained by us possess high cytotoxic activity, inhibit the migration activity of tumor cells due to arrest of the cell cycle.

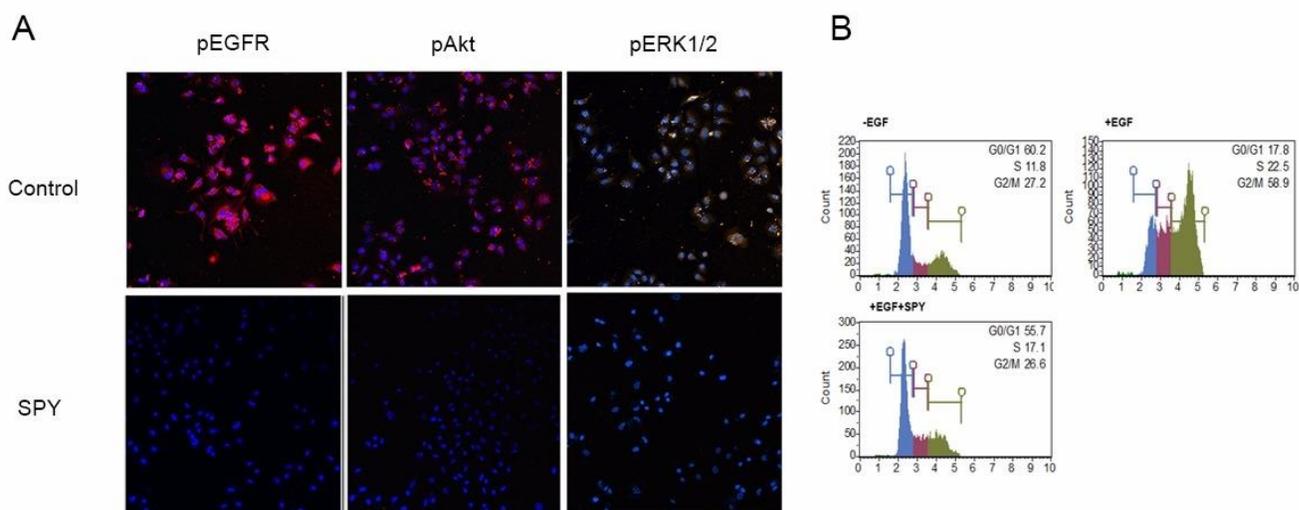


## MEDI 302

### Novel imidazo[2,1-*B*]thiazoles as potential EGFR tyrosine kinase inhibitors: Synthesis and *in vitro* evaluation

**Alexander S. Bunev**<sup>1</sup>, [a.s.bunev@gmail.com](mailto:a.s.bunev@gmail.com), **Dmitriy Khochenkov**<sup>1,2</sup>, **Yuliya Khochenkova**<sup>2</sup>, **Evgeniya Stepanova**<sup>2</sup>. (1) Medicinal Chemistry Center, Togliatti State University, Togliatti, Samara Region, Russian Federation (2) Laboratory of biomarkers and tumor angiogenesis mechanisms, N.N. Blokhin National medical research center for oncology, Moscow, Russian Federation

Epidermal growth factor receptor – a member of ErbB family of receptors that extensively expressed on many types of cancer cells (breast cancer, non-small cell lung cancer, colon cancer, head and neck cancer) and often takes part in the tumor development, induction of angiogenesis, survival and invasion. The antitumor activity of a series of imidazo[2,1-*b*]thiazole derivatives against selected EGFR-expressing cancer lines (lung cancer cell line – A549, breast cancer cell line – MCF7) and immortalized fibroblast cell line BJ-5ta was evaluated. Among the designed structures exhibited potential anticancer activity, with the IC<sub>50</sub> values ranging from 12.5 μM to 47.0 μM in three cell lines. Selected SPY-41 compound could inhibit the expression of p-EGFR, p-Akt under EGF stimulation (Fig.1A). and efficiently induced cell cycle arrest of tumor cells evaluated by flow cytometry at Muse cell analyzer (Fig.1B). Our study suggested that synthesized polyfunctional imidazo[2,1-*b*]thiazole derivatives can be developed as novel tyrosine kinase inhibitors for cancer therapy.



## MEDI 303

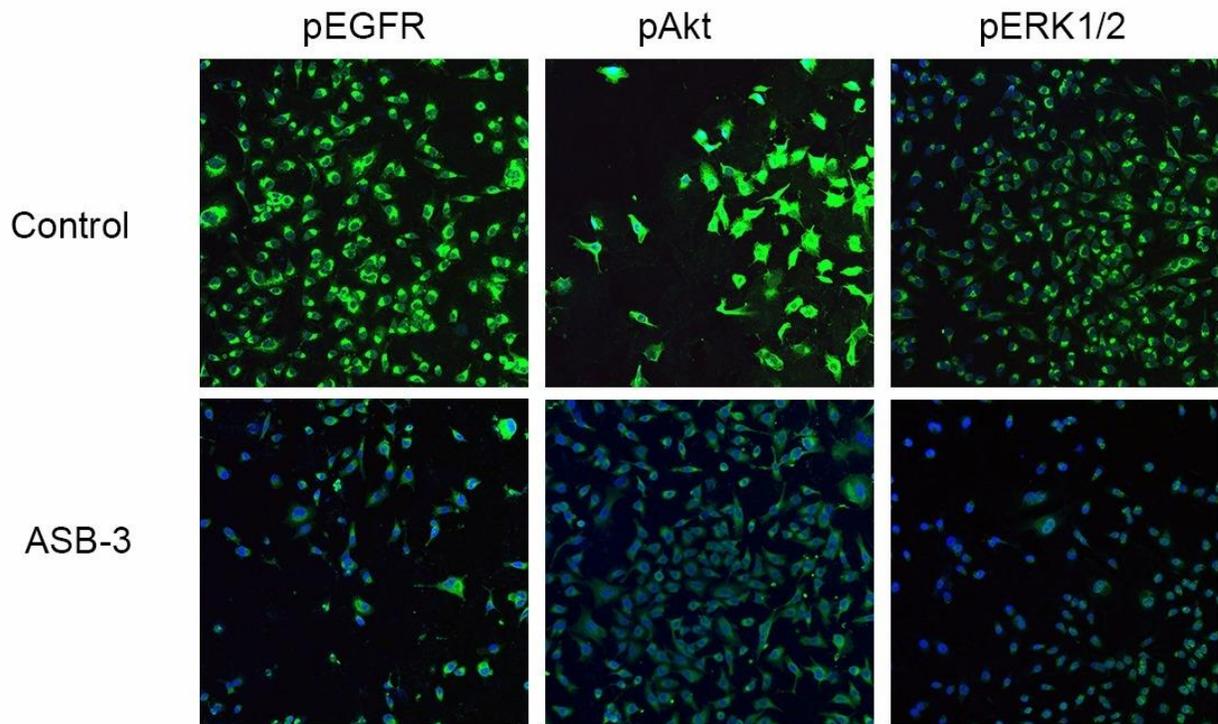
### 4-Amino-5- (thiazol-2-yl) pyrimidine derivatives: New effective inhibitors of EGFR-dependent signal cascades

**Alexander S. Bunev**<sup>1</sup>, *a.s.bunev@gmail.com*, **Dmitriy Khochenkov**<sup>1,2</sup>, **Yuliya Khochenkova**<sup>2</sup>, **Evgeniya Stepanova**<sup>2</sup>. (1) Medicinal Chemistry Center, Togliatti State University,, Togliatti, Samara Region, Russian Federation (2) Laboratory of biomarkers and tumor angiogenesis mechanisms, N.N. Blokhin National medical research center for oncology, Moscow, Russian Federation

The development of new highly effective inhibitors of the receptor tyrosine kinases, in particular, receptors of the epidermal growth factor family (EGFR), is an urgent task for the creation of targeted anti-cancer compounds.

There we summarize the results of molecular modeling, chemical synthesis, and in vitro studies of a number of compounds containing 4-amino-5-(thiazol-2-yl) pyrimidine fragment as a basic scaffold. The cytotoxic effect on the A549 lung cancer cell line, abundantly expressing EGFRwt, has been shown to be at IC<sub>50</sub> level 4.39 – 420 μmol and for some compounds, such as ASB1–ASB3, exceeds the cytotoxicity of erlotinib and gefitinib by 5-10 times. In a study on immunofluorescent staining of A549 cells, it was shown that a significant decrease in the expression of phosphorylated signaling kinases pEGFR, pAkt and pERK1 / 2, relative to the EGF-induced control, is particularly high for ASB3.

The obtained results are the starting point for the identification of a new chemotype of inhibitors of receptor kinases of the epidermal growth factor family.



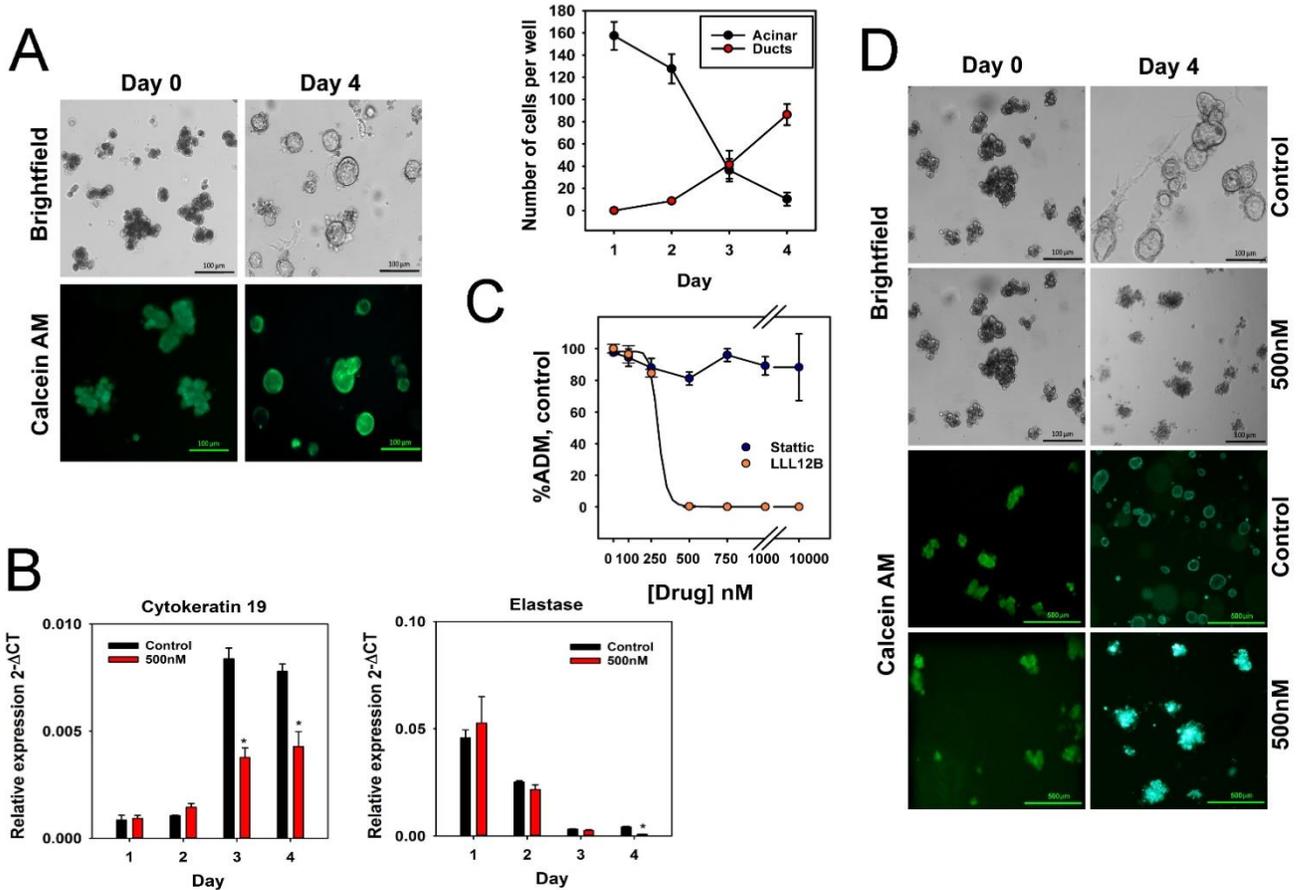
## MEDI 304

### Inhibition of pancreatic acinar ductal metaplasia by a novel STAT3 inhibitor LLL12B

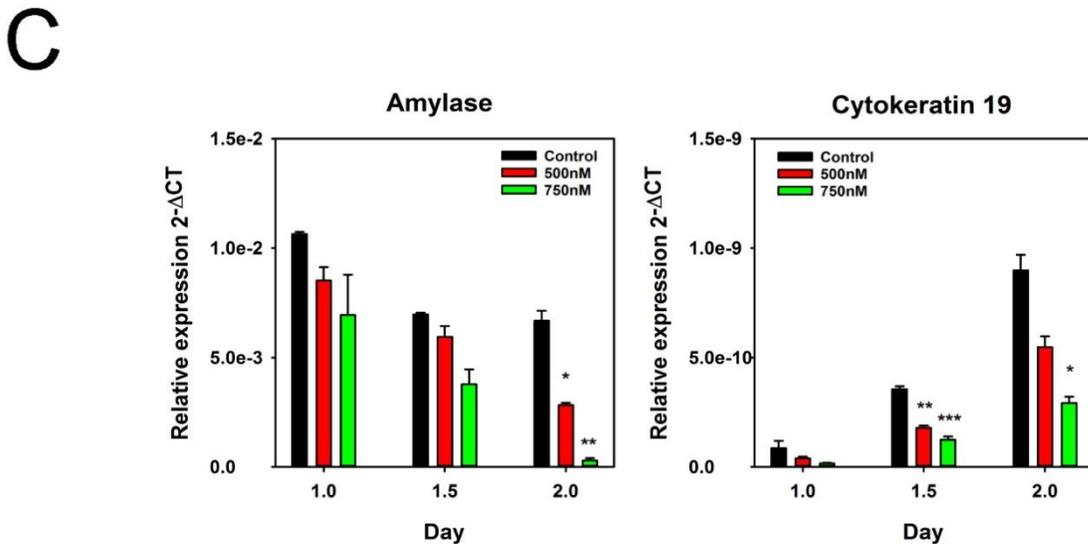
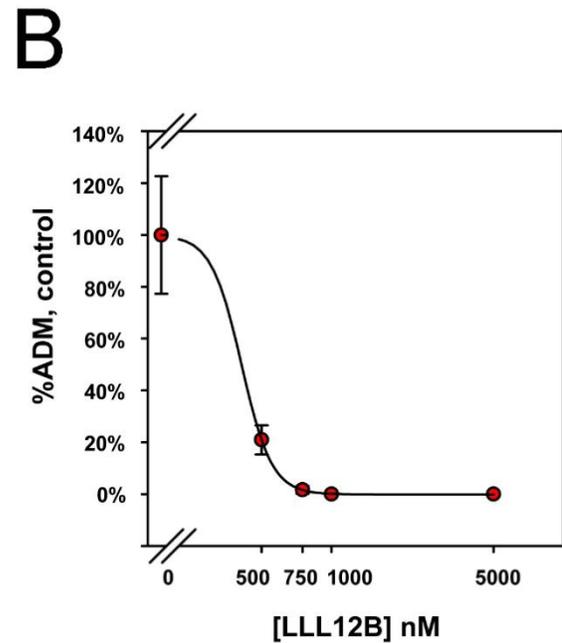
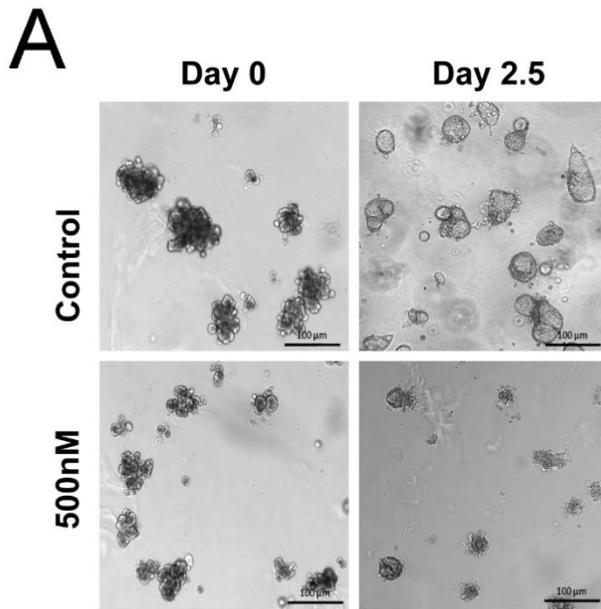
Lais Da Silva<sup>2</sup>, **Jinhua Song**<sup>1</sup>, *jhsong\_bai@yahoo.com*, James Matthews<sup>1</sup>, Jinmai Jiang<sup>2</sup>, Hendrik Luesch<sup>1</sup>, Chenglong Li<sup>1</sup>, Thomas D Schmittgen<sup>2</sup>. (1) Medicinal Chemistry, University of Florida, Gainesville, Florida, United States (2) Department of Pharmaceutics, University of Florida, Gainesville, Florida, United States

The Jak-Stat pathway is activated in pancreatic ductal adenocarcinoma (PDAC) and has been linked to acinar ductal metaplasia (ADM), an early event in the development of PDAC. To discover compounds that inhibit ADM via Stat3 inhibition, we report the design, synthesis and biological activity of LLL12B. LLL12B is a small molecule that was designed to bind to the SH2 domain of Stat3 to prevent Tyr705 phosphorylation and STAT3 dimerization. To evaluate the ability of LLL12B to inhibit ADM, pancreatic acini from wild type mice and those mice with *Kras* conditionally mutated in the pancreas (*Kras*<sup>G12D</sup>) were transdifferentiated to ductal like cells when cultured onto the extracellular matrix matrigel. A 3 day exposure of LLL12B inhibited transdifferentiation on wild type acini with an IC<sub>50</sub> of 323 nM while the pan[SD1] Stat3 inhibitor Stattic was ineffective at inhibiting ADM. LLL12B also inhibited ADM of acini from the *Kras*<sup>G12D</sup> mice with an IC<sub>50</sub> of 403 nM. Cell viability, as assessed by calcein AM staining or MTT, was maintained during the LLL12B exposure in wild type and *Kras*<sup>G12D</sup> mice, demonstrating that inhibition of ADM by LLL12B was not a result of cytotoxicity. We report the

successful development of a novel inhibitor of pancreatic transdifferentiation that may be used as a chemical probe to study ADM or as a therapeutic to potentially treat PDAC.



**LLL12B inhibits ADM in wild type mouse acini.**



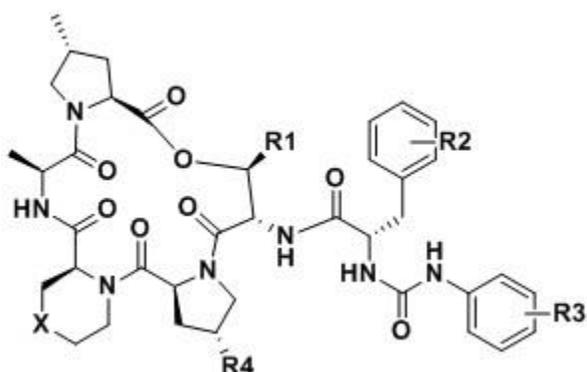
LLL12B inhibits pancreatic ADM in *Kras*<sup>G12D</sup> mice.

MEDI 305

Structure-activity relationships of UDEPs as caseinolytic protease activators

Ying Zhao<sup>1</sup>, ying.zhao@stjude.org, Elizabeth Griffith<sup>1</sup>, Anu ARYA<sup>2</sup>, michael LaFleur<sup>2</sup>, Richard E. Lee<sup>1</sup>. (1) Mail Stop 1000, St Jude Childrens Research Hospital, Memphis, Tennessee, United States (2) Arietis Pharma, Boston, Massachusetts, United States

Casein lytic protease (Clpp), a tetradecameric serine protease comprised of two stacked heptameric rings, is a distinctive family of cylindrical energy-dependent serine proteases that is conserved throughout bacterial species. Acyldepsipeptides (ADEP) is a unique class of antibiotics that bind and activate ClpP to induce uncontrolled proteolysis which lead to inhibition of bacterial cell division and eventually cell death. We have designed and synthesized a series of ADEP4 analogs by replacing acyl side chain with urea substitution. The resulted urea analogs present comparable activation but have better solubility and stability than that of ADEP4. The design, synthesis and minimal inhibitory activities against different strains of these compounds will be presented and discussed.



## MEDI 306

### Design, synthesis, and biological evaluation of flavones showing inhibitory effects on aurora kinases

Ji Hye Lee, **Dongsoo Koh**, [dskoh@dongduk.ac.kr](mailto:dskoh@dongduk.ac.kr). Department of Applied Chemistry, Dongduk women's University, Seoul, Korea (the Republic of)

Flavones have been known to inhibit growth of cancer cells. For the systematic studies to discover flavones showing cancer cell growth inhibitory effects, we prepared 36 synthetic flavone derivatives containing various substituent groups. The half-maximal cell growth inhibitory concentration (GI<sub>50</sub>) values of 36 flavone derivatives against HCT116 human colon cancer cell lines were determined and they ranged between 0.50 and 41.21  $\mu$ M. Clonogenic long-term survival assay was used because this method can distinguish the cytotoxicities of the compounds with similar chemical structures. The structural conditions to show better cytotoxicity were derived based on the structure-activity relationships, and the pharmacophores obtained based on the CoMFA and CoMSIA models were addressed. *In vitro* kinase assay relating with cancer at the cellular level was performed. Of kinases tested, aurora kinase was inhibited effectively by synthesized flavone compounds. Western blotting analysis revealed that compound **31**, which showed the best GI<sub>50</sub> value, inhibited aurora kinases in a time-dependent manner as well as a dose-dependent manner. To elucidate the binding modes between compound **31** and aurora kinases at the molecular level, *in silico* docking experiments were also carried out.

## MEDI 307

### Synthesis and evaluation of novel multifunctional opioid peptidomimetics

**Mason A. Baber**<sup>1,2</sup>, *mason.a.baber@gmail.com*, Deanna Montgomery<sup>3</sup>, Jessica P. Anand<sup>4</sup>, Lennon DeLong<sup>4</sup>, John R. Traynor<sup>4</sup>, Henry I. Mosberg<sup>2</sup>. (1) Chemistry, Rollins College, Winter Park, Florida, United States (2) Medicinal Chemistry, University of Michigan, Ann Arbor, Michigan, United States (4) Pharmacology, University of Michigan, Ann Arbor, Michigan, United States

Studies have shown that activation of the kappa opioid receptor (KOR) can reduce cocaine self-administration, presumably by inhibiting dopamine production and/or release. However, KOR agonism also causes dysphoria, or intense unease and discontent. The introduction of partial agonism at the mu opioid receptor (MOR) may provide an opportunity to overcome this side effect due to its ability to induce euphoria. Multifunctional ligands with a KOR/MOR profile could potentially be used to curb or treat cocaine addiction. Recently, modifications and additions to the DMT-Tic scaffold have been made, and the resulting compounds demonstrate this desired profile. This work expands on that research by synthesizing novel compounds with various substituted benzyl and acetophenone pendants at the 7 position of the tetrahydroisoquinoline core and evaluating them for binding affinity, efficacy, and potency at KOR and MOR. The benzyl pendant compounds with electron-withdrawing groups at the ortho position demonstrated a KOR agonist/MOR partial agonist profile while the meta-hydroxy benzyl pendant compound showed a more balanced profile. The acetophenone pendant compounds exhibited a preference in efficacy at MOR over KOR.

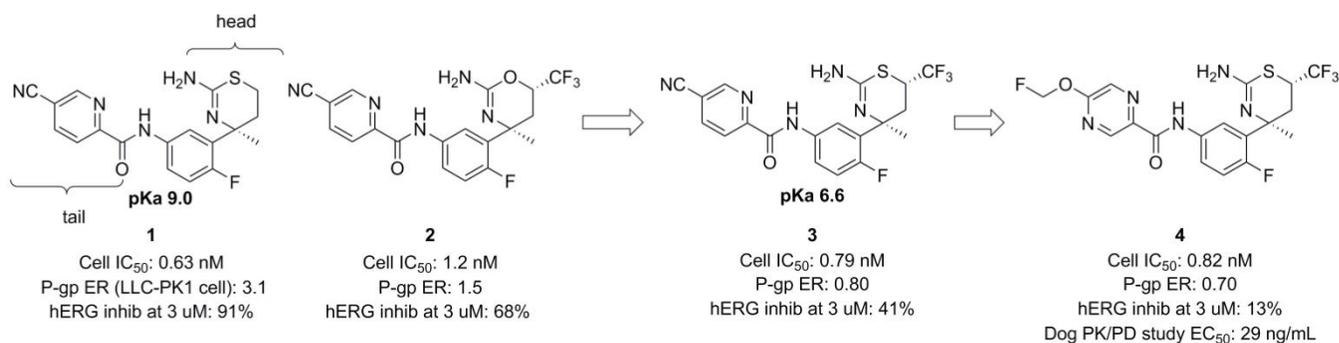
## MEDI 308

### Trifluoromethyl thiazine-based BACE1 Inhibitors: Synthesis, *in vivo* efficacy, cardiovascular side effects, and covalent binding burden

**Takuya Oguma**<sup>1</sup>, *takuya.oguma@shionogi.co.jp*, Kenji Nakahara<sup>1</sup>, Kosuke Anan<sup>1</sup>, Yasuyoshi Isou<sup>1</sup>, Shinji Suzuki<sup>1</sup>, Takahiko Yamamoto<sup>1</sup>, Yasuto Kido<sup>1</sup>, Naoki Kanegawa<sup>1</sup>, Tamio Fukushima<sup>1</sup>, Yutaka Tonomura<sup>1</sup>, Hisanori Ito<sup>1</sup>, Gaku Sakaguchi<sup>1</sup>, François Bischoff<sup>2</sup>, Harrie Gijsen<sup>2</sup>, Ken-ichi Kusakabe<sup>1</sup>. (1) Shionogi & Co., Ltd., Osaka, Japan (2) Janssen, Beerse, Belgium

Alzheimer's disease (AD) is the most common type of dementia. The accumulation of amyloid  $\beta$  ( $A\beta$ ) peptides is considered to be a causal factor of AD, and  $\beta$ -secretase (BACE1) is a rate-limiting enzyme in  $A\beta$  peptide production. Therefore, inhibiting BACE1 should be beneficial as a disease-modifying treatment. Our hit-to-lead SAR efforts identified thiazine **1** as a lead, which had a promising *in vitro* activity although it possessed high P-gp efflux and hERG inhibition. In parallel with our efforts, scientists at Roche reported a 6-trifluoromethyl oxazine **2** that reduced P-gp efflux, albeit still showing high hERG inhibition. Therefore, we commenced to develop centrally active BACE1 inhibitors with reduced hERG inhibition. We designed trifluoromethyl thiazine **3** by

replacing the oxygen in **2** with sulfur and synthesized it *via* DAST-mediated thiazine ring formation. Thiazine **3** showed low P-gp efflux and hERG inhibition without loss of *in vitro* BACE1 potency, probably due to a reduced pKa value of the amidine group as a result of the electron-withdrawing nature of CF<sub>3</sub> group. Further optimization of the tail group of the cyano-pyridine led to **4** with improved hERG inhibition relative to **3**. Thiazine **4** showed significant Abreduction *in vivo* in both mice and dogs. In addition, cardiovascular (CV) safety was evaluated in anesthetized guinea pigs, confirming a sufficient CV safety margin. Since **4** possesses a isothioureia moiety, the potential of reactive metabolite formation was investigated using <sup>14</sup>C labelled **4** in human hepatocytes. The covalent binding burden, calculated based on the covalent binding and estimated human dose, was found to be less than 1 mg/day.



## MEDI 309

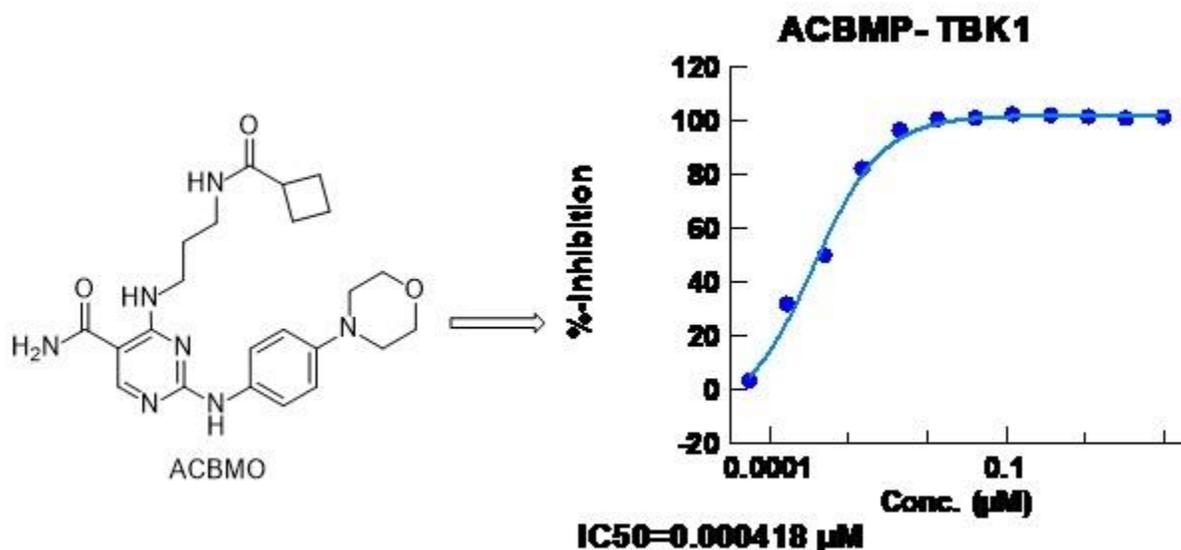
### Medicinal chemistry and chemical biology approach in order to design and synthesize of TBK1/ IKK-ε small molecules inhibitors

**Amir Assadieskandar**<sup>1</sup>, [assadies@usc.edu](mailto:assadies@usc.edu), **Chao Zhang**<sup>2</sup>. (1) University of Southern California, Los Angeles, California, United States (2) Department of Chemistry, University of Southern California, Los Angeles, California, United States

Nowadays, 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. TANK-binding kinase 1 (TBK1) and IκB kinase subunit epsilon (IKK-ε) are highly homologous serine/threonine kinases that are involved in diverse cellular functions like innate immune response, tumorigenesis and development. The biology of TBK1 and IKK-ε is complicated and is not well understood. Some studies have showed that these kinases phosphorylate numerous targets that have a role in immune responses, inflammation, and proliferation.

Recently, a few scaffolds have been reported as TBK1/ IKK-ε inhibitors but there is a great need to improve the selectivity of the inhibitors for these two highly homologous kinases. As a result, design and synthesis of highly potent and selective TBK1/ IKK-ε inhibitors is an interesting topic in medicinal chemistry and chemical biology. We started this project by inspiration of previously reported scaffolds and eventually designed and synthesized a library of non-covalent small molecule inhibitors of TBK1/ IKK-ε. Selectivity of the optimized molecules over around 300 kinases has been evaluated.

The liver enzyme stability and pharmacokinetic property of best inhibitors were investigated in order to administer the inhibitor in an *in vivo* study. To improve the selectivity of inhibitors, a series of covalent inhibitors of TBK1 were designed and synthesized by taking advantage of the optimized structure as well chemical biology approaches. Additionally, the DNA construct of TBK1 has been prepared to make co-crystal structures with the optimized compound. Finally, the antiproliferative efficacy of compounds on multiple cancer cell lines and luciferase reporter signaling pathway is currently under investigation.



## MEDI 310

### Development of a new series of bacterial topoisomerase inhibitors for antibiotic-resistant infections

*Linsen Li*<sup>1</sup>, *napoleon21@163.com*, *Sheri Dellos-Nolan*<sup>2</sup>, *Anthony English*<sup>1</sup>, *Jack C. Yalowich*<sup>1</sup>, *Daniel Wozniak*<sup>2</sup>, *Mark J. Mitton-Fry*<sup>1</sup>. (1) College of Pharmacy, The Ohio State University, Columbus, Ohio, United States (2) Microbial Infection and Immunity, The Ohio State University, Columbus, Ohio, United States

Novel Bacterial Type II Topoisomerase Inhibitors (NBTIs) represent a promising new class of antibiotics. We report the synthesis of a series of NBTIs with a dioxane linker, as well as their evaluation using a variety of biochemical, microbiological, and safety assays.

All compounds were synthesized by short sequences from commercially available materials, and characterized using NMR spectroscopy and mass spectrometry. Minimum inhibitory concentrations (MICs) were determined using drug-sensitive and methicillin-resistant *Staphylococcus aureus* (MRSA). Additionally, selected compounds showed potent whole cell activity for other Gram-positive pathogens, including vancomycin-resistant *Enterococcus faecium* (VRE) and penicillin-resistant *Streptococcus pneumoniae*. Limited anti-Gram-negative activity was also

seen, especially for *Acinetobacter baumannii*. Inhibition of DNA gyrase and topoisomerase IV (TopoIV) was evaluated using supercoiling and decatenation assays, respectively. Consistent with other NBTIs, the new compounds inhibited DNA gyrase more potently than TopoIV. Growth inhibitory experiments using K562 human leukemia cells and a human topoisomerase II-deficient cloned subline strongly suggested that the compounds do not inhibit human topoisomerase IIa. hERG IC<sub>50</sub> values were determined for select compounds, many of which displayed reduced hERG inhibition compared with previously reported analogs.

NBTI **83** inhibited MRSA with an MIC of 1 µg/mL, showed selectivity compared to K562 cells (IC<sub>50</sub> > 186 µM), and yielded a hERG IC<sub>50</sub> value >90 µM, making it a promising lead compound for further optimization.

## MEDI 311

### Hydrazolyl linked hybrids of sulfonate esters and 4-thiazolidinone: Design, synthesis, and biological evaluation as potent α-glucosidase inhibitors

**RAMANDEEP KAUR**, KULARRK91\_PHARMA@YAHOO.COM, Manoj Kumar. University Institute of Pharmaceutical Sciences, Panjab University Chandigarh, Chandigarh, Chandigarh, India

Diabetes mellitus is a chronic multifarious metabolic disorder characterized by high blood glucose levels that is recognized as a serious global health problem. α-Glucosidase is actively engaged in hydrolysis of dietary carbohydrates into smaller absorbable monosaccharides. Inhibition of this enzyme can directly control the postprandial increase in blood glucose levels by delaying the carbohydrate absorption therefore, considered as strategic therapeutic target for the design and development of drugs for type 2 diabetes. Thus, a series of 4-thiazolidinone linked to suitably substituted sulfonate esters through hydrazolyl spacer was rationally designed, synthesized and evaluated for *in vitro* α-glucosidase inhibition. The synthesized compounds exhibited outstanding α-glucosidase inhibition with IC<sub>50</sub> values in micromolar range. Inhibitory potential of synthesized analogues was many folds better than standard drug acarbose. Compounds were also assessed for *in vitro* antioxidant activity by potassium ferricyanide reducing power (PFRAP) assay. All synthesized derivatives demonstrated significant antioxidant potential. In order to substantiate the results, *in silico* binding studies of these newly synthesized compounds were carried out using molecular docking. The results obtained from the study may further be used to optimise the observations and identify “lead”.

## MEDI 312

### Design, synthesis, and antimicrobial evaluation of substituted urea derivatives containing alkyl/aryl moieties

Mahadev Patil<sup>3</sup>, Noonikara Poyil<sup>3</sup>, Alejandro Bugarin<sup>2</sup>, Shrinivas Joshi<sup>3</sup>, siddappa patil<sup>3</sup>, **Shivaputra Patil<sup>1</sup>**, shivaputrap@yahoo.com. (1) Pharmaceutical Sciences,

Rosalind Franklin University, North Chicago, Illinois, United States (2) Box 19065, UT Arlington, Arlington, Texas, United States (3) Centre for Nano & Material Sciences, Jain University, Bengaluru, Karnataka, India

A series of new substituted urea derivatives containing alkyl/aryl moieties was designed and synthesized. The proposed structures of all the synthesized compounds were confirmed using IR, <sup>1</sup>HNMR, <sup>13</sup>C NMR and mass spectroscopy. Also, the molecular structure of one urea derivative was unambiguously established by single crystal X-ray diffraction analysis. All compounds were evaluated for antimicrobial activity against five bacterial strains (*Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*) and two fungi (*Candida albicans* and *Cryptococcus neoformans*). Our *in vitro* antimicrobial screening identified efficacious antibacterial agent (**3a**: *Staphylococcus aureus*; 32.30±0.84% inhibition) and antifungal agent (**3b**: *Cryptococcus neoformans*; 53.60±6.92% inhibition).

### MEDI 313

#### Recombinant expression of xenobiotic and steroidogenic cytochrome P450 enzymes

**Laura Sanchez**<sup>1</sup>, [lsan009@yahoo.com](mailto:lsan009@yahoo.com), **Simone Brixius-Anderko**<sup>2</sup>, **Emily Scott**<sup>2</sup>. (1) Chemistry, Monmouth College, Monmouth, Illinois, United States (2) Medicinal Chemistry, University of Michigan College of Pharmacy, Ann Arbor, Michigan, United States

Cytochrome P450 enzymes catalyze key reactions in human drug metabolism and steroid hormone biosynthesis, but they can be difficult to study because these membrane proteins are difficult to generate recombinantly. The human drug-metabolizing P450 CYP3A5 has not been studied in depth due to difficulty with expression in *E. coli* and purification of this membrane protein. Recently, modification of the amino acid sequence permitted CYP3A5 expression in *E. coli*, making purification possible. Construction of the CYP3A5-expressing plasmid was accomplished by ligating the modified CYP3A5 cDNA into of the pCWori<sup>+</sup> vector. During purification the addition of the tight-binding ligand clotrimazole helped stabilize the CYP3A5 protein, while sonication as a method of cell lysis allowed for a greater recovery of CYP3A5. The human steroidogenic P450 CYP11B1 had recently been expressed as a fusion protein with its redox partner adrenodoxin (Adx) to examine their crucial protein-protein interaction, but protein expression yields were low. Conditions were altered to improve expression levels to permit further assays and crystallization. Promising amounts of Adx/CYP11B1 fusion protein were obtained using autoinduction as a preferred method of induction, and a 24-hour expression period, compared to Terrific Broth media, induction by IPTG, and longer growth periods. In addition, different arabinose concentrations were used to determine the optimal concentration for induction of chaperone proteins that assist with Adx/CYP11B1 folding and improve protein expression. Generation of recombinant protein will permit the study of the structure and

functions of important enzymes in human drug metabolism and steroid hormone synthesis.

## **MEDI 314**

### **Exploratory synthesis of novel cyclic and straight-chain 1,3-azaborines as potential HIV-1 protease inhibitors**

**Katia Hawley**, *Katia.Hawley@cwu.edu*, **Rachel Latsis**, *Rachel.Latsis@cwu.edu*, **Cheyenne Suarez**, *Cheyenne.Suarez@cwu.edu*, **Katherine Norris**, **Audrey Vulcano**, *Audrey.Vulcano@cwu.edu*, **Sean Dawson**, *Sean.Dawson@cwu.edu*, **Alexandria Williams**, *Alexandria.Williams@cwu.edu*, **Aleksey Lanin**, **Julianna Murray**, **Levente Fabry-Asztalos**, *fabryl@cwu.edu*. *Central Washington University, Ellensburg, Washington, United States*

Drug discovery for Human Immunodeficiency Virus (HIV) has resulted in life-saving therapies, making a large impact on modern medicine. However, current treatments are being met with high resistance rates towards HIV due to constant viral mutations, poor bioavailability, and patient noncompliance due to side effects. Consequently, there is an imperative need for the development of new lead compounds with lower toxicity, increased bioavailability, and higher binding affinity. Recent studies have shown boron-modified inhibitors have a higher inhibitory affinity for HIV-1 protease than the corresponding non-boron analogs. The main goal is to synthesize a library of cyclic and straight-chain boronates that may function as dual-mode, both associative and competitive, inhibitors of the HIV-1 protease. Cyclic boronates are expected to be more successful inhibitors due to their structural rigidity. The target boronates have the potential for greater affinity towards the protease enzyme, increased bioavailability, and fewer adverse side effects. In addition, the cyclic and straight-chain boronates being synthesized will serve to expand molecular diversity, as well as organoboron chemistry in general.

## **MEDI 315**

### **Examination of aminophenol-containing compounds designed as antiproliferative agents and potential atypical retinoids**

**Sarah Altman**<sup>1</sup>, *chb126@my.utsa.edu*, **Masahiko Ima**<sup>2</sup>, **Noriko Takahashi**<sup>2</sup>, **Terrence R. Burke**<sup>1</sup>. (1) *Chemical Biology Laboratory, Center for Cancer Research, National Cancer Institute, Frederick, Maryland, United States* (2) *Laboratory of Physiological Chemistry, Institute of Medicinal Chemistry, Hoshi University, Shinagawa, Japan*

Retinol, also known as Vitamin A, plays a role in vision, immunity, growth, and cellular differentiation. All-*trans* retinoic acid (RA) is an oxidized form of retinol that binds to retinoic acid receptors (RARs), resulting in modulation of gene expression related to vital physiological processes including cell growth, differentiation, survival, and death. In contrast, the isomeric RA variant, 9-*cis* retinoic acid, binds to retinoid X receptors

(RXRs), which can exist as heterodimers with RARs or other nuclear receptors. Retinoids (synthetic ligands that engage RARs) and rexinoids (RXR-binding compounds) have therapeutic value against a variety of metabolic diseases and cancer, particularly for the treatment of promyelocytic leukemia. Because retinoids, and to a lesser extent rexinoids, exert unwanted side-effects, there is a need to develop new therapeutic agents that are less toxic. "Atypical retinoids" are synthetic analogs that bind and transactivate RARs and have therapeutic promise as anticancer drugs. However, the mechanism of action of these agents is not completely understood. Fenretinide, [N-(4-hydroxyphenyl)retinamide], is an atypical retinoid that has chemopreventative and anti-proliferative properties, but it has side effects that include night blindness and ocular toxicity. Studies have shown *p*-dodecylaminophenol (DDAP, which contains structural elements of Fenretinide), to be even more potent in suppressing cancer activity in various cancer cell lines. Because DDAP achieves its effects without binding to RARs and RXRs, it might be possible to enhance its anticancer activity by introducing motifs found in retinoids and rexinoids. The current presentation will cover the design, synthesis, and biological evaluation of a series of analogs that explore this possibility.

## **MEDI 316**

### **Synthesis and biological evaluation of 1,2,3-triazole analogs of CFTR corrector VX-809**

**Jonathon Brace**<sup>1</sup>, [jon.brace@vikings.berry.edu](mailto:jon.brace@vikings.berry.edu), Savannah J. Post<sup>1</sup>, Nathan L. Thacker<sup>1</sup>, Liping Tang<sup>2</sup>, Steven M. Rowe<sup>2</sup>, Stephen G. Aller<sup>3</sup>, Mark L. Turlington<sup>1</sup>. (1) Chemistry and Biochemistry, Berry College, Mount Berry, Georgia, United States (2) Gregory Fleming James Cystic Fibrosis Research Center, University of Alabama, Birmingham, Birmingham, Alabama, United States (3) Pharmacology and Toxicology, University of Alabama, Birmingham, Birmingham, Alabama, United States

Cystic fibrosis (CF) is a lethal pulmonary disease caused by mutations to the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The most common CFTR mutation, deletion of phenylalanine at the 508<sup>th</sup> position (F508del), results in CFTR misfolding that causes significant protein degradation. VX-809 is a drug known to partially correct the misfolding of F508del-CFTR; however, better corrector drugs are needed for CF treatment. As a means to investigate the potential for generating improved correctors using the VX-809 scaffold as a starting point, the synthesis of 1,2,3-triazole analogs of VX-809 was explored. Synthesis of triazole analogs of VX-809 in which the central amide in VX-809 was replaced with the triazole bioisostere was accomplished via the copper-catalyzed azide-alkyne cycloaddition reaction. While triazole analogs of VX-809 displayed corrective activity in F508del-CFTR, the corrective activity was observed to be significantly decreased in comparison with VX-809. These findings suggest that the 1,2,3-triazole functionality is not optimal within the VX-809 structural framework.

## **MEDI 317**

## Discovery of novel anti-tubercular agent for the treatment of MDR/XDR TB

**Junghwan Choi**<sup>1</sup>, junghwan.choi@ip-korea.org, Sunhee kang<sup>1</sup>, Young Mi Kim<sup>1</sup>, Inhee Choi<sup>1</sup>, Aram Lee<sup>1</sup>, Guanghai Jin<sup>1</sup>, Vincent Delorme<sup>2</sup>, **Kaapjoo Park**<sup>1</sup>, kaapjoo.park@ip-korea.org. (1) Medicinal Chemistry, Institut Pasteur Korea, Seongnam-si, Korea (the Republic of) (2) Tuberculosis Lab, Institut Pasteur Korea, Seongnam-si, Korea (the Republic of)

### Background:

The most urgent clinical need is to discover potent agents capable of reducing the time of M-XDR tuberculosis therapy with a success rate comparable to susceptible tuberculosis. The last decade has seen the discovery of promising new agent classes for the management of tuberculosis, several of which are currently in clinical trials. However, given the high attrition rate during clinical development and emergence of resistance, the discovery of additional clinical candidates is clearly needed.

Our drug discovery was accelerated by applying our unique assay system which is more relevant with *in vivo* condition. We reported on a promising novel class of thienothiazolocarboxamide (TTCA) compounds as potential leads that block Mycobacterium tuberculosis growth. In this study, we synthesized TTCA derivatives by structural modification. Through lead optimization, they showed good activity against TB replicating not only in the liquid broth culture medium but also within macrophage.

### Material/methods:

In order to search for the novel scaffold which can be developed as potential antitubercular agents, about 30,270 compounds were subjected for phenotypic high-throughput screening (HTS) against not only to bacteria directly (extracellular) but also to infected bacteria inside the macrophages (intracellular). Compounds were subjected to screening in each HTS, and finally compounds which were active in both assays were selected. Once the hit was selected, synthesis was carried out in order to develop lead compounds supported by ADME/PK analyses of derivatives.

### Results:

In this study, we synthesized TTCA derivatives by structural modification. We designed and synthesized around 360 derivatives of TTCA. We have successfully synthesized two lead candidates with different R groups. TTCA compounds have better potency against intracellular bacteria. Also, TTCA compounds were active against tested clinical MDR strains with MIC less than 1 $\mu$ M. *In vitro* ADME and physicochemical properties profiling suggested that TTCA series have drug-like properties. In addition, TTCA series displayed not only potent *in vivo* efficacy but also orally available good *in vivo* pharmacokinetic(PK) properties.

## MEDI 318

**Development of novel treatments against inherited blinding diseases *Retinitis pigmentosa* and Leber's congenital amaurosis**

**Elisa Pileggi**<sup>1</sup>, *pileggie@cardiff.ac.uk*, **Gaia Pasqualetto**<sup>1</sup>, **Malgorzata Rozanowska**<sup>2</sup>, **Andrea Brancale**<sup>1</sup>, **Marcella Bassetto**<sup>1</sup>. (1) Medicinal Chemistry, School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff, Wales, United Kingdom (2) School of Optometry and Vision Sciences, Cardiff University, Cardiff, Wales, United Kingdom

Retinitis Pigmentosa (RP) and Leber's Congenital Amaurosis (LCA) are two of the most severe blinding diseases. Both of them can be caused by aggregation of the protein opsin, which transmits the visual signal in the retina. A cure for these conditions is not available.

Opsin aggregation is caused by mutations in its gene or to the absence of 11-*cis*-retinal, the endogenous ligand that binds the protein and stabilises its structure. Our approach is to consider pathologic opsin aggregation as a protein conformational disease, and design new small-molecule chemical chaperones which help opsin stability and prevent the protein-protein interactions leading to aggregation.

Using molecular modelling, different novel compounds with high predicted affinity for opsin have been identified. These compounds were synthesised and preliminary evaluated in a competitive binding assay using wild-type opsin and 9-*cis*-retinal. Several small-molecules were found to stabilise the protein and/or increase its affinity for the natural substrate, providing hits for structural optimisation.

These results led to the selection of structural analogues of the initial hits to identify more potent stabilisers for opsin: the design, synthesis and evaluation for efficacy and safety in cellular assays of these new compounds will be discussed.

## **MEDI 319**

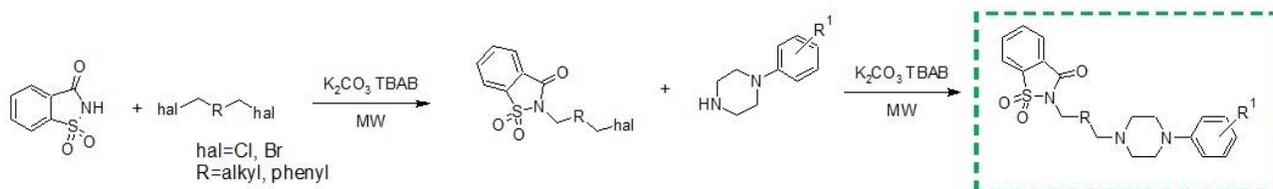
### **Synthesis and biological activity of a new saccharine derivatives as a dual D<sub>2</sub>/5-HT<sub>1A</sub> receptor ligands**

**Damian Kulaga**, *dkulaga@chemia.pk.edu.pl*. Cracow University of Technology, Kraków, Poland

Modern methods of drug design rely not only on developing a compound that exhibits a good pharmacological parameters but also should be easy to synthesize. This approach will significantly reduce the possible production costs of the future drug [1]. Ipsapiron is a partial agonist to the 5-HT<sub>1A</sub> receptor [2], belonging to the group of long-chain arylpiperazines (LCAPs) and having antidepressant and anti-anxiety properties [2]. Recent work of our team allowed to simplify the synthetic path and shorten the synthesis time of Ipsapiron from dozen hours to 2 minutes. Now it was decided to study the structure-activity relationship (SAR) by modifying the length of the alkyl chain and the aryl ring at the piperazine moiety.

The new compounds were obtained in solvent-free reactions supported by a microwave irradiation. This method can be considered as fast, efficient and consistent with the

trends of green chemistry. In the first step, the bromoalkyl / aryl saccharin was synthesized, and then obtained intermediate was alkylated with the corresponding arylpiperazines. The reaction time usually did not exceed 5 minutes. The final product was purified by crystallization or by chromatographic methods. A new compounds, were designed using molecular modelling and computational methods (*Cresset* and *Schroödinger* software packages). The calculated physicochemical parameters determining the properties of drug-like compounds were also considered. Each of the ligands obtained was tested in *in vitro* assay for the binding to the D<sub>2</sub> and 5-HT<sub>1A</sub> receptor. Preliminary results of biological tests for saccharin derivatives with a hexyl chain show that the compounds have very good affinity to the D<sub>2</sub> and 5-HT<sub>1A</sub> receptor.



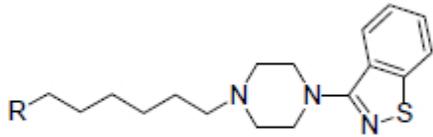
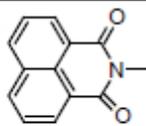
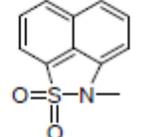
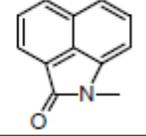
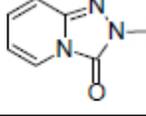
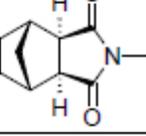
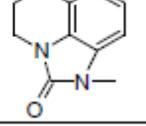
## MEDI 320

### New long-chain derivatives of 1-(1,2-benzisothiazol-3-yl)piperazine with high affinity for selected serotonin receptors

**Przemysław Zareba**, *przemeg13@gmail.com*, *Jolanta Jaskowska*, *Anna Drabczyk*. *Institute of Organic Chemistry and Technology, Cracow University of Technology, Cracow, Malopolskie, Poland*

The number of people suffering from depression exceeded 300 million, as shown a report of WHO (World Health Organization)<sup>[1]</sup>. The genesis of depression is associated with an inadequate level of some neurotransmitters, especially serotonin<sup>[2]</sup>. Currently, many drugs that control serotonin level are known, however, they are not effective enough and cause many side effects<sup>[3]</sup>. This is the reason to look for new, more effective antidepressants. Among the commercially available drugs, a group of compounds with a strong affinity for serotonin receptors is distinguished. These ligands belong to long-chain arylpiperazines having a 1,2-benzisothiazol-3-yl fragment attached to the piperazine ring. To this group belong Lurasidone<sup>[4]</sup>, Perospirone<sup>[5]</sup> and Ziprasidone<sup>[6]</sup>.

In the presented studies a new long-chain derivatives of 1-(1,2-benzisothiazol-3-yl)piperazine were synthesized. The obtained compounds were characterized for their affinity for selected receptors: D<sub>2</sub>, 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>6</sub> and 5-HT<sub>7</sub>. In addition, a new ecological, microwave assisted method of synthesis for the described compounds was developed. The obtained compounds were characterized by high affinity for mentioned receptors, which makes it possible to use them as potential drugs.

		Very active, Active				
R		D <sub>2</sub>	5-HT <sub>1A</sub>	5-HT <sub>2A</sub>	5-HT <sub>6</sub>	5-HT <sub>7</sub>
1		Yellow	Yellow	Yellow	Yellow	White
2		Yellow	Yellow	Yellow	White	Yellow
3		Yellow	Yellow	Yellow	White	Yellow
4		Green	Yellow	Green	White	White
5		Green	Yellow	Green	White	Green
6		Green	Yellow	Yellow	White	Yellow

## MEDI 321

### Structure-activity relationships of fragment-based inhibitors of *Trichomonas vaginalis* uridine nucleoside ribohydrolase

**Julia K. Persaud**<sup>1</sup>, [juliapersaud@mail.adelphi.edu](mailto:juliapersaud@mail.adelphi.edu), Samantha F. Thuilot<sup>1</sup>, Shannon Auletta<sup>1</sup>, Wagma Caravan<sup>1</sup>, Angelica Leonardo<sup>1</sup>, Tian Li<sup>1</sup>, Zaafir Dulloo<sup>1</sup>, Nafeesathul Hanan Kabir<sup>1</sup>, Dean G. Brown<sup>2</sup>, David W. Parkin<sup>1</sup>, Melissa A. Vanalstine-Parris<sup>1</sup>, Brian J. Stockman<sup>1</sup>. (1) Department of Chemistry, Adelphi University, Garden City, New York, United States (2) AstraZeneca Pharmaceuticals, Waltham, Massachusetts, United States

Trichomoniasis is the most prevalent non-viral sexually transmitted disease that infects an estimated 276 million people worldwide. Trichomoniasis is caused by *Trichomonas vaginalis*, a flagellated parasitic protozoan. Current 5-nitroimidazole treatments are

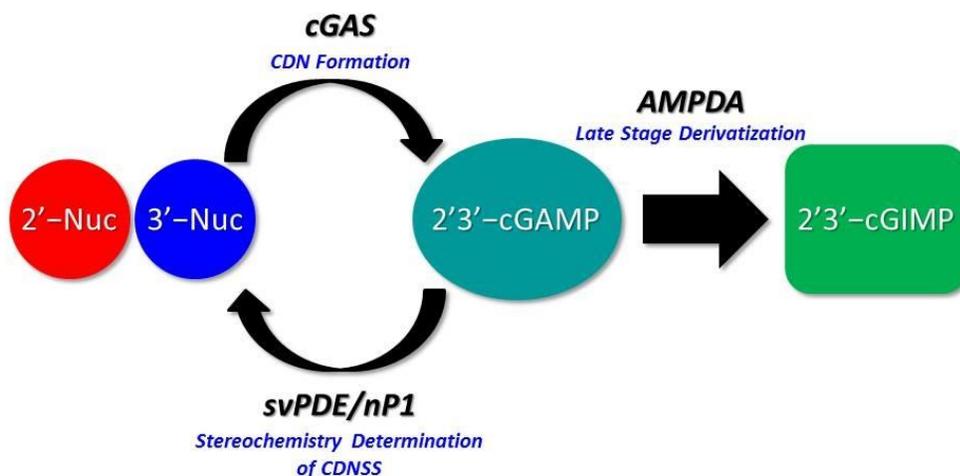
becoming less effective due to developing resistance by the parasite. For this reason, the advancement of improved treatments with novel mechanisms is crucial. *T. vaginalis* is incapable of *de novo* biosynthesis of nucleobases, and therefore its nucleoside ribohydrolases must scavenge them from the host. The uridine nucleoside ribohydrolase enzyme was previously screened against the NIH Clinical Compound Collection as well as a diversity fragment library using  $^{19}\text{F}$  NMR spectroscopy to monitor the hydrolysis of 5-fluorouridine. The most common fragment scaffolds identified were acetamides, benzimidazoles, cyclic ureas, pyridines, and pyrrolidines. These fragment scaffolds were used to select available similarity compounds and to synthesize new compounds in order to explore molecular complementarity within the enzyme active site. Collectively, the data defined emerging structure-activity relationships that suggest likely vectors and chemical modifications for improving inhibition potency while maintaining ligand efficiency. The structure-activity relationships suggest that the fragment scaffolds interact primarily with the nucleobase regions of the active site. Thus, larger compounds with substituents that extend into the ribose and  $\text{Ca}^{2+}$  binding regions are particularly attractive. The data establishes a platform for ongoing medicinal chemistry development of compounds with nM potency that will provide the tools for *in vitro* target validation against both 5-nitroimidazole-sensitive and 5-nitroimidazole-resistant *T. vaginalis* strains.

## **MEDI 322**

### **Novel applications of biocatalysis to late stage derivatization and stereochemistry determination of 2'3'-cyclic dinucleotide bisphosphorothioates**

*Jongwon Lim, jongwon\_lim@merck.com, Lisa Nogle, Hai-Young Kim, Josep sauri, yiping chen, jennifer piesvaux, Jared Cumming, Wes Trotter. Merck & Co., Inc., Boston, Massachusetts, United States*

Metazoan second messenger 2'3'-cGAMP, produced by DNA-activated cGAS, is a cyclic dinucleotide (CDN) that binds to and activates the ER-transmembrane adaptor protein STING, ultimately inducing secretion of type I interferons and immune system activation. This discovery has led to intense interest in CDNs as potential vaccine adjuvants and immunotherapeutics. The conversion of ATP and GTP into 2',3'-cGAMP by cGAMP synthase (cGAS) represents an impressive biocatalytic synthesis of a complex molecule. In the field of CDN biocatalysis, we have discovered a late stage derivatization of 2'3'-cGAMP to 2'3'-cGIMP via a highly efficient adenosine monophosphate deaminase (AMPDA) deamination. This biocatalytic transformation offers a substantial efficiency advantage over typical lengthy chemical synthetic routes to CDNs. Separately, we have also developed a novel biocatalytic method employing snake venom phosphodiesterase (svPDE) and nuclease P1 (nP1) and successfully applied it to stereochemistry determination of 2'3'-cGAMP bisphosphorothioates (2'3'-cG<sup>S</sup>A<sup>S</sup>MP). This method unambiguously assigned the phosphorothioate stereochemistry of the four diastereomers of 2'3'-cG<sup>S</sup>A<sup>S</sup>MP. The scope of reactivity and specificity of AMPDA, and regio- and stereo-specificity of svPDE and nP1 toward 2'3'-cyclic dinucleotide bisphosphorothioates (2'3'-CDNSS) will be presented.



## MEDI 323

### (1-4)-S-thiodisaccharides induction of ER stress as possible mechanism of glioblastoma cells death

Joanna Sarnik<sup>2</sup>, Anna Macieja<sup>2</sup>, **Zbigniew J. Witczak**<sup>1</sup>, [zbigniew.witczak@wilkes.edu](mailto:zbigniew.witczak@wilkes.edu), Tomasz Poplawski<sup>2</sup>. (1) Dept of Pharm SCI Sch of Phar, Wilkes Univ, Wilkes Barre, Pennsylvania, United States (2) Department of Molecular Genetics, Faculty of Biology and Environmental Protection, University of Lodz, Lodz, 90-232, Poland

(1-4)-S-thiodisaccharides with 1-4-thio bridge are possessing anti-cancer properties. They induced oxidative stress and apoptosis in cancer cells at the micromolar level [1,2]. However, the mechanism of their action is not clearly established. Many reports showed that induction of reactive oxygen species (ROS) is directly or indirectly provoked by ER stress. In this condition unfolded protein response (UPR) is activated. ER stress is sensed by three transmembrane proteins: PERK, ATF6 and IRE1 and activation this three signaling pathways is characteristic for UPR. Cell death is induced if the cell cannot deal with ER stress. We investigated the mechanism of action of two (1-4)-S-thiodisaccharides with sulfur bridge denoted respectively as FCP6 and FCP8 [Fig1] on glioma cells (U87 cell line). In order to determine the mechanism of activity we performed a series of tests including expression analysis at the mRNA and protein level. The methods are based on analysis of UPR-induced transcripts by qPCR (the following markers will be analyzed: EDEM, Grp78, ERP72, CHOP, ATF4, HERP, P58ipk and also XBP1 cleavage), and ELISA/ Western blot-based analysis of UPR-induced proteins or their modifications (CHOP, eIF2 $\alpha$ , Phospho-eIF2 $\alpha$ , GRP78, XBP1s, ATF6). These methods are able to monitor activation of all three sub-pathways of the UPR. We also analyzed cytosolic Ca<sup>2+</sup> influx using Fluoro-4-AM which generates green fluorescence upon interaction with Ca<sup>2+</sup>. Both (1-4)-S-thiodisaccharides induced ER stress and induction of apoptosis of glioma cell. We postulated that the anticancer mechanism of FCPs is a consequence of oxidative stress, endoplasmic reticulum stress, inhibition of protein synthesis and inhibition of thioredoxin reductase activity (as previously reported

1,2). The FCP6 was the most effective with low micromolar concentrations [ $IC_{50}$ = 65,2  $\mu$ M on U87 cell line].



### MEDI 324

#### Synthesis of 1,2,3-triazole analogs of CFTR potentiator VX-770

**Britton Ody**, *britton.ody@vikings.berry.edu*. Chemistry and Biochemistry, Berry College, Mount Berry, Georgia, United States

Cystic fibrosis (CF) is a lethal lung disease caused by mutations to the cystic fibrosis transmembrane conductance regulator (CFTR) protein that leads to loss of protein stability and/or function. VX-770 is an FDA-approved potentiator drug for the treatment of CF that combats CF by increasing the function of mutant forms of the CFTR protein. While VX-770 has revolutionized CF therapy, the search for additional CFTR potentiators remains a priority. In a variety of drug discovery projects, the substitution of amides with the bioisosteric 1,2,3-triazoles has been reported to increase potency and/or physicochemical properties of medicinal compounds. We report the synthesis of 1,2,3-triazole analogs of VX-770 in which the amide bond present in VX-770 was replaced with the triazole bioisostere in order to determine if this substitution would be beneficial. The synthesis of triazole-containing VX-770 analogs required the use of a suitable nitrogen protecting group for the quinolin-4(1H)-one scaffold found in VX-770 due to the incompatibility of this moiety with the Cu-catalyzed azide-alkyne cycloaddition reaction. The development of a synthetic method to access triazole analogs of VX-770 has enabled evaluation of the suitability of the triazole as an amide bioisostere in this chemical scaffold.

### MEDI 325

#### Design, synthesis, and antimicrobial evaluation of dibenzothiophene sulfones derivatives

**Sawsan Alelaiwi**, *salelaiwi@mail.usciences.edu*. Chemistry and biochemistry, University of the sciences, Philadelphia, Pennsylvania, United States

The Centers for Disease Control and Prevention (CDC) has estimated that there are 2 million people infected with microorganisms that are resistant to antibiotics leading to

23,000 death cases each year in the United States. Consequently, there is an urgent need for the discovery of new antibiotics. Sulfa drugs continue to be an important class of synthetic antibiotics because they have significant biological activities, are inexpensive to produce, have low toxicity and a wide spectrum of activity (eg. anti-HIV, anti-malarial). The aim of this work is to design sulfone molecules as active compounds against antibiotic-resistant bacteria. A computational approach was used for the design of novel analogs of dibenzothiophene sulfones. We will then use these results to prioritize initial synthetic efforts. Newly synthesized compounds will be evaluated in a biochemical assay to confirm and/or refine computational predictions. This work will provide the foundation for further efforts to identify and synthesize structures with the improved potency.

### **MEDI 326**

#### **Discovery of *in situ* click chemistry compatible analogs of F508del-CFTR corrector VX-809**

*Olivia R. Brown, olivia.brown2@vikings.berry.edu, Mark L. Turlington. Chemistry and Biochemistry, Berry College, Mt. Berry, Georgia, United States*

Cystic Fibrosis (CF) is an obstructive and chronic disorder that affects the mucosal linings of multiple organs. CF results from mutations to the cystic fibrosis transmembrane conductance regulator (CFTR) protein, with the most prominent mutation being the deletion of phenylalanine 508 or the F508del mutation. The FDA-approved drug Lumacaftor (VX-809) has been found to partially correct the folding defect of F508del-CFTR. However VX-809 produces only modest gains in lung function of CF patients, and drugs which more effectively improve the folding of F508del-CFTR are necessary for the next generation of improvement in CF therapy. *In situ* click chemistry (isCC) represents a drug discovery strategy that uses the biological target to catalyze the azide-alkyne cycloaddition reaction to form triazole containing small molecules that inherently have strong interactions with the target of interest. We report the synthesis and biological evaluation of analogs of VX-809 that are compatible with the *in situ* click chemistry approach. Several isCC-compatible VX-809 analogs were found to be active correctors of F508del-CFTR, making possible further studies to test the implementation of the isCC strategy to discover improved correctors for F508del-CFTR.

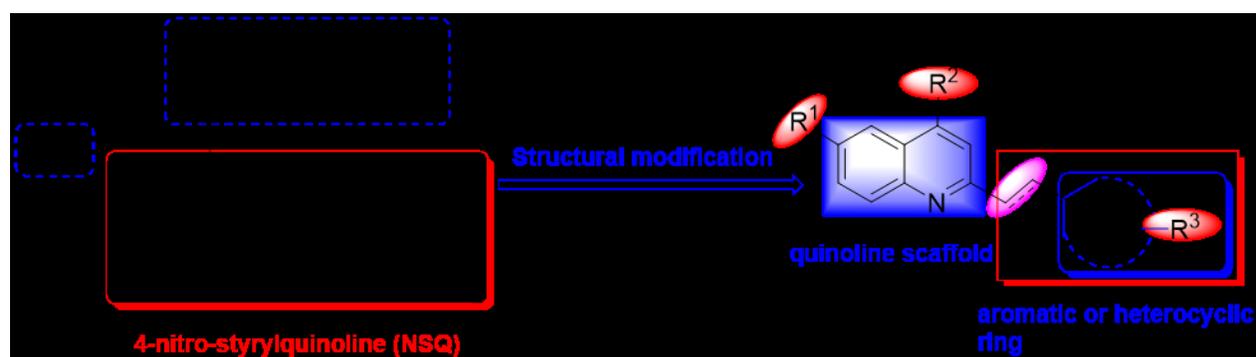
### **MEDI 327**

#### **Design, synthesis, and structural activity relationships of styrylquinoline derivatives as potent antimalarial agents**

*Guang Huang<sup>1</sup>, guanghuangmedchem@hotmail.com, Claribel Solano<sup>2</sup>, Joshua Kreisel<sup>1</sup>, Arash K. Arshad<sup>2</sup>, Debopam Chakrabarti<sup>2</sup>, Yu Yuan<sup>1</sup>. (1) Department of Chemistry, University of Central Florida, Orlando, Florida, United States (2) College of*

Medicine/Division of Molecular Microbiology, University of Central Florida, Orlando, Florida, United States

Malaria is one of the most prevalent parasitic infections for mankind, with over 40% of the world's population at risk for malaria. The effectiveness of current antimalarial therapies, even that of gold-standard antimalarial drugs (artemisinin-based combination treatments, ACTs), is under threat by the emergence of drug-resistant parasites. Therefore, there is a pressing need for new antimalarials. Our previous investigations demonstrated that 4-nitro-styrylquinoline analogue (**NSQ**) exhibited promising antimalarial activity and excellent selectivity. Herein, we report a part of our follow-up study on the relationship between structure ( $R^1$  and  $R^2$  groups located at position C6 and C4 respectively, as well as the absence of styryl moiety or double bond between quinoline scaffold and  $R^3$ -substituted aromatic or heterocyclic ring) and antimalarial activity of styrylquinoline, the aim of which was to identify new compounds with significantly enhanced activity over **NSQ** towards *P. falciparum* *in vitro* and murine *P. berghei* ANKA *in vivo*, holding the potential for the treatment of malaria.



Design, synthesis and structural-activity relationships of styrylquinoline derivatives as potent antimalarial agents

MEDI 328

NMR-based counter screens of fragment inhibitors of *Trichomonas vaginalis* uridine nucleoside ribohydrolase confirm reversible, target-specific inhibition

**Samantha F. Thuilot**<sup>1</sup>, [samanthathuilot@mail.adelphi.edu](mailto:samanthathuilot@mail.adelphi.edu), **Julia K. Persaud**<sup>1</sup>, **Dean G. Brown**<sup>2</sup>, **David W. Parkin**<sup>1</sup>, **Brian J. Stockman**<sup>1</sup>. (1) Department of Chemistry, Adelphi University, Garden City, New York, United States (2) AstraZeneca Pharmaceuticals, Waltham, Massachusetts, United States

Trichomoniasis, the most prevalent, non-viral sexually transmitted infection in the world, is caused by the parasitic protozoan *Trichomonas vaginalis*. The parasite is incapable of *de novo* synthesis of purine and pyrimidine rings; therefore it relies on salvage pathway enzymes such as pyrimidine preferring uridine nucleoside ribohydrolase to

obtain them from the host. Strains of the parasite have shown increasing resistance to the current metronidazole therapies, indicating the need for novel therapies. Uridine nucleoside ribohydrolase was previously screened against inhibitors from a fragment diversity library using a  $^{19}\text{F}$  NMR-based activity assay to monitor substrate hydrolysis, using 5-fluorouridine as the substrate. Several classes of inhibitors emerged from the library including acetamides, cyclic ureas, pyrrolidines, and pyridines. In order to validate those compounds as target-specific inhibitors, three different counter screen assays were carried out on several compounds from each class. Assays in the absence and presence of 0.01% Triton X-100 ruled out aggregation based inhibition. Jump-dilution assays carried out at 200  $\mu\text{M}$  and 20  $\mu\text{M}$  confirmed non-covalent, reversible inhibition. Four-fold increased substrate assays provided evidence for active site binding. The NMR assays proved remarkably robust for all the counter screens. Collectively, the counter screens demonstrated that all classes of compounds are well-behaved, target-specific, reversible inhibitors.

## **MEDI 329**

### **Molecular modeling and NMR-based counter screens of fragment inhibitors of *Trichomonas vaginalis* adenosine/guanosine nucleoside ribohydrolase**

**Abinash Kaur**<sup>1</sup>, [abinashkaur@mail.adelphi.edu](mailto:abinashkaur@mail.adelphi.edu), **Juliana Gonzalez**<sup>1</sup>, **Dean G. Brown**<sup>2</sup>, **David W. Parkin**<sup>1</sup>, **Brian J. Stockman**<sup>1</sup>. (1) Department of Chemistry, Adelphi University, Garden City, New York, United States (2) AstraZeneca Pharmaceuticals, Waltham, Massachusetts, United States

Trichomoniasis is the most prevalent, non-viral sexually transmitted disease in the world. It is caused by the parasitic protozoan, *Trichomonas vaginalis*, which is incapable of de novo synthesis of purine and pyrimidine rings. Since current 5-nitroimidazole drug treatments show common repeat infections due to increased resistance by the parasite, the development of a novel drug therapy is necessary. A key nucleoside salvage pathway enzyme, adenosine/guanosine nucleoside ribohydrolase, is a distinct, druggable target. Inhibition would prevent the production of free purine nucleobases which the parasite requires. A  $^1\text{H}$  NMR-based activity assay was previously used to screen the enzyme against a fragment diversity library, resulting in the identification of nine inhibitor classes. Representative fragments from each structural class were subjected to two independent counter screens in order to confirm reversible, target-specific inhibition. A ten-fold jump dilution assay proved that the inhibitors were reversible, while the addition of Triton X-100 detergent validated target-specific activity. The NMR-based activity assay was very useful for these counter screens since it provided direct observation of substrate, product, and inhibitor resonances simultaneously. In the absence of a crystal structure, molecular modeling was then used to map the binding orientation of fragment inhibitors in the active site. A predicted apoenzyme model was built based on structurally similar nucleoside ribohydrolase enzymes within the PDB using I-TASSER. IONCOM was then used to add the conserved calcium cation to the active site. BSP-SLIM molecular docking was then utilized to project predicted orientations of the adenosine ligand and fragment inhibitors

onto this predicted model. Molecular modeling in combination with structure-activity relationships is being used to guide ongoing medicinal chemistry efforts to discover nM inhibitors of the enzyme for in vitro target validation.

## **MEDI 330**

### **Novel class of STING agonists that self-assemble into nanostructures are potent anti-cancer immuno-therapeutic agents**

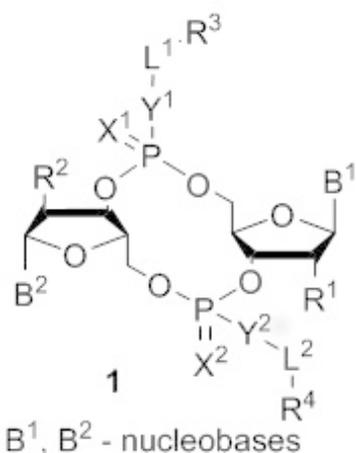
*Anjaneyulu Sheri<sup>1</sup>, anjan@springbankpharm.com, Seetharamaiyer Padmanabhan<sup>1</sup>, Geeta Meher<sup>1</sup>, Rayomand H. Gimi<sup>1</sup>, Dillon Cleary<sup>1</sup>, Santosh Khedkar<sup>2</sup>, Sreerupa Challa<sup>1</sup>, Shenghua Zhou<sup>1</sup>, Vishal Nair<sup>1</sup>, Leena Suppiah<sup>1</sup>, Diane Schmidt<sup>1</sup>, Nezam Afdhal<sup>1</sup>, Radhakrishnan Iyer<sup>1</sup>. (1) Spring Bank Pharmaceuticals Inc, Milford, Massachusetts, United States (2) ChembBio Discovery Solutions, Lexington, Massachusetts, United States*

**Background:** The activation of innate and adaptive immunity via Stimulator of Interferon Genes (STING) signaling is a potentially transformative immuno-therapeutic strategy in cancer. Using structure-based drug design and focused library synthesis, we have discovered novel cyclic dinucleotides, that self-assemble into nanostructures, show potent STING agonist activity in vitro, and profound anti-tumor activity in syngeneic mouse tumor models when administered by i.v., i.p., and i.t., routes.

**Methods: (a) Synthesis.** Focused libraries of cyclic dinucleotides (**1**) were prepared using phosphoramidite chemistry.

**(b) Binding affinity** of compounds with human STING CTD was determined by SPR assay, **(c) STING-dependent Induction of IRF and NF-KB** was assessed as % fold-change in luminescence by treating cells, carrying reporter constructs, with compounds, **(d) Self-assembly to nanostructures** was determined using Scanning Electron Microscopy, **(e) In vivo efficacy** was assessed by measurement of mean tumor volumes of lead compounds administered by i.v. (3 to 6mg/kg) or i.t. (10 to 100mg) in the A20 lymphoma, CT26 carcinoma, B16 melanoma, and 4T1 breast cancer models. Flow cytometry, multiplexing assays and immuno-histochemistry of blood, and tissues were carried out to assess MOA.

**Results:** Lead compounds (EC<sub>50</sub> 1 to 10 nM) were found to self-assemble into 1 mM nanostructures that facilitated their uptake by immune cells. Highly potent and durable antitumor response in multiple tumor models was observed with M.E.D 10 mg (i.t.), and 1 mg/kg (i.v.). IND-enabling studies are in progress.

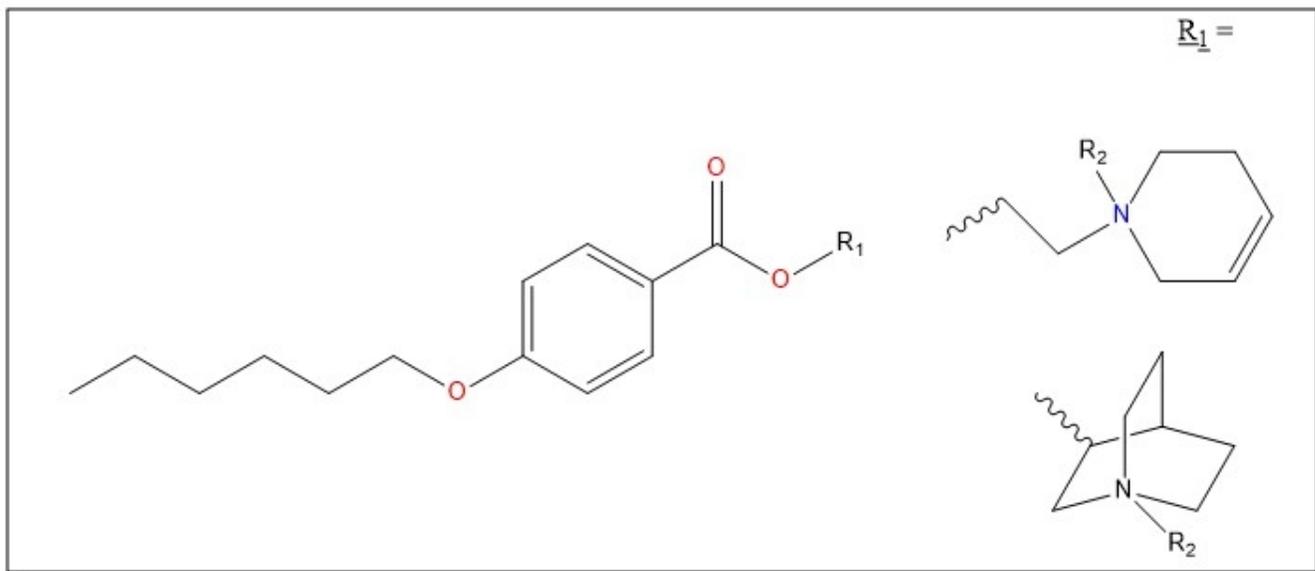


## MEDI 331

### Synthesis of novel functionally selective and long-acting muscarinic antagonists

**Lilyveth Mesa**, *lilyveth.mesa@mymail.barry.edu*, **Chelsea Martin**, *chelsea.martin@mymail.barry.edu*, John Boulos. *Physical Sciences, Barry University, Miami Shores, Florida, United States*

Muscarinic acetylcholine receptors, belonging to the G protein-coupled receptor (GPCR) family, are known to play important biological roles due to their extensive distribution in various tissue types. Due to highly conserved orthosteric sites amongst the receptor family, the design and synthesis of selective and efficacious muscarinic receptor dualsteric ligands may provide a viable approach for the treatment of certain central nervous and peripheral system disorders. Derivatives of 4-hexyloxy-1-[2-(4-oxidobenzoyloxy)ethyl]-1,2,3,6-tetrahydropyridin-1-ium and 4-hexyloxy-(4-oxidobenzoyloxy)-3-quinuclidinyl-1-ium were found to non-competitively antagonize functional response to carbachol with high potencies in the nanomolar range. Under washing condition, the half-life of antagonistic actions was found to be several hours. Overall, compounds were determined to be potent long-acting antagonists. These novel prototypical functionally selective antagonists may be of therapeutic interest for the treatment of several disease states.



### MEDI 332

#### Cyclooxygenase-2 inhibitory activity of metal-curcumin complexes

**James Harder**, *jharder1@live.maryville.edu*, **Anuradha Vummenthala**, *avummenthala@maryville.edu*, **Marilyn Vazquez**, *mvazquez1@live.maryville.edu*. Maryville University of St. Louis, St. Peters, Missouri, United States

Cyclooxygenase-2 (COX-2) is an enzyme responsible for inflammation and pain. COX-2 inhibitors are known to possess anti-inflammatory activity. Curcumin, a major chemical constituent of the spice turmeric, is known to possess variety of biological activities including anti-cancer, anti-bacterial, anti-Alzheimer's, and anti-inflammatory. The major drawback in the biological activity of curcumin is its poor bioavailability. Literature results suggested that conversion of Curcumin to a metal complex not only addressed the poor bioavailability, but also showed increasing anti-cancer and anti-oxidant activities. This research study focusses on the synthesis of various Metal-Curcumin complexes and evaluating their COX-2 inhibitory activity. ELISA results suggested that some of the metal complexes inhibited COX-2 better than Curcumin.

### MEDI 333

#### Synthesis of new $\beta$ -benzyloxy-*N*-phenethylamines as biogenic amine neurotransmitter transporter blockers

**Sebastian Almendras**<sup>1</sup>, **Angélica Fierro**<sup>1</sup>, **Jorge Campusano**<sup>2</sup>, **Jose Eltit**<sup>3</sup>, **Edwin G. Pérez**<sup>1</sup>, *egperezh@gmail.com*. (1) Organic Chemistry, Pontifical Catholic University of Chile, Santiago, RM, Chile (2) Cellular and molecular biology, Pontifical Catholic University of Chile, Santiago, RM, Chile (3) Physiology and Biophysics, Virginia

We designed and prepared a series of  $\beta$ -benzyloxy-*N*-phenethylamines compounds with potential activity as monoamine transporter uptake inhibitors. The new compounds were based on the structure of an analogue of the commercial antidepressant fluoxetine. These compounds were synthesized using, as the key step, the copper-catalyzed aminooxygenation or aziridinization of styrenes. Taking advantage of this chemical reactivity, we made a new series of compounds varying the aromatic moieties one at a time. See Figure 1. All the new compounds were tested as monoamine neurotransmitter transporter blockers using a fluorescence assay and molecular modeling studies were performed to rationalize possible interactions of our compounds with the different monoamine neurotransmitter transporters.

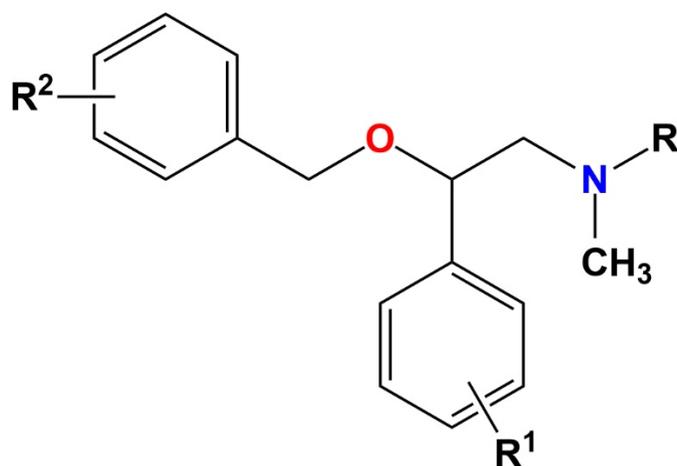


Figure 1. General structure of compounds synthesized as monoamine transporter blockers. R=H or CH<sub>3</sub>, R<sup>1</sup> and R<sup>2</sup> = different functional groups such as F, Cl, Br, CH<sub>3</sub> or CF<sub>3</sub>.

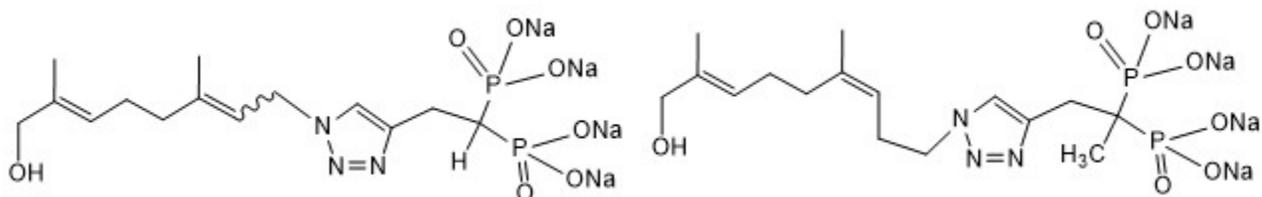
## MEDI 334

### Synthesis of $\omega$ -hydroxy isoprenoid bisphosphonates as potential GGDPS inhibitors

**Nazmul Bhuiyan**<sup>1</sup>, [mdnazmulhasan-bhuiyan@uiowa.edu](mailto:mdnazmulhasan-bhuiyan@uiowa.edu), Michelle Varney<sup>2</sup>, Sarah A. Holstein<sup>2</sup>, David F. Wiemer<sup>1</sup>. (1) Chemistry, Univ of Iowa, Iowa City, Iowa, United States (2) Internal Medicine, Univ of Nebraska Medical Center, Omaha, Nebraska, United States

Malignant plasma cells produce and secrete large amounts of monoclonal protein which contributes significantly to the morbidity of multiple myeloma. A novel therapeutic strategy may be achievable by disrupting the secretion of monoclonal protein through the inhibition of the isoprenoid biosynthetic pathway enzyme geranylgeranyl diphosphate synthase (GGDPS). Our previous work has demonstrated that some isoprenoid triazole bisphosphonates are potent and selective inhibitors of GGDPS. In an

extension of that research new analogues with  $\omega$ -hydroxy groups have been synthesized, and evaluation of their enzymatic and cellular activity is currently underway. If the biological activity can be preserved despite this modification, inclusion of the  $\omega$ -hydroxy group would allow for linkage to selective delivery agents. The synthesis of these compounds together with their bioactivity in human-derived myeloma cell lines will be presented.



### MEDI 335

#### Design, synthesis, and biological evaluation of water-soluble amino acid prodrugs of a rhein-derived anti-cancer agent

**Abiodun Anifowose**, [aanifowose1@gsu.edu](mailto:aanifowose1@gsu.edu), Zhengnan Yuan, Xiaoxiao Yang, Yueqin Zheng, Zhixiang Pan, Zhongwei Zhang, Binghe Wang. Chemistry, Georgia State University, Atlanta, Georgia, United States

Over the years, our lab has been working on some rhein-derived anthraquinone-based anti-cancer agents. A systematic approach was made to improve their aqueous solubility. **BW-AQ-238**, an analog of the lead compound was synthesized by introducing two hydroxyethyl groups. *In vitro* studies confirmed its comparable activity and mechanism of action with the lead compound. Prodrugs of **BW-AQ-238** were made by esterification of the hydroxyl group with various natural amino acids. Solubility and enzyme-catalyzed release kinetics of the parent drug as well as cytotoxicity in Hela and EU-1 cells were studied. The results suggested that the amino acid prodrugs significantly improved the solubility while maintaining the potency of the parent drug, therefore, could be considered as candidates for overcoming solubility problems.

### MEDI 336

#### Synthesis and biological evaluation of selective tubulin inhibitors as anti-trypanosomal agents

**Viharika Bobba**, [v.bobba17@vikes.csuohio.edu](mailto:v.bobba17@vikes.csuohio.edu). Chemistry, Cleveland State University, Copley, Ohio, United States

Human African trypanosomiasis, also known as African sleeping sickness disease, is a vector-borne parasitic disease in sub-Saharan Africa, is still a considerable burden on rural communities, most notably in central Africa. In the absence of vaccine, disease control relies on case detection followed by treatment, and vector control. Most of the available drugs are suboptimal, but ongoing clinical trials provide hope for safer and

simpler treatments. Previously, our lab developed a library of compounds which have exhibited selective inhibition of trypanosome cells, which was based on the tubulin protein structural difference, that showed promise to the treatment of this disease. In this study, we developed a synthetic scheme to derivatize and generate more potent tubulin inhibitors. Cell Proliferative assays were performed using MTS assay for *Trypanosoma brucei brucei* cells as parasite model, and MTT assay for human normal kidney cells and mouse macrophage cells as host model to evaluate the compounds. One new analog showed great potency with an IC<sub>50</sub> of 70 nM to inhibit the growth of trypanosome cells and did not affect the viability of mammalian cells. Western blot analyses reveal that the compound decreased tubulin polymerization in *T. brucei* cells (Shown in Fig-1). Hence, I hypothesize that, our compounds showed better selectivity to inhibit the parasite cell growth.

### **MEDI 337**

#### **Synthesis of triclosan derivatives that function as azo dyes**

*Sabrina Desmond, sdesmond@stetson.edu, Paul Sibbald. Chemistry, Stetson University, Deland, Florida, United States*

Triclosan is an antimicrobial compound commonly used in personal care products. There is a rising concern about the effect that triclosan has on the environment and human health as it bioaccumulates and deteriorates over time. This project illustrates the synthesis of two new azo dyes that are derived from triclosan's structure. The compounds were subjected to general biological tests and were shown to have antimicrobial properties.

### **MEDI 338**

#### **Synthesis and design of CRB, a resveratrol analog, reduces cell injury caused by surgery mimicking deep brain stimulation**

*Moses Lee<sup>1</sup>, mosesl@murdocktrust.org, Sara Gallemore<sup>2</sup>, Abigail Linberg<sup>2</sup>, Zachary DeBruine<sup>2</sup>, Balaji Babu<sup>2</sup>, Kimberly A. Brien<sup>2</sup>, Gregory Fraley<sup>2</sup>. (1) Senior Director, Scientific Research and Enrichment Programs, M. J. Murdock Charitable Trust, Vancouver, Washington, United States (2) Hope College, Holland, Michigan, United States*

Brain-implantable devices such as those used in deep brain stimulation (DBS) have a promising future in end-stage Parkinson's disease. However, inserting electrodes into the brain can cause astrocytic gliosis, inflammation and cell dystrophy, which is a major source of failure in chronically implantable electrodes. It is known from previous experiments that resveratrol significantly reduced tissue damage caused by DBS, however, because the metabolic half-life of resveratrol is short, an analog with longer biological activity is necessary. Our main hypothesis in this study is to test the effectiveness of CRB, a synthetic derivative of resveratrol, on reducing tissue damage

caused by DBS. In this presentation the design and synthesis of CRB will be described, along with the effects of CRB on preventing neuronal damage *in vivo* inflicted by DBS.

### **MEDI 339**

#### **Synthesis, optimization, and analysis of hexavalent sulfoglycodendrimers as anti-viral agents**

**Cory Vierra**<sup>1</sup>, *coryvierra@csus.edu*, **Katherine D. McReynolds**<sup>2</sup>. (1) *Chemistry, California State University, Sacramento, Orangevale, California, United States* (2) *California State Univ, Sacramento, California, United States*

A study into the optimization and green synthesis of a series of sulfated glycodendrimers (SGDs) has been conducted. In present research, a hexavalent dendrimer core was synthesized through a four-step green pathway to which discrete oligosaccharides were coupled. The glycodendrimers were synthesized utilizing low molar equivalents, mild reaction conditions and a laboratory grade microwave whenever possible. The ability of dendrimers to exhibit the multivalent effect makes them prime candidates for study. The multivalent effect refers the simultaneous attachment of multiple binding sites on one entity with multiple receptors on another. When studied, SGD's have shown inhibitory activity towards viral binding. This study focuses on the synthesis and evaluation of multiple SGDs to elucidate the structural features necessary for optimal antiviral activity. The SGD's antiviral efficacy will be analyzed through multiple methods to determine the inhibitory characteristics, cytotoxicity and binding strength. It is believed that the SGDs generated here will have significant antiviral characteristics.

### **MEDI 340**

#### **Synthesis and biological evaluation of nitrogen containing marine natural products**

**Christina Martinez-Brokaw**, *cdmarti3@ncsu.edu*, **Kaylib R. Robinson**, **Joshua G. Pierce**. *Chemistry, NC State University, Durham, North Carolina, United States*

The diverse molecular architectures of natural products have been a major source of inspiration for both novel reaction development and therapeutic lead molecules. The marine environment is regarded as one of the most prolific sources of chemical and biological diversity. Monanchocidin A, a pentacyclic guanidinium alkaloid, and the unique 4-oxazolidinone containing lipoxazolidinone A, are two recently isolated marine natural products that have shown to be potent anti-tumoral and antibacterial agents, respectively. Herein, progress towards the synthesis and biological evaluation of these two nitrogen-containing compounds is reported.

### **MEDI 341**

## 2-Amino-quinolin-4(1H)-ones as novel anti-coronavirus agents

**Chul Min Park**<sup>1</sup>, parkcm@kriict.re.kr, **Jong Hwan Song**<sup>1</sup>, **Jun Young Lee**<sup>1</sup>, **Jihye Lee**<sup>2</sup>, **Seungtaek Kim**<sup>2</sup>, **Hyoung Rae Kim**<sup>1</sup>. (1) KRICT, Daejeon, Korea (the Republic of) (2) Institut Pasteur Korea, Seongnam-si, Korea (the Republic of)

Middle East Respiratory Syndrome (MERS) is viral respiratory illness that was recently recognized in humans. It was first reported in Saudi Arabia in 2012 and has since spread to several other countries. Most people, identified as infected with MERS coronavirus (MERS-CoV), developed severe acute respiratory illness, including fever, cough, and shortness of breath. Many of them have died.<sup>1,2</sup>

MERS-CoV belongs to the coronavirus family, the same family of viruses that cause the common cold. MERS-CoV has so far shown to infect humans, camels, and bats. From camels, it can pass to humans, but how this happens is also unclear.

The lack of effective drug treatment and associated high morbidity and mortality rates of coronaviruses as well as their potential to cause epidemics highlight the need for novel drug discovery for the treatment of CoV infections.<sup>3</sup>

We tried to develop therapeutic agents against newly emerged MERS-CoV, which showed unique phenotype of persistency in the environmental settings, using antibody which can bind with spike proteins of MERS-CoV. We found 2-amino-quinolin-4(1H)-one scaffold after screening 200,000 compounds in Korean Chemical Bank (KCB). This presentation will discuss the synthesis and SAR of 2-amino-quinolin-4(1H)-ones which show good inhibition of infection and high cell viability.

## MEDI 342

### Translation of <sup>1</sup>H and <sup>19</sup>F NMR-based activity assays to *in vitro* characterization of nucleoside hydrolase activity in cell extracts and whole cells

**Madison Canestrari**, madisoncanestrari@mail.adelphi.edu, **Maham Mahmood**, **Samantha F. Thuilot**, **Brian J. Stockman**. Department of Chemistry, Adelphi University, Garden City, New York, United States

Trichomoniasis, the most prevalent non-viral sexually transmitted infection in the world, is caused by the parasitic protozoan *Trichomonas vaginalis*. Studies have indicated an association between *T. vaginalis* and a higher susceptibility to various other infections including chlamydia, HIV, and syphilis. The parasite has shown increasing resistance to the current treatment of 5-nitroimidazole drugs such as metronidazole. *T. vaginalis* is incapable of *de novo* synthesis of purine and pyrimidine rings, so it must rely on salvage pathway enzymes such as adenosine/guanosine preferring nucleoside ribohydrolase (AGNH) and uridine nucleoside ribohydrolase (UNH) to scavenge nucleobases. Both enzymes have been screened to identify fragment inhibitors with high ligand efficiencies to use as starting points for drug design. AGNH and UNH can be validated as antitrichomonal targets by demonstrating a correlation between enzyme inhibition and antitrichomonal activity. *Escherichia coli* cells with endogenous nucleoside ribohydrolase gene expression of *rihA* (*ybeK*), *rihB* (*yieK*) and *rihC* (*yaaF*) were used as

a surrogate to develop protocols for observing *in vitro* enzyme activity. A  $^1\text{H}$  NMR-based activity assay for AGNH using adenosine as the substrate and an  $^{19}\text{F}$  NMR-based activity assay for UNH using 5-fluorouridine as the substrate were previously developed for compound screening. These assays proved remarkably robust for observing nucleoside hydrolase activity in cell extracts and in whole cells. Signals for substrate and product are clearly distinguishable from background signals arising from the cell contents. Reactions have been shown to be cell-dependent, indicating that both enzymes are intracellular and that substrate can rapidly enter the cells. Similar experiments are now in progress using *T. vaginalis* strains to validate the molecular mechanisms of inhibition.

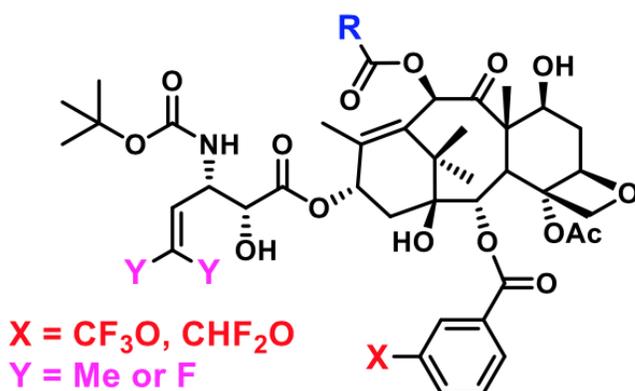
## MEDI 343

### Design, synthesis, and biological evaluations of next-generation taxoids, bearing *m*-OCF<sub>3</sub> and *m*-OCF<sub>2</sub>H groups at the C2 benzoate moiety

**Lei Chen**<sup>1</sup>, lei.chen.5@stonybrook.edu, Changwei Wang<sup>1,2</sup>, Wanrong Guo<sup>2</sup>, Xin Wang<sup>1</sup>, Yunrong Jing<sup>1</sup>, Yi Sun<sup>3</sup>, Iwao Ojima<sup>1,4</sup>. (1) Chemistry, Stony Brook University, Centereach, New York, United States (2) Chinese Academy of Sciences, Guangzhou Institute of Biomedicine and Health, Guangzhou, China (3) Chemistry Department, Stony Brook University, Mount Sinai, New York, United States (4) Institute of Chemical Biology and Drug Discovery, Stony Brook, New York, United States

Our SAR studies of taxane anticancer agents led to the discovery and development of new-generation taxoids bearing non-aromatic substituents (isobutenyl or isobutyl) at the C3' position and various acyl groups at the C10 position, as well as *meta*-substituted benzoyl groups at the C2 position. These taxoids exhibited 2–3 orders of magnitude higher potency than paclitaxel and docetaxel against MDR cancer cell lines. The primary metabolism of new-generation taxoids that bear a 3'-isobutenyl group was found to be the hydroxylation of the allylic methyl groups by CYP3A4. In the current drug design and discovery, fluorine is ranked second after nitrogen as “favorite heteroatom”. Thus, in order to prevent this allylic hydroxylation, we successfully introduced a difluorovinyl group in place of the 3'-isobutenyl group.

It has been shown that Ar-OCF<sub>3</sub> takes a unique conformation with dihedral angle of ca. 90 degrees, while the OCHF<sub>2</sub> moiety in F<sub>2</sub>HCO-arenes resides in between the planar OCH<sub>3</sub> and the orthogonal OCF<sub>3</sub>. The unique ability of the OCHF<sub>2</sub> group to adopt different conformations in polar and nonpolar environments can provide unusual combination of attractive properties, such as good aqueous solubility and cellular permeability, as well as low lipophilicity. Therefore, In this study, a series of next-generation 3'-isobutenyl- and 3'-difluorovinyl-fluorotaxoids, bearing *m*-OCF<sub>3</sub> or *m*-OCF<sub>2</sub>H group at the C2-benzoate moiety was designed, synthesized and examined for their potencies and pharmacological properties. A number of these next-generation fluorotaxoids possess two orders of magnitude greater potency against different drug-resistant cancer cell lines as compared to that of paclitaxel, and exhibited impressive killing curve profiles than a second-generation taxoid, SB-T-1214. SAR and some MOA studies will be discussed.



## MEDI 344

### Improved synthetic approach to CA IX selective inhibitors featuring one-pot cyclization/deprotection

**Haoxi Li<sup>1</sup>**, [h12500@chem.ufl.edu](mailto:h12500@chem.ufl.edu), **Akilah B. Murray<sup>2</sup>**, **Marta Quadri<sup>1</sup>**, **Robert McKenna<sup>2</sup>**, **Nicole Horenstein<sup>1</sup>**. (1) Department of Chemistry PO Box 117200, University of Florida, Gainesville, Florida, United States (2) McKnight Brain Institute, Department of Biochemistry and Molecular Biology, College of Medicine, University of Florida, Gainesville, Florida, United States

Carbonic anhydrase IX (CA IX) is an extra-cellular membrane-bound isoform of the  $\alpha$ -CA enzyme family. Upregulation of CA IX has been associated with tumor growth and proliferation, and identified as a potential anticancer drug target. Currently there are over 20 clinically used CA inhibitors, but to date none show CA IX isoform selectivity over other  $\alpha$ -CA isoforms. Cyclic secondary sulfonamides, such as saccharin (SAC), can inhibit CA IX with up to 60-fold isoform selectivity. Application of the “tail-approach” to develop inhibitors with higher CA IX selectivity have been achieved by connecting SAC (anchor) to a  $\beta$  glucoside (tail) with a methylene triazole linker, generated by copper mediated cycloaddition of acetylenic glycons and SAC derived azides. The selectivity towards CA IX was increased by up to 1000-fold for the SAC derivatization. When designing and synthesizing new inhibitors for CA IX, we found a problem in the final deprotection step of the existing synthetic scheme, which involved acid-catalyzed removal of a t-butyl protecting group of the SAC nitrogen. Therefore, we developed an improved synthetic approach for these compounds with a mild “one pot” deprotection and SAC ring formation in the final step. In this route, we utilized a ring-opened version of SAC with a sulfonamide nitrogen that was amenable to the required copper mediated cycloaddition. We also applied this method to the synthesis of new galactosyl and glucosyl conjugates.

With this approach, we are not only able to succeed in the click reaction with 76-95%

yields, but also cleave the acetyl protecting groups and cyclize the SAC ring under mild conditions in good yields (71-85%).

## **MEDI 345**

### **Synthesis, evaluation, and *in silico* study of structural analogs of colchicine as potential anticancer agents**

**Sabesan Yoganathan**, *yoganats@stjohns.edu*, Nishant Karadkhelkar, Pranav Gupta, Zhe-Sheng Chen. Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, St. Johns University, Jamaica, New York, United States

Cancer is characterized as a disease where uncontrolled growth of abnormal cells affects the normal physiological function of major organs. When cancer becomes metastatic, and affects the healthy function of cells, tissues and organs, it can lead to death in most cases. According to a report by American Cancer Society, the estimated new cases of cancer in 2018 is about 1.7 million and the estimated fatality due to cancer is more than 600,000. Despite the available treatment options, it has been extremely difficult to completely cure many types of advanced cancers. This deadly disease considerably diminishes the quality of life for millions of people. Hence, novel and more effective treatments are in high demand, especially new chemotherapeutics that can cure many difficult-to-treat cancers, and exhibit lower toxicity and overcome drug resistant. Our proposed program focuses on investigating novel structural analogs of colchicine, a known anticancer natural product. Colchicine exhibits poor therapeutic margin and a known substrate for P-glycoprotein (Pgp), a drug efflux pump. Tumors become resistant to many anticancer drugs via Pgp mediated efflux strategy. To address these limitations, we have designed and synthesized a library of structural analogs of colchicine that could potentially exhibit improved activity. The analogs are designed to include either dimethoxybenzoic acid (DMBA) or trimethoxybenzoic acid (TMBA) motifs as part of the structure due to their importance in anticancer activity. We have performed a cell viability assay to determine the anticancer activity of our first generation analogs. We are currently investigating the cell cycle analysis via flow-cytometry, and microtubules binding assay to probe the mechanism of action of most potent analogs. The second part of the study focuses studying the binding affinity of the synthetic analogs towards the drug-efflux pump, Pgp, using computational modeling. The *in silico* experiments will assist us in understanding the interaction of these molecules with Pgp and assist us in designing a second generation library of compounds. In conclusion, we have synthesized a library of new structural analogs of colchicine and their preliminary anticancer data are promising in guiding us to further fine-tune the biological profile of these new structures.

## **MEDI 346**

### **Synthesis of inhibitors of 1-deoxylulose- 5-phosphate reductoisomerase**

**Giulia Mancini**<sup>1</sup>, *gmancini1000@mail.usciences.edu*, John W. Tomsho<sup>2</sup>. (1) Chemistry & Biochemistry, University of the Sciences in Philadelphia, Philadelphia, Pennsylvania, United States (2) Department of Chemistry and Biochemistry, University of the Sciences in Philadelphia, Philadelphia, Pennsylvania, United States

Malaria and tuberculosis infections are the most widespread infectious diseases in the world. Approximately eight million new cases of tuberculosis are diagnosed every year and 500,000 deaths worldwide are attributed to malaria every year. Tuberculosis infections are caused by the bacteria *Mycobacterium tuberculosis* (*M. tuberculosis*) while malaria is caused by the parasite *Plasmodium falciparum* (*P. falciparum*). Certain strains of both *P. falciparum* and *M. tuberculosis* have become highly resistant to a wide variety of current drugs therefore new antimalarial and antituberculosis drugs with novel modes of action are urgently needed. For several reasons, the 2C-methyl-D-erythritol-4-phosphate (MEP or non-mevalonate) pathway constitutes an attractive target for the development of new anti-infective agents. This pathway is not present in humans but only in pathogens such as bacteria, fungi and protozoa. Also, it is responsible for the biosynthesis of the isoprenoid precursors isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) which play an important role in the life cycle of many pathogens. These isoprenoids are essential for the synthesis of the cell wall in *M. tuberculosis* and *P. falciparum*. Fosmidomycin is a potent, natural product inhibitor of the MEP pathway that acts via inhibition of the enzyme 1-deoxyxulose-5-phosphate reductoisomerase (IspC). Despite potent *in vitro* activity against IspC, fosmidomycin is highly hydrophilic and has poor bioavailability thus limiting its use as a therapeutic. For these reasons, the overall goal of this work is the design of a library of fosmidomycin analogs with increased lipophilicity, to improve cellular penetration and bioavailability. All compounds will be evaluated as inhibitors of *E.coli* IspC. We will also investigate their ability to inhibit *in vitro* growth of *E.coli* and *M. Smegmatis*.

## **MEDI 347**

### **Studies toward an amide core for zampanolide mimics as potential anti-prostate cancer agents**

**Maricarmen Gonzalez**, *mariglz913@outlook.com*, Guanglin Chen, Qiaohong Chen. Chemistry, California State University, Fresno, Arvin, California, United States

Zampanolide is a marine natural product that was first isolated in 1996 from the marine sponge *Faciospongia rimosa* in Okinawa, Japan. It possesses low nanomolar cytotoxicity against several cancer cell lines, including those that are drug resistant. Zampanolide is a unique microtubule stabilizing agent whose C9 binds covalently to the His229 of  $\beta$ -Tubulin. The limited supply prevents its further development towards clinical use. Additionally, the low metabolic stability of zampanolide is envisioned, at least partly, due to the easy cleavage of the lactone moiety catalyzed by esterase. Consequently, the overarching goal for this project is to develop a simplified zampanolide mimic, containing a stable lactam moiety yet retain its anticancer activity, through a manageable synthesis method. To this end, fragment C1-C8 of the

zampanolide mimic has been synthesized in 10 steps and fragment C13-C18 in seven steps, both starting with commercially available 2-butyn-1-ol. Furthermore, an amine group has been incorporated to fragment C13-C18 at the position of C17. This leads us to the position that is very close to the construction of the critical amide bond through the fusion of both fragments and our simplified lactam mimic core.

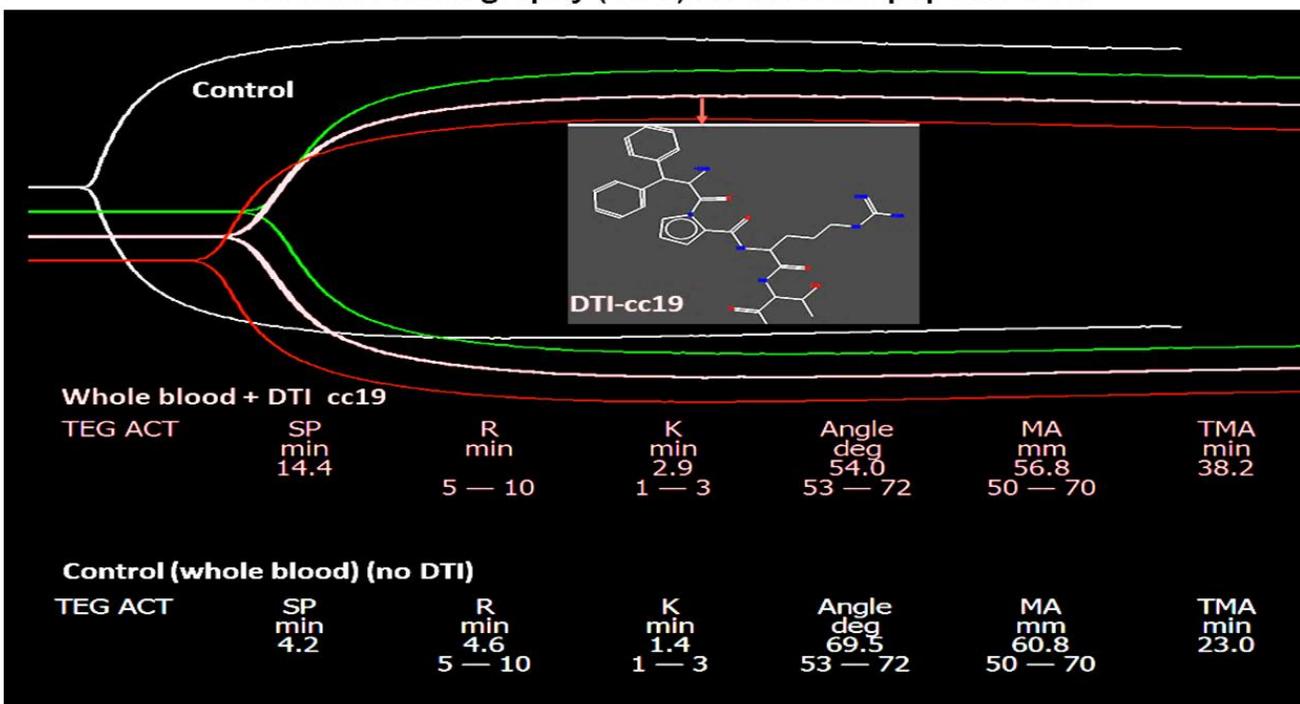
## **MEDI 348**

### **Structure-based design, synthesis and evaluation of D-3,3-diphenylalanine-based tetrapeptides inhibitors of thrombin-activated platelets aggregation and potent anticoagulants**

**Cristina C. Clement**<sup>1</sup>, *clement.cristina624@gmail.com*, Janet Gonzalez<sup>2</sup>, Anna Babinska<sup>3</sup>, Morayma R. Gil<sup>4</sup>. (1) Pathology Chemistry, Albert Einstein Coll Med CUNY, Bronx, New York, United States (2) Natural Sciences, LaGuardia Community College, Long Island City, New York, United States (3) Department of Medicine, State University of New York, Downstate Medical Center, Brooklyn, New York, United States (4) Hematology and Coagulation Labs Pathology, Montefiore Medical Center, Bronx, New York, United States

Thrombosis-related disorders such as myocardial infarction, stroke, and pulmonary embolism remain a major cause of morbidity and mortality worldwide, a fact that is driving increasing interest in thrombin inhibitors as potential antithrombotic drugs. In 2012, Clement CC et al. published the biochemical and structural characterization of three noncovalent, direct thrombin inhibitors (DTI) that contain the common sequence D-Phe(P3)-Pro-(P2)-DArg(P1)-P1'-CONH<sub>2</sub>. Herein, we report the optimization of the tetrapeptide scaffold by replacing D-Phe in the P3 position with the un-natural Phe-analog, D-3,3-Di-Phenylalanine. We performed a structure-based drug design (SBDD) and structure-activity relationship (SAR) at the P1' position by replacing L-amino acids with their D-isomers and other unnatural amino acids analogs. Two types of binding experiments were employed to assess the inhibitory constant (K<sub>i</sub>): (1) kinetics of alpha-thrombin inhibition of chromogenic substrate S2238; and (2) surface plasmon resonance (SPR) with immobilized alpha-thrombin. All D-3,3-Diphenylalanine-DTI analogs competitively inhibited alpha-thrombin's cleavage of the S2238 chromogenic substrate with K<sub>i</sub> of 500-20 nM that were further confirmed by the SPR assays. Remarkably, the novel DTIs inhibited the aggregation of human platelets in the "whole blood" thromboelastography (TEG) assay, as well as in the *ex-vivo* thrombin-activated platelets treatment. In addition, the peptidic DTIs showed potent inhibition of blood clotting monitored by aPTT, PT, and TT assays. These novel DTI tetrapeptides could be used as pharmacophore scaffolds for the development of inhibitors of thrombin-mediated platelets aggregation aiding the treatment of acute coronary syndrome (ACS). Moreover, the reported peptidic DTIs could be optimized as potential biomaterials with improved haemocompatibility for blood-contacting medical devices.

### Thromboelastography (TEG) for selected peptidic DTIs



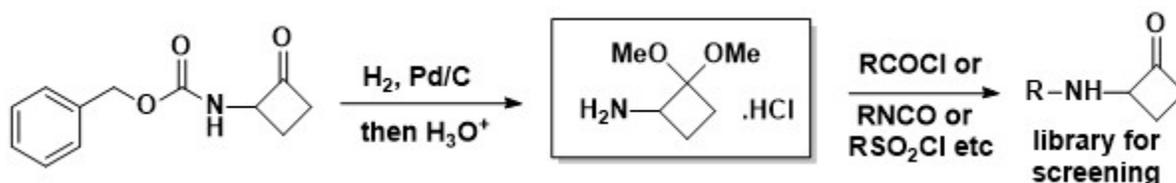
### MEDI 349

#### Synthesis of 2-aminocyclobutanones as potential serine- and metalloprotease inhibitors

**Thahani Shifna Habeeb Mohammad**<sup>1</sup>, [thabeebmohammad@luc.edu](mailto:thabeebmohammad@luc.edu), **Cory Reid**<sup>2</sup>, **Daniel P. Becker**<sup>1</sup>. (1) Chemistry and Biochemistry, Loyola University Chicago, Chicago, Illinois, United States (2) Chemistry, Northwestern University, Evanston, Illinois, United States

N-functionalized  $\alpha$ -aminocyclobutanones can act as peptidomimetics, and as the carbonyl is electrophilic due to ring strain, they may offer either specific or broad-spectrum inhibitors of serine- and metallo-  $\beta$ -lactamases, transpeptidases, serine proteases, and also provide inhibitors of serine hydrolases that are novel medicinal chemistry leads and targets for a variety of indications. We envisioned the utility of a free 2-aminocyclobutanone as a modular unit to employ in the preparation of libraries of cyclobutanone derivatives, including amides, carbamates, ureas, and sulfonamides, and have succeeded in preparing the building block 2-aminocyclobutanone protected as the dimethyl acetal and as the hydrochloride salt in 87% yield via single-pot debenzoylation/acetalization of the readily-available Cbz-2-aminocyclobutanone. This salt was subjected to an electrophilic functionalization reaction with a hydrolytic workup to give  $\alpha$ -benzamide- and  $\alpha$ -thiourea-cyclobutanones. The synthesis of a small library of peptidomimetic cyclobutanones including  $\alpha$ -benzamide-,  $\alpha$ -thiourea-, and  $\alpha$ -sulfonamide-cyclobutanones is in progress and the inhibitory potency will be tested

against a battery of serine and metallo  $\beta$ -lactamases, di-zinc enzymes and serine proteases.



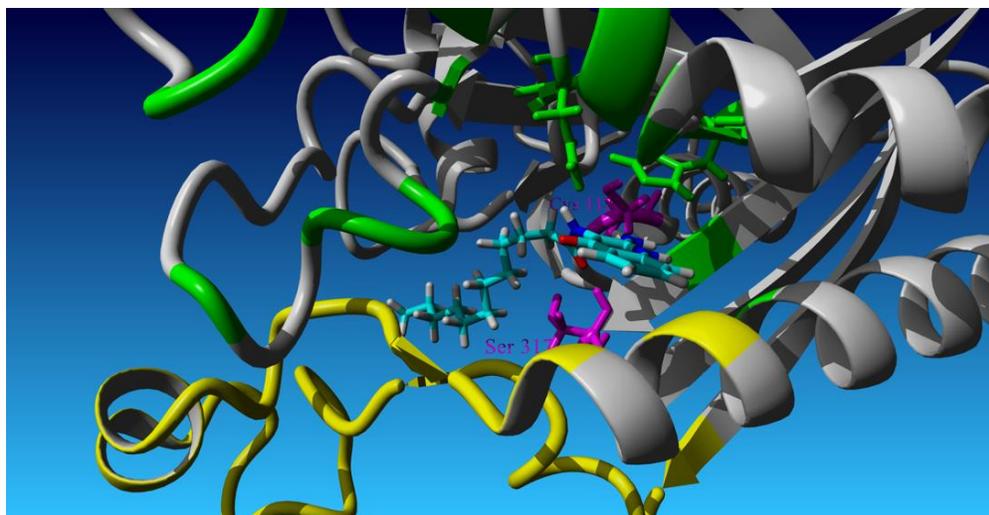
Synthesis of  $\alpha$ -aminocyclobutanone derivatives via one-pot debenzylation/acetalization of Cbz-2-aminocyclobutanone

### MEDI 350

#### Synthesis, *in silico*, and *in vitro* evaluation of long chain alkyl amides from 2-amino-4-quinolone derivatives as biofilm inhibitors

Marco A. Loza-Mejía<sup>2</sup>, **Sara Borbolla-Alvarez**<sup>1</sup>, sara96bo@gmail.com, **Ana E. Delgado**<sup>1</sup>, anaae1310@gmail.com, **Mariana Paola P. Espinosa Valdes**<sup>1</sup>, marpaoespval@gmail.com, Juan Fco. S. Tejeda<sup>1</sup>, Anabelle Cerón-Nava<sup>1</sup>, Osvaldo Javier Quintana-Romero<sup>3</sup>, Armando Ariza-Castolo<sup>3</sup>, Diego Fernando García-del Río<sup>1</sup>. (1) School of Chemistry, Universidad La Salle, Mexico, Mexico (2) Chemical Sciences School, Universidad La Salle Mexico, Nezahualcoyotl, Mexico (3) Química, CINVESTAV, Mexico DF, Mexico

Infection from multidrug resistant bacteria has become a growing health concern worldwide, increasing the need for developing new antibacterial agents. Among the strategies that have been studied, biofilm inhibitors have acquired relevance as a potential source of drugs that could act as a complement for current and new antibacterial therapies. Based on the structure of 2-alkyl-3-hydroxy-4-quinolone and *N*-acylhomoserine lactone, molecules that act as mediators of quorum sensing and biofilm formation in *Pseudomonas aeruginosa*, we have designed, prepared and evaluated the biofilm inhibition properties of long chain amide derivatives of 2-amino-4-quinolone in *Staphylococcus aureus* and *P. aeruginosa*. All compounds had higher biofilm inhibition activity in *P. aeruginosa* than in *S. aureus*. Particularly, compounds with an alkyl chain of 12 carbons exhibited the highest inhibition of biofilm formation. Docking scores and molecular dynamics simulations of the complexes of the tested compounds within active sites of proteins related to quorum sensing had good correlation with experimental results, suggesting the diminution of biofilm formation induced by these compounds could be related to inhibition of these proteins.



Docking pose of one of the compounds within the active site of PqsD

### **MEDI 351**

#### **Synthesis of small molecules based on novobiocin and the biphenylcyclohexane system that inhibit the Hsp90 molecular chaperone**

**Ang Zuo**, *azuo@nd.edu*, **Penchala N. Meka**, **Bradley Keegan**, **Brian S. Blagg**, *Chemistry, University of Notre Dame, Notre Dame, Indiana, United States*

Hsp90 C-terminal inhibitors were investigated based on promising data from preliminary studies and their potential application to cancer chemotherapy. Novobiocin and biphenylcyclohexane systems and analogues thereof were proposed to exhibit more potent inhibitory activity compared to the lead scaffolds. Consequently, synthetic pathways were designed and developed, and the inhibitory effects of the new compounds determined, all of which will be provided in this presentation.

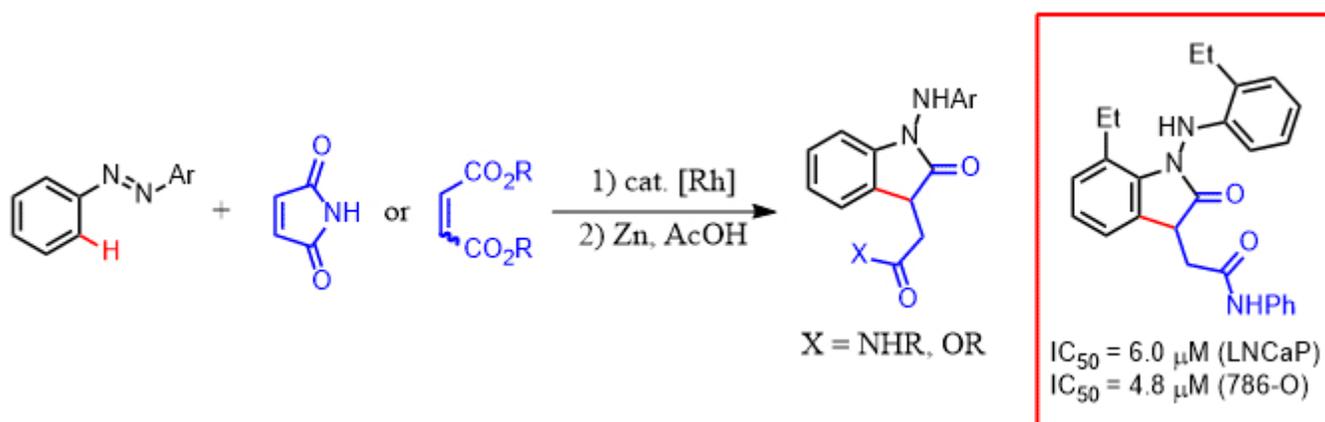
### **MEDI 352**

#### **Synthesis of oxindole derivatives via C-H alkylation and intramolecular cyclization: Access to Hit compound for anti-tumor agent**

**Sang Hoon Han**, *Sang0306@nate.com*, *Sungkyunkwan university, Suwon, GYEONGGI-DO, Korea (the Republic of)*

The Rh(III)-catalyzed site-selective C-H alkylation of azobenzenes with internal olefins, such as maleimides, maleates and fumarates, followed by reductive intramolecular cyclization is described. A cationic rhodium catalyst in the presence of acetic acid additive in DCE solvent was found to be the optimal catalytic system for the synthesis of *ortho*-alkylated azobenzenes, which smoothly underwent the annulation reaction leading to the formation of C3-functionalized oxindoles in the presence of zinc powder

and acetic acid. Actually, oxindole scaffold has been recognized as a ubiquitous heterocycle found in various natural compounds and synthetic products with medicinal applications. Particularly noteworthy was the resulting 1-amino-indolic framework, which represents a biologically important scaffold found in various synthetic molecules. Thus, the synthesized oxindoles have been screened cytotoxicity against human prostate adenocarcinoma cell lines (LNCaP), human breast cancer cell lines (MCF-7), human ovarian cancer cell lines (SKOV3), human lung carcinoma cell lines (A459) and human renal adenocarcinoma cell lines (786-O). With a rational design based on C-H alkylation and subsequent annulation process, we herein reported efficient access to the construction of oxindoles through Rh(III)-catalyzed site-selective alkylation of azobenzenes and internal olefins, such as maleimides, maleates and fumarates, followed by reductive intramolecular cyclization. The formed oxindole framework could be also an important architecture towards the development of novel bioactive molecules. Notably, some synthesized products were found to display potent anti-tumor activity.



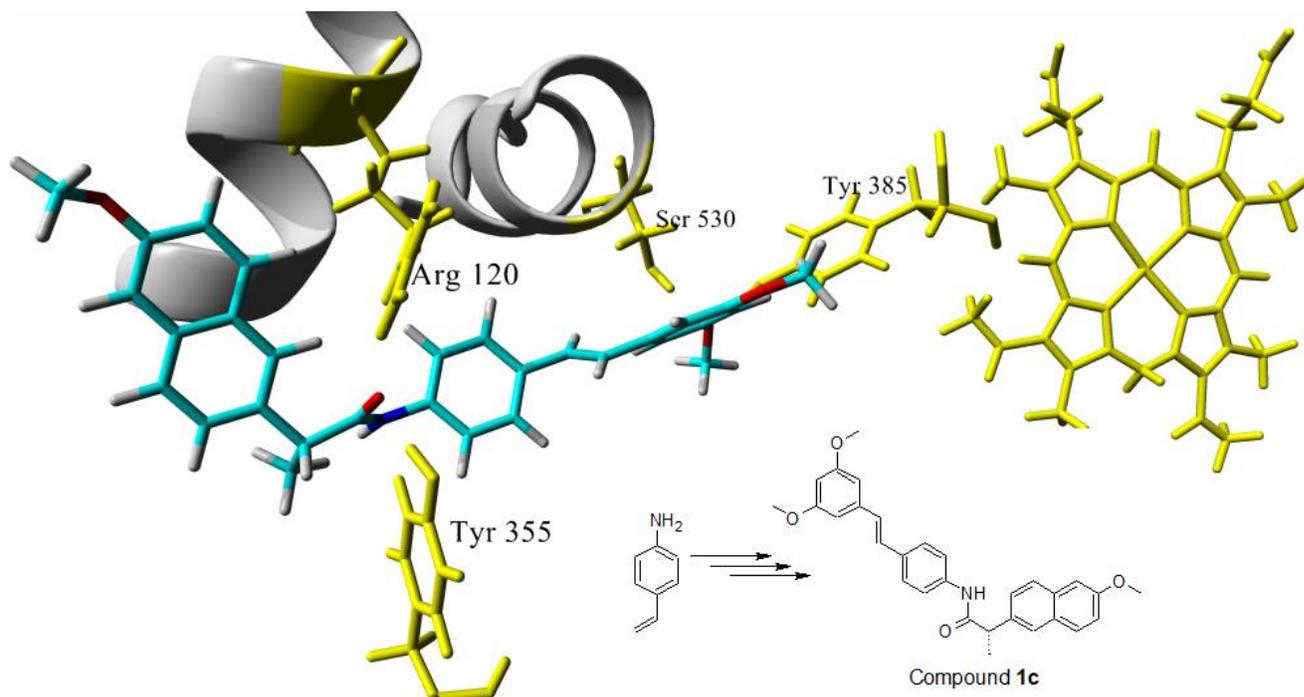
## MEDI 353

### Design, synthesis, and evaluation of resveratrol-NSAID hybrids as potential antioxidants and anti-inflammatories

**Miguel A. Enriquez-Pichardo**, Miguel.Angel.EP@outlook.com, **Salma S. Medina-Rosas**, salma\_smr@hotmail.com, **Guillermo Sánchez-Tejeda**, g\_sancheztejeda@outlook.com, Itzayana Rodríguez-Nuño, Jessica García-Ibarra, Héctor Mancilla-Díaz, Juan R. Salazar, Marco A. Loza-Mejía. Chemical Sciences School, Universidad LaSalle Mexico, Ciudad de México, Mexico

Resveratrol is a natural polyphenol which has been studied for its potential benefits for several pathological processes including cancer, aging, CVS disorders, chronic inflammation, and neurodegenerative diseases. Nevertheless, its poor ADME profile limits its application. Aiming to improve its pharmacokinetic properties and anti-inflammatory activity, we designed, prepared and evaluated some methylated resveratrol-NSAID hybrids connected through an amide bond. These compounds were prepared from 4-vinylaniline using a palladium-catalyzed oxidative-Heck coupling as the

key step in moderate yields. Docking studies predicted that they could bind to both COX-1 and COX-2 with the NSAID template interacting via hydrogen bonds with Arg 120 and Tyr 355 and the dimethoxystilbene moiety accommodates closer to the heme group. All compounds had from moderate to good in vitro antioxidant properties, though lower than resveratrol. Compound 1c had the best anti-inflammatory properties in the TPA-induced edema test and could be considered a good starting point for the design of novel hybrids with better antioxidant and anti-inflammatory properties.



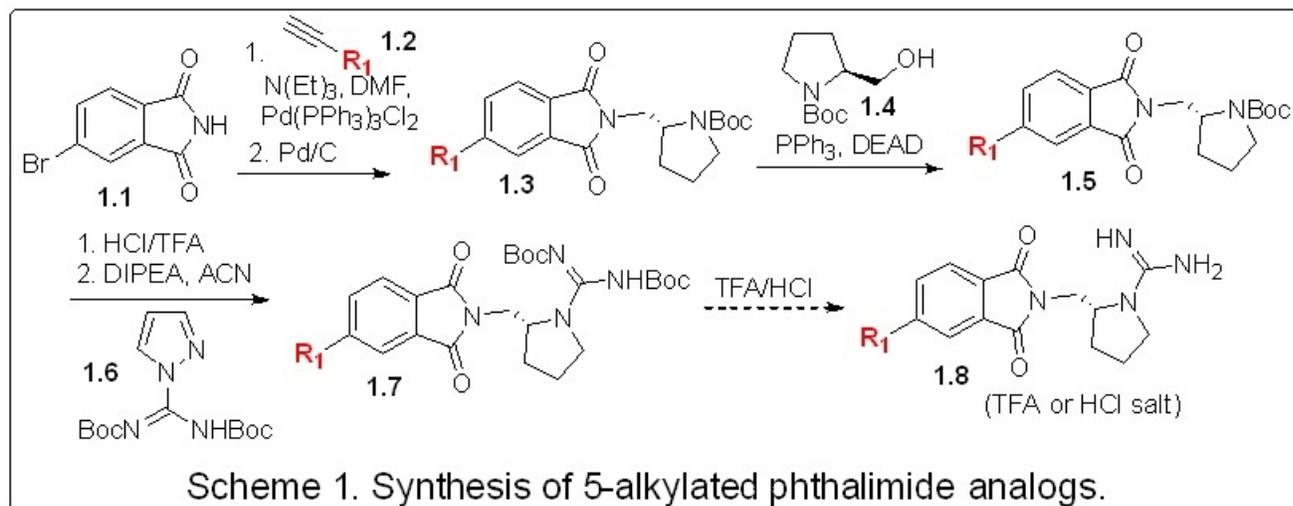
## MEDI 354

### Design, synthesis, and structure-activity relationship studies of phthalimide-based sphingosine kinase inhibitors

**Farjana Afrin**<sup>1</sup>, afrifarj@isu.edu, Katherine Obuch<sup>1</sup>, Yugesh Khare<sup>3</sup>, Webster L Santos<sup>2</sup>, Kevin R Lynch<sup>3</sup>, Srinath Pashikanti<sup>1</sup>. (1) Biomedical and Pharmaceutical Sciences, Idaho State University, Pocatello, Idaho, United States (2) Department of Chemistry and Center for Drug Discovery, Virginia Tech., Blacksburg, Virginia, United States (3) Pharmacology, University of Virginia, Charlottesville, Virginia, United States

Sphingosine-1-phosphate (S1P) is a bioactive sphingolipid that regulates growth, survival, and migration of several cell types. S1P is a ligand for five transmembrane G-protein-coupled receptors S1P<sub>1-5</sub> and for several intracellular targets such as histone deacetylases 1 and 2. Cellular biosynthesis of S1P occurs through phosphorylation of sphingosine (Sph) catalyzed by two isoforms of sphingosine kinase (SphK1 and 2). Pharmacologically, ceramide and Sph are associated with growth arrest and apoptosis. On the contrary, S1P is associated with pro-survival roles. SphKs & S1P have been implicated in a variety of disease states including cancer, sickle cell disease,

atherosclerosis, asthma, diabetes, and fibrosis, among others. Our extensive studies resulted in highly specific and potent SphK1 and SphK2 analogs. Current study is aimed at developing a phthalimide linker based Sphk inhibitors with improved solubility retaining the potency and selectivity. An efficient palladium-catalyzed cross-coupling followed by Mitsunobu strategy was employed in developing these analogs. Synthesis, *invitro* screening results will be discussed.



Scheme 1. Synthesis of 5-alkylated phthalimide analogs.

## MEDI 355

### Design, synthesis, and biological evaluation of truxillic acid-based fatty acid binding protein 5 (FABP5) inhibitors as anti-nociceptive and anti-inflammatory agents

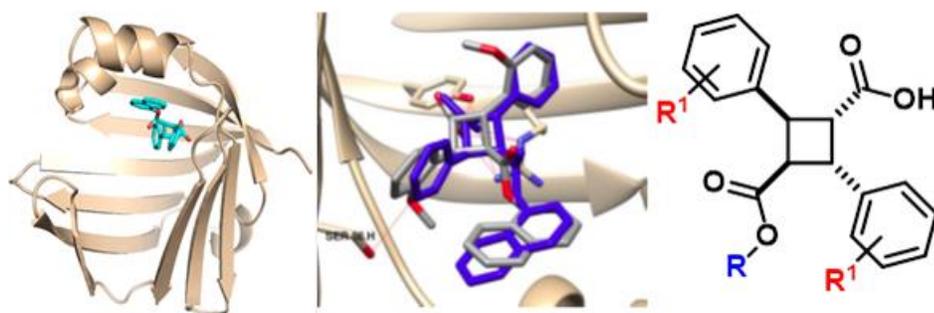
**Timothy S. Clement**<sup>1</sup>, [timothy.clement@stonybrook.edu](mailto:timothy.clement@stonybrook.edu), Monaf Awwa<sup>1</sup>, Adam Taouil<sup>1</sup>, Atri Maharaj<sup>1</sup>, Jinwoo Kim<sup>1</sup>, Yi Sun<sup>2</sup>, Antonella Pepe<sup>1</sup>, Huilin Li<sup>3</sup>, Dale G. Deutsch<sup>4,5</sup>, Matthew W. Elmes<sup>4</sup>, Martin Kaczocha<sup>4,5,7</sup>, Iwao Ojima<sup>6</sup>. (1) Chemistry, SUNY Stony Brook, Jamesport, New York, United States (2) Chemistry Department, Stony Brook University, Mount Sinai, New York, United States (3) Cryo-EM Structural Biology Laboratory, Van Andel Research Institute, Grand Rapids, Michigan, United States (4) Department of Biochemistry and Cellular Biology, SUNY Stony Brook, Stony Brook, New York, United States (5) Institute of Chemical Biology and Drug Discovery, SUNY Stony Brook, Stony Brook, New York, United States (6) Chem Dept/ICBDD, Stony Brook University, Stony Brook, New York, United States (7) Department of Anesthesiology, SUNY Stony Brook, Stony Brook, New York, United States

Fatty acid binding proteins (FABPs) modulate intracellular levels of the endocannabinoid arachidonoyl ethanolamide (anandamide, AEA). Inhibition of tissue specific FABPs results in increased levels of brain AEA, which acts upon type-1 cannabinoid receptors (CB1R) and thereby causes a suppression of pain transmission

and other therapeutically beneficial effects.

Previous work by our group has identified SB-FI-26, a monoester analog of  $\alpha$ -truxillic acid, as an inhibitor of the epidermal FABP (E-FABP, FABP5), and has shown both antinociceptive and anti-inflammatory effects in mice models.

To optimize the lead compound, we have conducted an extensive SAR study to identify selective FABP5 inhibitors. Each analog was selected based on its docking energy score to FABP5 and selectivity against FABP3 and 7 isoforms, using the Autodock 4.2 program. Our computational model used the co-crystal structures of SB-FI-26 with FABP5 and FABP7, recently determined by us, and the apoprotein structure of FABP3. We have expanded our study to include compounds with the  $\alpha$ ,  $\gamma$ , and  $\epsilon$ -truxillic acid scaffolds. The computational model we developed has disclosed structural features that affect the affinity to FABP5 and selectivity against FABP3 and 7 isoforms, which are very useful for drug design. The computer-aided design, synthesis and biological evaluations of a new series of FABP5 inhibitors will be discussed.



## MEDI 356

### TB or not TB? That is not the only question

**Jordan Trant**, [jordan.trant@lyon.edu](mailto:jordan.trant@lyon.edu), **Natalie Milligan**, [natalie.milligan@lyon.edu](mailto:natalie.milligan@lyon.edu),  
**Amanda Ford**, **Zachary Hodge**, **Irosha N. Nawarathne**. Chemistry, Lyon College,  
Batesville, Arkansas, United States

Multi-drug resistant tuberculosis (MDR-TB) remains a public health crisis and a health security threat with 600,000 new cases with resistance to rifamycins (RR-TB), of which 490,000 had MDR-TB. Among reported MDR-TB patients, 6.2% were diagnosed with extensively drug resistant (XDR) TB. The rifamycins, long considered a mainstay of tuberculosis treatment, particularly rifampin (RMP) – the most effective first-line drug in combination therapy, bind to the  $\beta$  subunit of *Mycobacterium tuberculosis* RNA polymerase (MTB RNAP) and block RNA synthesis. TB is fully curable using combination therapy that includes rifamycins; the average treatment cost per TB case is about \$0.045 million. However, numerous drug resistant strains (MDR and XDR-TB) disrupt interactions between rifamycins and modified MTB RNAP, via single mutations in the  $\beta$  subunit, leading to drug resistance. In our lab, we strategically explore the ways to develop rifamycin derivatives those can reconstitute the binding interactions with the mutated MTB RNAP of the prevalent MDR/XDR-TB strains. Some of these modified

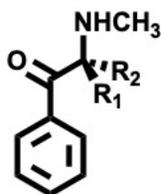
rifamycins also demonstrate the potential to be developed as an imaging agent to facilitate diagnosis through TB screening, thus promoting prevention and/or early treatment of the disease. Our target is to prevent the global epidemic through multiple TB outbreaks and to reduce the financial burden related to TB.

## **MEDI 357**

### **Pharmacology and modeling of methcathinone (MCAT) isomers and achiral analogs at the monoamine transporters (MATs)**

**Rachel A. Davies**<sup>1</sup>, *racheld193@gmail.com*, **Farhana Sakloth**<sup>1</sup>, **Brian Ruiz**<sup>2</sup>, **Jose Elti**<sup>2</sup>, **Richard A. Glennon**<sup>1</sup>. (1) *Department of Medicinal Chemistry, Virginia Commonwealth University, Richmond, Virginia, United States* (2) *Department of Physiology and Biophysics, Virginia Commonwealth University, Richmond, Virginia, United States*

Synthetic cathinones (e.g. methcathinone, or MCAT) represent an international drug abuse problem, and their structure activity relationships are not well-understood. We have found that the C=O group can be replaced with a methoxy group, but this results in two chiral centers (i.e., four possible optical isomers for synthesis and evaluation). This problem can be simplified a) by eliminating the  $\alpha$ -methyl (i.e., **3**), or b) by adding a second methyl group (i.e., **4**). Here, the individual isomers of MCAT **1** and **2**, and analogs **3** and **4** were prepared and examined: pharmacologically, and in docking studies at homology models. A calcium flux assay was used to determine mechanism of action and potency. For the MCAT isomers, this was the first time they were directly compared at their molecular targets. All the compounds were found to act as substrates, and the  $\alpha$ -position chiral center was favored, but not required, at the human dopamine transporter (hDAT) and human serotonin transporter (hSERT), depending on the approach. Any tolerated modification resulted in a reduction in potency. This suggested both: unfavorable interactions with the  $\alpha$ -methyl of (*R*)-MCAT, and favorable interactions with the same substituent in (*S*)-MCAT. To investigate this possibility, homology models of the MATs were prepared and docking studies were conducted. Common binding modes were identified for the MCAT isomers and analogs, which were in keeping with the binding mode of a substrate cocrystallized with the related drosophila dopamine transporter (i.e. amphetamine). These binding modes supported our conclusions, showing steric blockade on the side of the (*R*)-MCAT  $\alpha$ -methyl, but were unable to explain the advantageous nature of the same group in (*S*)-MCAT, suggesting that other protein-ligand interactions are involved in substrate transport and selectivity.



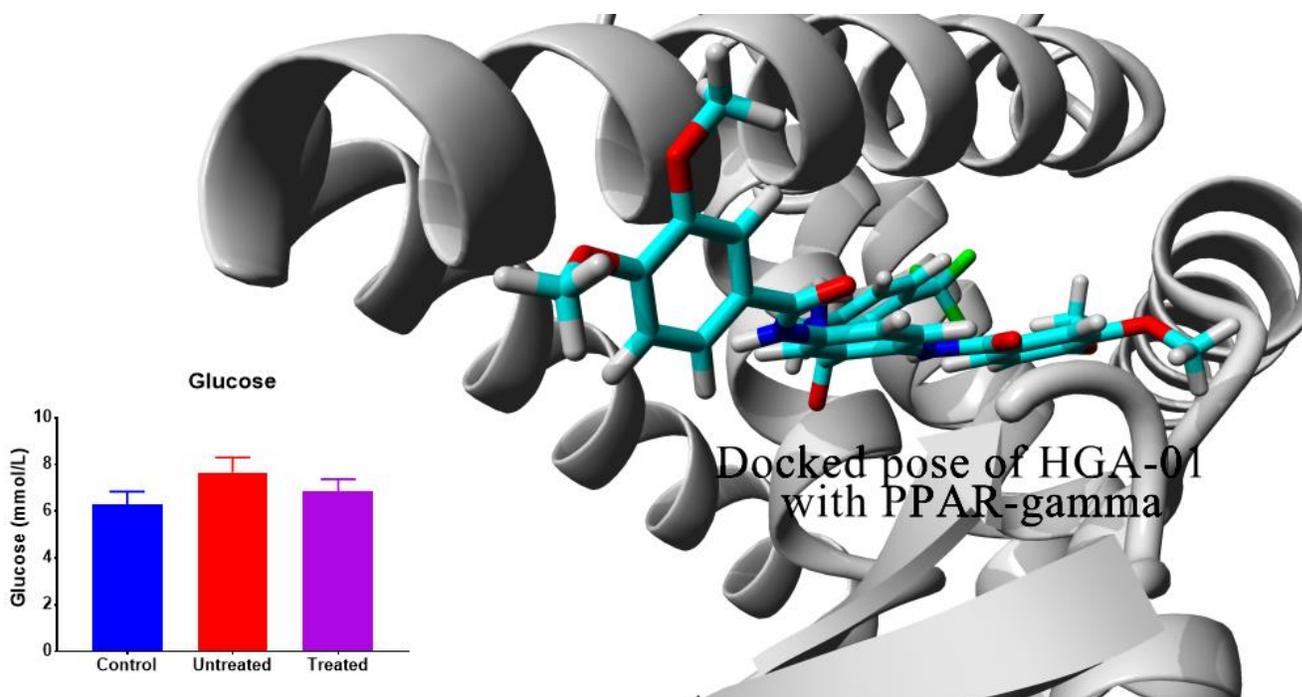
- 1 R<sub>1</sub> = CH<sub>3</sub>, R<sub>2</sub> = H
- 2 R<sub>1</sub> = H, R<sub>2</sub> = CH<sub>3</sub>
- 3 R<sub>1</sub> = R<sub>2</sub> = H
- 4 R<sub>1</sub> = R<sub>2</sub> = CH<sub>3</sub>

## MEDI 358

### Design, synthesis, and evaluation of the anthranilic acid derivative HGA-01 as a potential multitarget drug for the management of metabolic syndrome

**Héctor González Álvarez**<sup>1</sup>, [hectorg\\_extremo@hotmail.com](mailto:hectorg_extremo@hotmail.com), **Maria Astrid Bravo Jimenez**<sup>1</sup>, [astriidjmz@gmail.com](mailto:astriidjmz@gmail.com), **Marco A. Loza-Mejia**<sup>1</sup>, [marcoantonio.loza@gmail.com](mailto:marcoantonio.loza@gmail.com), **Rodolfo Pinto-Almazán**<sup>2</sup>, **Karina Gallardo-Ignacio**<sup>2</sup>, **Lino A. González-Hernández**<sup>2</sup>, **Edwin Chávez-Gutiérrez**<sup>2</sup>. (1) School of Chemistry, Universidad La Salle, Mexico City, Mexico (2) Hospital Regional de Alta Especialidad de Ixtapaluca, Mexico City, Mexico

Metabolic syndrome (MetS) is a complex disease in which diabetes, obesity, hyperglycemia, high cholesterol, and high blood pressure are the most common disorders. It is estimated that around 20-25 % of the adult population worldwide has MetS and they are twice as likely to die from some of their complications compared to people without the syndrome. Currently, the research of multitarget drugs has been a challenging task in medicinal chemistry, and it has been proposed as an interesting approach for developing drugs for the treatment of complex diseases. In our group, we have studied anthranilic acid derivatives as potential drugs for the management of some metabolic disorders. In this work, we present the *in silico* and the *in vivo* evaluation of HGA-01. This compound was identified as a potential multitarget drug from an inverse docking study carried out on several targets involved in MetS, showing high theoretical affinity to aldose reductase, PPAR- $\alpha$ , PPAR- $\gamma$ , and HMG-CoA reductase. HGA-01 was prepared from anthranilic acid in just four steps with good yields. Then, it was evaluated in a diet-induced obesity rat model and induced diminution in blood pressure, glucose, triglycerides, and cholesterol levels compared with the untreated group. Hence, HGA-01 is an interesting advance for the development of new multitarget drugs for the management of MetS.

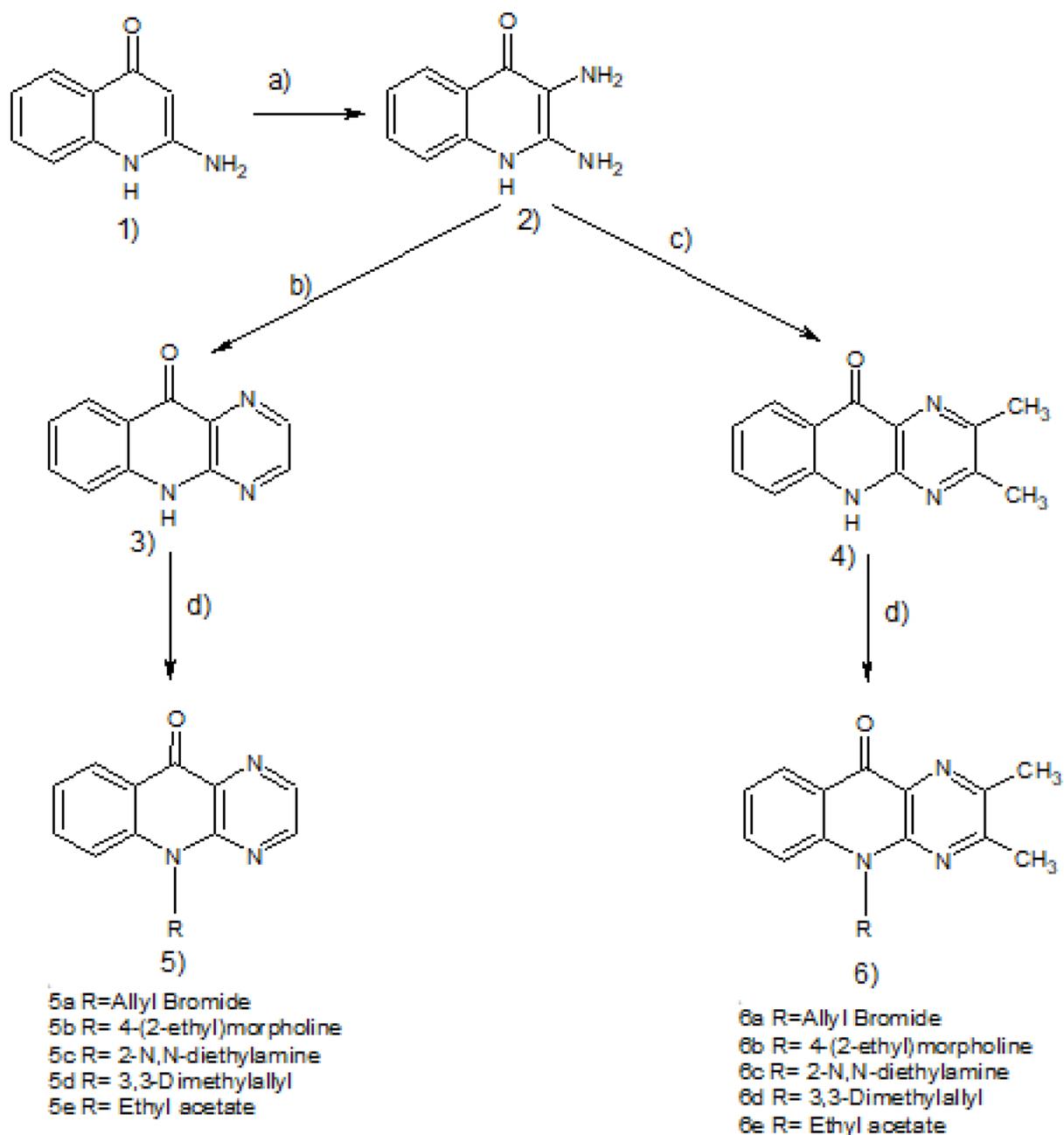


## MEDI 359

### Synthesis and bioevaluation of new pyrazino[2,3-*b*]quinolinones as potential antitumorals: Effect of the nature of alkyl substituents in position 5

**Dante G. Juan Guadarrama**<sup>2</sup>, [dante-322@hotmail.com](mailto:dante-322@hotmail.com), **Liliana Jazmin J. Jimenez Sanchez**<sup>2</sup>, [jazmin.js22@hotmail.com](mailto:jazmin.js22@hotmail.com), **Julio Villalobos**<sup>2</sup>, **José Solano**<sup>1</sup>, **Alfonso Lira**<sup>1</sup>, **Laura Martino**<sup>2</sup>, **Marco A. Loza-Mejía**<sup>2</sup>. (1) Facultad de Química, Depto. de Farmacia, UNAM, Mexico D F, Mexico (2) Faculty of Chemical Sciences, Universidad La Salle, Mexico city, Mexico city, Mexico

DNA intercalating agents are among the most studied compounds for the development of antitumorals. In our group, we have prepared and evaluated several tricyclic templates and some of them have exhibited interesting cytotoxic activity against tumoral cell lines. In this work, we present the synthesis, *in vitro* cytotoxic activity, DNA intercalation properties and *in vivo* genotoxicity of some pyrazino[2,3-*b*]quinolones with different substituents in position 5 (see Figure). These compounds were readily prepared from isatoic anhydride in good yields. Evaluation of their cytotoxicity against some tumoral cell lines revealed that compound **5a** exhibited the highest bioactivity ( $IC_{50} < 10$  mM in leukemia, colon and cervix cell lines) but with poor DNA intercalative properties. From our experience, the incorporation of side chain of tertiary amines (compounds **5b-c** and **6b-c**) usually increases cytotoxicity but compounds with these structural characteristics were among the less active, despite they have from moderate to good DNA intercalative properties. *In vivo* acute lethal dose of compound **1b** was tested and was determined to be higher than 500 mg/Kg. Further studies for determining its genotoxicity and additional toxicological test are on course.



## MEDI 360

### Synthesis of small molecules for protein control

**Elena Bray**<sup>1</sup>, [braye@mail.usf.edu](mailto:braye@mail.usf.edu), **Carmelo Alvarez**<sup>4</sup>, **James Leahy**<sup>1,2,3</sup>, **Michael W. White**<sup>3,2</sup>. (1) Chemistry, University of South Florida, Tampa, Florida, United States (2) Florida Center of Excellence for Drug Discovery and Innovation, Tampa, Florida, United

*States (3) Molecular Medicine, University of South Florida, Tampa, Florida, United States (4) Global Health, University of South Florida, Tampa, Florida, United States*

Toxoplasmosis is a disease caused by *Toxoplasmosis gondii*, a protozoan parasite that infects more than 60 million people in the world chronically and is listed by the CDC as one of five Neglected Parasitic Infections. Although symptoms commonly manifest as asymptomatic, immunocompromised people are at high risk for severe symptoms such as blindness, death, etc. The protozoan lifecycle goes through dormant and active phases controlled by specific genes in the parasite. Although treatment in the active phase can be done with current medicines, the dormant phase of the parasite is a lifelong infection with no treatment or cure. Shield-1 is a small molecule that has been used for protein control in biological systems. In this study, we have developed and synthesized novel analogs of Shield-1 to study transcription factors of the parasite designed to improve their pharmacokinetic properties with an eye toward in vivo utilization.

## **MEDI 361**

### **Development of a selective phosphatase inhibitor for neurodegenerative disorders**

*Jamie Nunziata<sup>1</sup>, jnunziata@mail.usf.edu, Benjamin J. Edful<sup>1</sup>, Yu Chen<sup>2</sup>, David Kang<sup>2</sup>, James Leahy<sup>1,3,2</sup>. (1) Chemistry, University of South Florida, Tampa, Florida, United States (2) Molecular Medicine, University of South Florida, Tampa, Florida, United States (3) Florida Center of Excellence for Drug Discovery and Innovation, Tampa, Florida, United States*

Alzheimer's disease (AD), a progressive and degenerative illness, affects more than 35 million people worldwide and costs the healthcare industry over \$100 billion every year. New discoveries within the last decade have given researchers and physicians further insight into the pathology of the disease. One of the manifestations of AD is the presence of amyloid- $\beta$  protein plaques between brain neurons causing synaptic loss and neurodegeneration.

Since its discovery, the slingshot homology (SSH) family of phosphatases have been highly studied, and their activity is believed to be a major factor in plaque formation. We have developed a synthesis of a series of small molecules that act as phosphatase inhibitors aimed at decreasing the activity of SSH1 and correspondingly reducing the amount of plaque formation. Recent results in these endeavors will be presented.

## **MEDI 362**

### **Synthesis of rhodacyanine derivatives as Hsp70 inhibitors for improved tau degradation in tauopathies**

*Andrea Lemus<sup>1</sup>, aalemus@mail.usf.edu, Shreya Patel<sup>1</sup>, Ronald Swonger<sup>1</sup>, Roy Blackburn<sup>3</sup>, John Koren<sup>3</sup>, Chad Dickey<sup>3</sup>, Laura Blair<sup>3</sup>, James Leahy<sup>1,2,3</sup>. (1) Chemistry,*

*University of South Florida, Tampa, Florida, United States (2) Florida Center of Excellence for Drug Discovery and Innovation, Tampa, Florida, United States (3) Molecular Medicine, University of South Florida, Tampa, Florida, United States*

Tauopathies such as Alzheimer's disease are a type of neurodegenerative disorder associated with tau protein aggregation into insoluble tangles. Tau is an intrinsically disordered protein whose function is to stabilize microtubules in cells. Mutations and hyperphosphorylation of tau disrupt microtubule stabilization and promote aggregation that leads to disrupted neural processes. Progression of these diseases cause memory, behavior, and cognition problems, as well as difficulty in carrying out daily activities. One potential target to discover new treatments for tauopathies is the Hsp70 family of molecular chaperones present in eukaryotic cells. In this family are heat shock protein 70 (Hsp70/HSPA1A) and heat shock cognate 70 (Hsc70/HSPA8), which bind to misfolded proteins and are essential to proteostasis. Hsp70 and Hsc70, together with other co-chaperones, target misfolded proteins for degradation in order to limit abnormal protein accumulation inside cells. Hsp70 and Hsc70 have 85% structure homology, but Hsp70 is more effective at degrading tau whereas Hsc70 is more closely linked to associating tau with microtubules. Hsc70 also interferes with Hsp70-promoted degradation. However, Hsc70 is constitutively expressed while Hsp70 is stress-induced, which may make Hsc70 a more suitable target. Rhodacyanine derivatives have been shown to act as inhibitors of Hsp70 family protein members. These inhibitors stabilize the ADP complex that activate and increase degradation of tau. Known inhibitors have been shown to bind allosterically to a deep pocket of Hsp70/Hsc70 and not at the ATP binding site. Docking studies further show a narrowing of the binding pocket. Therefore, a primary goal of our research is to synthesize analogs to exploit this pocket and improve binding interactions. At the same time, we wish to maintain or improve the tau reducing properties of this class of compounds and improve blood-brain barrier permeability. Recent results in these areas will be presented.

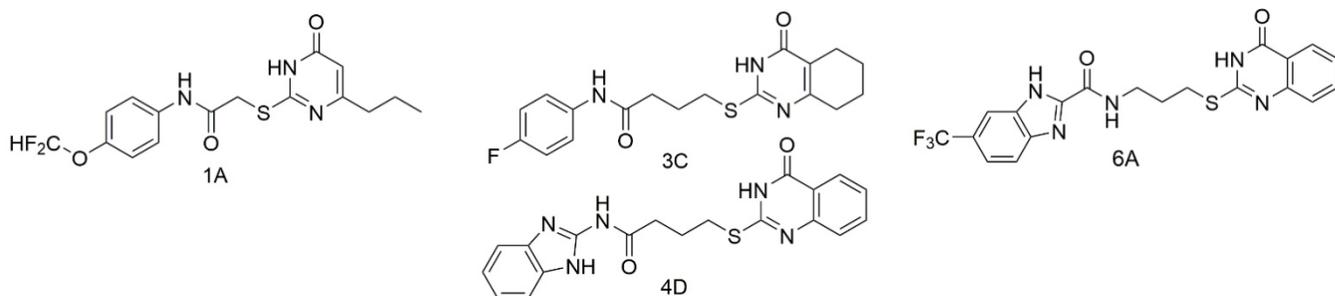
### **MEDI 363**

#### **Design, synthesis, and SAR of matrix metalloprotease 9 inhibitors as anti-metastasis agents**

**Monaf Awwa**<sup>1</sup>, *awwamonaf@hotmail.com*, Vincent M. Alford<sup>2</sup>, Xiaodong Ren<sup>1</sup>, Jian Cao<sup>5,6</sup>, Nicole S. Sampson<sup>3</sup>, Iwao Ojima<sup>4</sup>. (1) Chemistry, Stony Brook University, Stony Brook, New York, United States (2) Department of Molecular and Cellular Pharmacology, Stony Brook University, Stony Brook, New York, United States (3) Chemistry Dept, Stony Brook University, Stony Brook, New York, United States (4) Chem Dept/ICBDD, Stony Brook University, Stony Brook, New York, United States (5) Department of Medicine, Stony Brook University, Stony Brook, New York, United States (6) National Institutes of Health, Bethesda, Maryland, United States

One of the major complications of cancer is metastasis of a local tumor into other parts of the body. Small molecules that can prevent this process are therefore highly sought after due to their ability to keep a tumor in its local environment. Matrix metalloproteases

(MMPs) have emerged as vital proteins in the digestion of connective tissue and the metastasis of tumors. Virtual Screening of the haemopexin domain of MMP9 has yielded the discovery of a highly selective inhibitor of MMP9-mediated cellular migration. Compound 1A emerged as a hit compound and a congeneric series of compounds based on 1A have been synthesized and modeled providing a structural basis for the enhanced activity *in vivo* of the molecular analogs of 1A such as 3C and 4D. Addition of two methylene units between the ring moieties of 1A enhances hydrogen bonding and predicted binding energy at the dimerization interface between MMP9 and cell signaling proteins, reducing cellular migration *in vivo*. Thus, structure-based drug design continued from the most potent compounds via Autodock Vina. Design began from the most potent compounds 3C and 4A based on readily synthesizable analogues. The resulting docking yielded several compounds with over 1.4 kcal/mol more favorable binding score such as Compound 6A. Other interesting trends emerged such as the poor predicted affinity for ortho and meta substituents on the benzimidazole/aniline moieties. The results provide a guiding rationale for discovery of small molecules with even better *in vivo* activity as anti-metastasis agents.



## MEDI 364

### Conformational constraint of aromatic residues of the kappa opioid receptor antagonist arodyn using ring closing metathesis

**Solomon A. Gisemba**<sup>1,2</sup>, [sgisemba@ufl.edu](mailto:sgisemba@ufl.edu), **Jane V. Aldrich**<sup>1,2</sup>, **Thomas Murray**<sup>3</sup>. (1) Department of Medicinal Chemistry, The University of Kansas, Lawrence, Kansas, United States (2) Department of Medicinal Chemistry, The University of Florida, Gainesville, Florida, United States (3) Department of Pharmacology, Creighton University School of Medicine, Omaha, Nebraska, United States

While mu opioid receptors are the primary therapeutic target for treatment of pain and drug abuse, kappa opioid receptor (KOR) antagonists have recently shown potential for treating drug addiction and depression. Arodyn (Ac[Phe<sup>1,2,3</sup>,Arg<sup>4</sup>,D-Ala<sup>8</sup>]Dyn A(1-11)-NH<sub>2</sub>), an acetylated dynorphin A (Dyn A) analog synthesized in our laboratory, demonstrated potent and selective KOR antagonism but is rapidly metabolized by proteases. Cyclization of arodyn could enhance metabolic stability and potentially stabilize the bioactive conformation. Accordingly, a cyclization strategy involving ring closing metathesis (RCM) of *O*-allyl groups was pursued. However, side reactions involving olefin isomerization limited the scope of the RCM reactions, especially their

use to probe how modification of important aromatic residues affects the peptide's pharmacological activity. The optimization of the synthetic methodology (including employing microwave heating and isomerization suppressants) using a model dipeptide and its application to the synthesis of arodyn analogs will be presented. The resulting analogs were evaluated for their opioid receptor binding affinities, and promising cyclized analogs that retained high KOR affinity and selectivity were identified.

## **MEDI 365**

### **Synthesis and QSAR study of novel NSAID hybrid conjugates as potential anti-inflammatory agents**

*Hitesh H. Honkanadavar, HHONKANADAVAR@augusta.edu, Siva S. Panda. Chemistry & Physics, Augusta University, Augusta, Georgia, United States*

Non-steroidal anti-inflammatory drugs are one of the most common drugs used worldwide as an effective treatment plan for pain and pain-related diseases. Most drugs work by non-selective inhibition of the COX-1 and COX-2 enzyme system which leads to a decrease in inflammation; but also leads to gastric ulcers and renal dysfunction due to inhibition of the COX-1 enzyme system.

In continuation of our new drug development program and based on our previous observation herein, we developed a potential synthetic strategy to synthesize hybrid conjugates of existing non-steroidal anti-inflammatory drugs (NSAIDs) with 4-aminophenol. All the synthesized compounds were fully characterized by analytical tools. Computational chemistry studies, such as 2D-QSAR (quantitative structure-activity relationship) and molecular modeling, will be used to support the *in-vivo* biological activity. The details of the biological studies in comparison to standard NSAIDs will be discussed at the conference.

## **MEDI 366**

### **Design, synthesis, and characterization of new modulators of the leukotriene A<sub>4</sub> hydrolase aminopeptidase activity**

*Greg Petruncio<sup>1</sup>, gpetrunc@gmu.edu, Kyung Hyeon Lee<sup>1</sup>, Logan Jansen<sup>1</sup>, Schroeder Noble<sup>2</sup>, Y. Michael Shim<sup>3</sup>, Mikell Paige<sup>1</sup>. (1) Chemistry & Biochemistry, George Mason University, Manassas, Virginia, United States (2) Bacterial Diseases Branch, Walter Reed Army Institute of Research, Silver Spring, Maryland, United States (3) Division of Pulmonary & Critical Care Medicine, University of Virginia, Charlottesville, Virginia, United States*

Diphenylmethanes such as 4MDM and ARM1 are a class of compounds that activate the aminopeptidase activity of the leukotriene A<sub>4</sub> hydrolase enzyme for substrates such as alanine *p*-nitroanilide. These modulators represent a potential class of therapeutic agents for treating persistent inflammation such as found in emphysema. Herein, we developed a synthetic route using the Molander modification of the Suzuki reaction to

access  $sp^3$ - $sp^2$  cross-coupling adducts with organotrifluoroborates. The trifluoroborate cross-coupling partner was defined as the A-ring, which was reacted with benzyl halide derivatives as the B-ring. Modest yields (30-40% on 200-mg scale reactions) are attributed to the acidic proton of the 2-amino group of a heterocyclic 2-aminothiazol-4'-yl group on the A-ring. Enzyme kinetic analyses afforded a structure-activity relationship that correlated positioning of appendages to the B-ring with activation or inhibition of the enzyme.

## MEDI 367

### Structure-activity relationship-guided synthesis and identification of the GATA4 and NKX2-5 protein-protein interaction modulators

**Mikael Jumppanen**<sup>2</sup>, [mikael.jumppanen@helsinki.fi](mailto:mikael.jumppanen@helsinki.fi), Sini Kinnunen<sup>2</sup>, Mika Välimäki<sup>2</sup>, Samuli Auno<sup>1,2</sup>, Gustav Boije af Gennäs<sup>1</sup>, Henri Xhaard<sup>1</sup>, Virpi Talman<sup>2,3</sup>, Heikki Ruskoaho<sup>2</sup>, Jari T. Yli-Kauhaluoma<sup>1</sup>. (1) Drug Research Program, Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, Helsinki, Finland (2) Drug Research Program, Division of Pharmacology and Pharmacotherapy, Faculty of Pharmacy, University of Helsinki, Helsinki, Finland (3) National Heart and Lung Institute, Faculty of Medicine, Imperial College London, London, United Kingdom

Cardiovascular diseases are the leading cause of death worldwide and are characterized by unmet medical need. Cardiac transcription factors (TF), such as GATA4 and NKX2-5, regulate both physiological and pathophysiological processes in the heart. For example, a physical interaction of these two TFs leads to stretch-induced cardiomyocyte hypertrophy. In our previous studies we have demonstrated that a small molecule compound inhibiting the GATA4-NKX2-5 transcriptional synergy attenuates the cardiomyocyte hypertrophic response in vitro and improves cardiac function in vivo in experimental models of myocardial infarction and hypertension.

In this work, we continued the optimization of the original isoxazole hit compound by modifying its northern, central and southern parts. The new compounds were tested in the luciferase assay to examine the inhibition of the transcriptional synergy of the GATA4 and NKX2-5. Additionally, the most potent compounds were tested in luciferase assays for NKX2-5 and GATA4 activity individually. To identify compounds inhibiting transcriptional synergy of GATA4 and NKX2-5 but not interfering with GATA4 or NKX2-5 transcriptional activity, the generated multidimensional activity data was analyzed using hierarchical clustering and principal component analysis, which resulted in identification of two potentially interesting groups of compounds with different activity patterns. Furthermore, when cytotoxicity of the compounds was evaluated in MTT assay in the COS-1 cell line, it correlated with the inhibition of GATA4 activity.

In summary, we have synthesized and successfully used multidimensional data analysis

to identify a group of non-toxic GATA4 and NKX2-5 transcriptional synergy inhibitors, which do not interfere with GATA4 transcriptional activity.

## **MEDI 368**

### **Atypically substituted carbapenem antibiotics with improved activity against OXA-23-producing *Acinetobacter baumannii***

Noora M. Al-Kharji<sup>1</sup>, **Maha Alqurafi<sup>1</sup>**, malqurafi@mail.smu.edu, Thu Nguyen<sup>1</sup>, Weirui Chai<sup>1</sup>, Nichole K. Stewart<sup>2</sup>, Marta Toth<sup>2</sup>, Jean Kim<sup>1</sup>, Njeshi Nformi<sup>1</sup>, Siddhakshi Solanki<sup>1</sup>, Kaili Wong Wirth<sup>1</sup>, Monali Ardeshta<sup>1</sup>, Anusha Mehta<sup>1</sup>, Artur Jakubowski<sup>1</sup>, Byron Meshram<sup>1</sup>, Catherine Varner<sup>1</sup>, Angela He<sup>1</sup>, Madeline Pan<sup>1</sup>, Sergei B. Vakulenko<sup>2</sup>, John D. Buynak<sup>1</sup>. (1) Chemistry, Southern Methodist University, Dallas, Texas, United States (2) Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana, United States

Due to its ability to acquire resistance to antimicrobial agents and its persistence on surfaces, MDR *Acinetobacter baumannii* evolved to become a major nosocomial pathogen, thus presenting an urgent worldwide clinical problem. Production of the carbapenem-hydrolyzing class D carbapenemases or CHDLs constitutes the major mechanism of resistance to carbapenems in *A. baumannii*. OXA-23 is the most prevalent CHDL found in this deadly pathogen. The Buynak laboratory has been synthesizing atypically (i.e. non-C2) substituted carbapenem antibiotics. In collaboration with Entasis and with the Rhode research group at UCF, we have recently reported improved activity (relative to meropenem) against *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis* and *Mycobacterium abscessus*, respectively. In collaboration with the Fast research group at UT and the Palzkill group at BCM, we have also reported carbapenems with improved stability to the NDM-1 and KPC-2 carbapenemases, respectively. We now report that selected modifications of the carbapenem scaffold improve activity against carbapenem-resistant, OXA-23 producing *A. baumannii*. Synthesis and activity studies will be provided as well as comparisons of activity against susceptible and OXA-23 producing *A. baumannii* strains.

## **MEDI 369**

### **Synthesis of new $\beta$ -heteroarylmethoxy-*N*-phenethylamines as possible monoamine neurotransmitter transporter blockers**

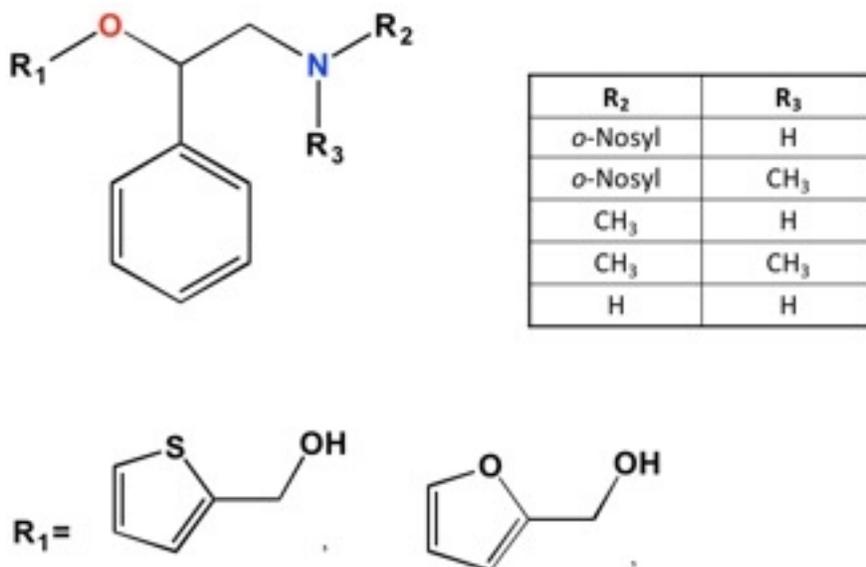
**Iriux Almodovar<sup>1</sup>**, iriux.almodovar@usach.cl, Edwin G. Perez<sup>2</sup>, Matías Madrid<sup>1</sup>. (1) Facultad de Química y Biología, Universidad de Santiago de Chile, Santiago, Region Metropolitana, Chile (2) Química, Pontificia Universidad Católica de Chile, Santiago, Region Metropolitana, Chile

A series of compounds, whose structure are analogs to that of commercial antidepressant duloxetine, were designed and prepared by means of a one-pot copper-catalyzed aziridinization and ring opening.. These were modified attaching thiophen-2-

yl-methoxy and furan-2-yl-methoxy moieties and employing *o*-nitrobenzenesulfonyl iminophenylidodine as both nitrogen source and oxidant. For primary amines, the nosyl group was removed directly from the obtained compounds. In addition, the nitrogen was then sequentially methylated and deprotected to obtain secondary amines. Tertiary amines were obtained using the classical reductive amination (Figure 1). Yields of reactions ranged 50-70%.

Figure 1. General structure of compounds synthesized.

All the new compounds were tested as monoamine neurotransmitter transporter blockers using a fluorescence assay and molecular modeling studies were performed to rationalize possible interactions of our compounds with the different monoamine neurotransmitter transporters.



## MEDI 370

### Identification, validation, and synthesis of small molecule inhibitors of the Lin28b/pre-Let-7 interaction in pancreatic ductal adenocarcinoma

**Hassan Ahamed**<sup>1</sup>, hahamed1@haverford.edu, **Tomas Aramburu**<sup>1</sup>, taramburu@haverford.edu, Robert L. Broadrup<sup>1</sup>, Raul Mostoslavsky<sup>2</sup>. (1) Chemistry, Haverford College, Haverford, Pennsylvania, United States (2) The Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts, United States

Pancreatic ductal adenocarcinoma (PDAC) is among the most aggressive types of cancer and is extremely challenging to treat. The sirtuin 6 protein (SIRT6), a multifunctional enzyme involved in gene regulation, was found to be associated with PDAC oncogenesis. SIRT6 inactivation induces overproduction of a miRNA-binding

protein, Lin28b, which subsequently impedes the maturation of the tumor suppressor miRNA, Let-7, through increased binding to its precursor. Inhibition of this pathway provides an attractive target for novel PDAC therapies. Previous research has resolved the crystal structure of the protein:miRNA complex and identified, *in vitro*, small molecule inhibitors of the binding interface. Drawing from these studies, a dual approach is presented, involving virtual high-throughput screening (vHTS) and *de novo* drug design, to identify novel potential inhibitors. Selected targets are purchased if commercially available or synthesized in our laboratory. An *in vitro* assay is concurrently being developed to validate the targets' abilities to competitively inhibit Lin28b binding to the Let-7 precursor. It is anticipated that successful inhibitors will be evaluated in human PDAC cells.

### **MEDI 371**

#### **Evaluation of the effects of differentially sulfated heparin/heparan sulfate analogs on MCF-7 cell migration**

**Anna M. Brown**, *anbrown@davidson.edu*, **Nicole L. Snyder**, *nisnyder@davidson.edu*. Chemistry, Davidson College, Davidson, North Carolina, United States

Heparin and heparan sulfate (HS) are a class of sulfated glycosaminoglycans that serve a wide variety of biological functions. Although heparin has been used for over a century as an anticoagulant, heparin and HS have recently been shown to play a key role in a variety of biological processes including cell growth, viral invasion, and tumor metastasis. One hypothesis is that the degree of sulfation and/or sulfation patterns play an important role in the way that heparin/HS interact with the proteins involved in these processes. However, little is known about the specific structural motifs that modulate these interactions. In this poster, we present the synthesis and evaluation of several selectively sulfated heparin/HS analogs with different sulfation patterns and degrees of sulfation to probe these effects on MCF-7 cell migration. Our preliminary results highlight the relative importance of the degree and positioning of sulfation along the glycosaminoglycan backbone in our studies.

### **MEDI 372**

#### **Synthesis and biological screening of praziquantel derivatives for use as pharmacological chaperones of arylsulfatase B**

**Karna Terpstra**<sup>1</sup>, *kterpstra20@my.whitworth.edu*, **Trisha A. Russell**<sup>2</sup>. (1) Whitworth University, Spokane, Washington, United States (2) Chemistry, Whitworth University, Spokane, Washington, United States

Mucopolysaccharidosis type VI, or Maroteaux-Lamy syndrome, is a lysosomal storage disorder in which glycosaminoglycans build up in the lysosome. Buildup is caused by absence or deficiency of arylsulfatase B (ASB) enzyme which results from misfolded

mutant forms of the enzyme. Pharmacological chaperones are small molecules which stabilize mutant enzyme and allow movement from the endoplasmic reticulum into the lysosome. Praziquantel has previously been shown to inhibit ASB in mice and was used as a lead compound to find small molecules capable of stabilizing ASB. Derivatives of praziquantel were synthesized and tested for thermal stabilization and inhibition effects on human wild-type ASB. Several new compounds were identified that increased thermal stability of ASB but did not inhibit enzyme activity.

### **MEDI 373**

#### **Synthesis and computational study of pyrazinoic acid conjugates as potential anti-infective agents**

*William F. Littlefield, wlittlefield@augusta.edu, Siva S. Panda. Chemistry & Physics, Augusta University, Augusta, Georgia, United States*

Bacterial resistance to the available antibiotics is a serious health problem. Pyrazinamide (PZA) is a first-line anti-tuberculosis prodrug often used in combinational therapy with drugs like isoniazid, ethambutol, streptomycin and/or rifampicin. Pyrazinamide also used for the treatment of other bacterial infections by inhibiting the enzyme fatty acid synthase (FAS). However, prolong use of pyrazinamide drugs leads to harmful side effects such as hepatitis, acute hypertension, thrombocytopenia, and gastrointestinal discomfort. Combination therapy is an alternative treatment plan to overcome the problem of toxicity and drug resistance.

In continuous to our ongoing research in conjugation chemistry where two or more pharmacophores are linked together covalently, and it is believed that these compounds act by inhibiting two conventional targets simultaneously. This multiple target strategy could lead to the development of bio-effective hybrid molecules.

In this study, we have developed a synthetic protocol for the synthesis of pyrazinoic acid hybrid conjugates with isoniazid *via* amino acid linkers in pure form. Most of our synthesized conjugates are potential antibacterial agents. The detail results will be discussed at the conference.

### **MEDI 374**

#### **Design and synthesis of quinolone-based hybrid conjugates as potential anticancer agents**

*Riham M. Bokhtia<sup>1,2</sup>, rbokhtia@augusta.edu, Tarek S. Ibrahim<sup>2,3</sup>, Amany M. Al-Mahmoudy<sup>2</sup>, Eatedal H. Abdel-Aal<sup>2</sup>, Siva S. Panda<sup>1</sup>. (1) Chemistry & Physics, Augusta University, Augusta, Georgia, United States (2) Department of Pharmaceutical Organic Chemistry, Zagazig University, Zagazig, Egypt (3) Department of Pharmaceutical Chemistry, King Abdulaziz University, Jeddah, Saudi Arabia*

Cancer and bacterial infections are two different class of life-threatening diseases. These diseases are the leading cause of deaths in the world. Several chemotherapeutic

agents were developed to treat or control different types of cancer and bacterial infections separately. However, bacterial infections are a major cause of complications and death in patients suffering from cancer. An agent with anticancer and antibacterial property is a much-needed scaffold, which can be used for prophylaxis as well as for treatment of bacterial superinfections in cancer patients while being effective in preventing the growth of tumor cells. Quinolone antibiotics are well known for antibacterial properties via inhibition of topoisomerase II enzyme. This enzyme is also a target for anticancer drugs.

This current research work is concerned with synthesizing potential quinolone-based drug candidates that could combat cancer and bacterial infection simultaneously. We used ciprofloxacin and norfloxacin as our starting moiety and modified the quinolones by coupling with amino acids and secondary amines covalently. All the synthesized conjugates were fully characterized by analytical methods. The anticancer and antibacterial studies are in progress and we believe good outcomes and look forward to unlocking the potential of these conjugates as effective antibacterial as well as anticancer agents.

## **MEDI 375**

### **Synthesis of indoles-based Schiff base complexes and spiro compounds as potential anticancer agents**

*Israa Seliem*<sup>1,2</sup>, *isliem@augusta.edu*, *Tarek S. Ibrahim*<sup>2,3</sup>, *Amany M. Al-Mahmoudy*<sup>2</sup>, *Zakaria K. Abdel-Sami*<sup>2</sup>, *Siva S. Panda*<sup>1</sup>. (1) *Chemistry & Physics, Augusta University, Augusta, Georgia, United States* (2) *Department of Pharmaceutical Organic Chemistry, Zagazig University, Zagazig, Egypt* (3) *Department of Pharmaceutical Chemistry, King Abdulaziz University, Jeddah, Saudi Arabia*

The indole moiety holds a prominent place in medicinal chemistry considered as a privileged scaffold since it is part of various natural and unnatural drug-like molecules. Indole based Schiff bases and spiro compounds are well known for their diverse biological activities. Our lab is engaged in developing drug-like molecules using amino acids via conjugate chemistry. In this study, we have used secondary amines, amino acids and substituted isatins for the development of indole-based potential molecules as anticancer agents

As a part of our ongoing research on the synthesis of biologically active molecules, here we have developed a synthetic protocol for the synthesis of several Schiff bases and their metal complexes. We are also in the process of preparing the spiro compounds. The synthesized compounds will be screened for anticancer properties and we hope the synthesized compounds will show potential antitumor activities. The details will be discussed at the conference.

## **MEDI 376**

### **Synthesis of carbon nitride dots for target-specific biomedical applications**

**Piumi Liyanage**<sup>1</sup>, *pyl5@miami.edu*, **Regina Graham**<sup>2</sup>, **Charles C. Chusuei**<sup>3</sup>, **Keenan J. Mintz**<sup>1</sup>, **Yiqun Zhou**<sup>4</sup>, **James Harper**<sup>5</sup>, **Roger M. Leblanc**<sup>6</sup>. (1) Chemistry, University of Miami, Miami, Florida, United States (2) Neurosurgery, University of Miami, Miami, Florida, United States (3) Chemistry Department, Middle Tennessee State University, Murfreesboro, Tennessee, United States (4) University of Miami, Miami, Florida, United States (5) Chemistry, University of Central Florida, Orlando, Florida, United States (6) Univ of Miami Dept of Chem, Coral Gables, Florida, United States

Target-specific treatment has become utterly important and immensely researched especially for cancer treatment in modern medicine. Most of the chemotherapeutic drugs and the radiotherapy treatments are not target-specific towards the affected cells or organs, therefore have adverse cytotoxic effects on normal healthy cells. This eventually results in side effects that could pertain to higher risks on a patient's quality of life. Carbon dots have emerged over time as a promising nano-carrier for drug delivery although specificity is not achieved by most of them. In addition, use of transferrin and folic acid receptors for transmembrane transport has achieved lower effective drug concentrations regardless of target. Therefore attention needs to be turned to other nanomaterials. Carbon nitride dots are another drug delivery material for which the biomedical applications have not being investigated much yet. Herein carbon nitride dots were synthesized with citric acid using two different N-precursors urea and selenourea separately. The prepared carbon nitride dots are found to have excellent photoluminescent properties and biocompatibility through studies using two cell lines, pediatric glioblastoma cancer (SJGBM2) and normal embryonic kidney (HEK293). Through fluorescence imaging carbon nitride dots were confirmed to selectively enter the cancer cell membrane while they barely penetrated into the normal cells. The proposed mechanism is that carbon nitride dots could be disguised as glutamine due to their functional groups on the surface, therefore cancer cells preferably take them up as an energy source needed for their rapid growth. In addition, carbon nitride dots are able to image with longer wavelength luminescence. Thus carbon nitride dots can have great potential for biomedical applications in target-specific drug delivery and imaging.

## **MEDI 377**

### **Heterocycle libraries based on natural anti-inflammatory**

**Brooks Maki**, *bmaki@ben.edu*. Chemistry, Benedictine University, Lisle, Illinois, United States

Several families of pyrrole-based natural products have recently been isolated and shown to possess interesting anti-inflammatory properties. These families of compounds share a similarity in structure. All of these compounds are derived from similar biological pathways which involve the combination of sugar metabolites and amines. Making use of a biomimetic approach, a concise and high-yielding synthesis of the pyrrole core of this family of natural products has been developed and used to produce a library of related compounds.

The members of the library are accessed through an Achmatowicz oxidation of a furfuryl alcohol to give a synthetic analog of the biosynthetic precursor. The product of this reaction can condense with amines to give the pyrrole core directly. A broad scope of pyrroles have been accessed using this method.

## **MEDI 378**

### **New tools for targeting the asialoglycoprotein receptor**

**Nicole L. Snyder**<sup>1</sup>, *nisnyder@davidson.edu*, **Alexander Strasser**<sup>1</sup>, *alstrasser@davidson.edu*, **Nika Fendler**<sup>2</sup>. (1) Chemistry, Davidson College, Davidson, North Carolina, United States (2) Davidson College, Davidson, North Carolina, United States

The asialoglycoprotein receptor (ASGPR) is a C-type II lectin located primarily on hepatocytes. ASGPR removes a broad range of desialylated glycoproteins from the bloodstream by binding selectively to terminal galactose (Gal) and *N*-acetylgalactosamine (GalNAc) residues presented in a multivalent fashion on the termini of glycans located on glycoproteins. The high specificity and selectivity of ASGPR for Gal and GalNAc has inspired the development of several classes of Gal and GalNAc-based carriers for delivering therapeutics to hepatocytes. In this poster, we present the synthesis and evaluation of two new classes of compounds designed to mimic natural desialylated glycans. Our preliminary results demonstrate that these compounds have the potential to selectively engage ASGPR and may be useful for delivering targeted therapeutics to hepatocytes.

## **MEDI 379**

### **Trehalose-based photosensitizers targeting *Mycobacterium tuberculosis***

**Logan A. Russell**<sup>1</sup>, *lorussell@davidson.edu*, **Ricarda C. Steffens**<sup>2</sup>, **Morgan B. Burch**<sup>1</sup>, **David G. Dennis**<sup>3</sup>, **Matthew Parris**<sup>3</sup>, **Joshua V. Ruppe**<sup>3</sup>, **Nicole L. Snyder**<sup>1</sup>, *nisnyder@davidson.edu*. (1) Chemistry, Davidson College, Davidson, North Carolina, United States (2) Organic and Macromolecular Chemistry, Heinrich-Heine-Universitaet, Duesseldorf, Germany (3) Chemistry, USC Upstate, Spartanburg, South Carolina, United States

*Mycobacterium tuberculosis* (Mtb) is a common bacterium that causes tuberculosis, an extremely infectious and deadly disease. Due to improper use of antibiotics, multi-drug resistant Mtb has increased in prominence, creating an urgent need for new treatment options. Trehalose is a glucose disaccharide that is vital to the survival of Mtb and other bacteria, plants, and invertebrates; however, it is not present in mammalian cells. In Mtb, trehalose has many functions, but is primarily used as a vital component in the structure of the cell wall. The enzyme that incorporates trehalose into the mycomembrane, Ag85, has a broad substrate tolerance, allowing it to incorporate

synthetically modified trehalose analogs. This inspired us to pursue the development of a class of trehalose-based photosensitizers with the potential to target Ag85 for incorporation into the mycomembrane. In this proposal, we present the synthesis and biological evaluation of a small library of trehalose-based photosensitizers using *Mycobacterium smegmatis* as a model system.

## **MEDI 380**

### ***In silico* models for predicting metabolism by Flavin-Containing Monooxygenases (FMOs)**

**Govinda KC<sup>1</sup>**, *gbkc@miners.utep.edu*, **Md Mahmudulla Hassan<sup>2</sup>**, **Suman Sirimulla<sup>3</sup>**. (1) Computational Science, The University of Texas at El Paso, El Paso, Texas, United States (2) Computer Science, The University of Texas at El Paso, El Paso, Texas, United States (3) School of Pharmacy, The University of Texas at El Paso, El Paso, Texas, United States

*In silico* models of drug metabolism have been widely used since past few years. They are applicable for minimization of human risk in clinical trials of drugs and also significantly reduces the time and cost. There have been significant achievements for the prediction of metabolisms of xenobiotics mediated by Cytochrome P450 (CYP). However, there are several drugs that needs to be metabolized by non-CYP enzymes. For example, some therapeutic agents such as benzydamine, itopride, and arbidol are primarily metabolized by Flavin-containing monooxygenases (FMOs). The metabolisms mediated by non-CYP enzyme have been overlooked and there is a greater need to study these enzymes. In this project, we focus on non-CYP mediated metabolism, especially FMO. We aim to build accurate computational models for predicting the substrate activity, sites of metabolism (SOM) and kinetic parameters such as Michaelis-Menten constant (Km) and maximum metabolic rate (Vmax). We have collected the 85 compounds from the literature by Chien-wei et al. and additional datasets are obtained mainly from BRENDA, ChEMBL and PubChem. In this poster, we report the performances of machine learning (ML) models such as Random Forest classifier (RFC), Support Vector machine (SVM), and Artificial Neural network (ANN) for the prediction of site of metabolism (SOM). The prediction performances for SOM on the test set are evaluated by accuracy (ACC), positive predictive value (PPV), Matthews correlation coefficient (MMC) and area under ROC curve. We have got better results compared to existing literatures. We will also report the performance of regression models for the prediction of kinetic properties of FMO enzymes.

## **MEDI 381**

### **Synthesis, characterization and reactivities of a new HDAC inhibitor**

**Dan Shao<sup>1</sup>**, *d\_shao@u.pacific.edu*, **Esther S. Guo<sup>2</sup>**, **Chao Feng<sup>1</sup>**, **Qinliang Zhao<sup>1</sup>**. (1) University of the Pacific, Stockton, California, United States (2) Pleasant Grove High School, Elk Grove, California, United States

The development of new tumors and growing resistance to existing anticancer drugs has always been motivating research for new drug discovery. Histone deacetylase (HDAC) is found to be overexpressed in some cancer cells, which condenses the chromatin structure of tumor suppressor genes, cell-cycle inhibitor genes and apoptosis inducer genes. Four HDAC inhibitors, specifically Vorinostat, Romidepsin, Belinostat and Panobinostat, have been approved by FDA for cancer treatment. A newly designed HDAC inhibitor comprises of a main scaffold, a zinc-binding group, a protein recognition cap and also a coordination site to metal ions. The compound was synthesized through an amide coupling condensation reaction in anhydrous condition, followed by acidification, deprotection and a final neutralization step. The HDAC inhibitor has been characterized by MS and NMR analysis. Metal ions (Pt or Cu) could anchor at the coordination site of the inhibitor, resulting in bifunctional metal complexes. HDAC enzyme inhibition and cell viability studies of the inhibitor and its metal complexes will be examined.

### **MEDI 382**

#### **Design, synthesis, and structure-activity relationship of novel 1,2,4-triazine-3-one derivatives as multimodal compounds intended to treat schizophrenia**

*bogaraju narasimha, bogarajunarasimha@gmail.com, Vanaja R. Middekadi, Mohammed Rasheed, Dharmendra S. Sisodaya, Venkat R. Mekala, Surendra Petlu, Ramakrishna Nirogi. Suven Life Sciences Ltd, Hyderabad, India*

Schizophrenia is a debilitating disorder that affects nearly 1% of the global population. For the goal of controlling symptoms, several new treatments are available for initial and maintenance therapy. However, most of the treatments cause a plethora of side effects. Thus, there is an un-met medical need for a therapy which alleviates neuropsychiatric symptoms with no or minimal side effects. A series of 1,2,4-triazine-3-one derivatives were designed synthesized and evaluated for their in-vitro potencies towards serotonin receptors like 5-HT<sub>2A</sub>, 5-HT<sub>1A</sub> receptors, serotonin transporter SERT, dopamine receptor D<sub>2</sub>, histamine receptor H<sub>1</sub>, and adrenergic receptor  $\alpha$ 1B. Most of the compounds showed potent in vitro potencies towards these receptors. The selected compounds were further evaluated in pharmacokinetic studies to assess their exposures in plasma and brain. Details of design, chemistry, structure activity relationship, *in vitro* potencies and pharmacokinetic studies of 1,2,4-triazine-3-one derivatives will be disclosed in this poster presentation.

### **MEDI 383**

#### **Design, synthesis, and structure-activity relationship of novel pyrazolo-pyrimidine carboxamides as Muscarinic<sub>1</sub> Positive Allosteric Modulators (M<sub>1</sub> PAM)**

*Shankar R. Gagginapally, gagginapallyshankar@gmail.com, Durga M. Kancharla, Meghana Dasoju, Nageswara R. Mudanna, Ramkumar Subramanian, Ramakrishna Nirogi. Suven Life Sciences Ltd, Hyderabad, India*

Positive allosteric modulation (PAM) of the muscarinic acetylcholine receptor subtype 1 (M<sub>1</sub>) has drawn the attention of the researchers across the world as novel therapeutic approach for the treatment of cognitive deficits associated with Alzheimer's disease (AD). Moreover, selective M<sub>1</sub> PAMs also showed disease modifying potential, in addition to symptomatic cognition enhancing properties. A series of pyrazolo-pyrimidine carboxamide derivatives were designed synthesized and evaluated for their in-vitro potencies towards muscarinic receptors. Most of the compounds showed potent in vitro potencies towards M<sub>1</sub> receptor and found to be selective against other sub types. The selected compounds were further evaluated in pharmacokinetic studies to assess their exposures in plasma and brain. Details of design, chemistry, structure activity relationship, *in vitro* potencies and pharmacokinetic studies of pyrazolo-pyrimidine carboxamides will be disclosed in this poster presentation.

#### **MEDI 384**

##### **Design, synthesis, and pharmacological characterization of novel series of 4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine derivatives as H<sub>3</sub> receptor antagonists**

**PRAMOD K. ACHANTA**, *pramod\_vikas@yahoo.co.in*, Sangram K. Saraf, Rajesh K. Badange, Ramkumar Subramanian, Nageswara R. Mudanna, Pradeep Jayarajan, Ramakrishna Nirogi. *Suven Life Sciences Ltd, Hyderabad, India*

H<sub>3</sub> receptors (H<sub>3</sub>R) are autoreceptors which regulate the release of histamine in the brain, particularly in the cortex, striatum, hippocampus, amygdala and substantia nigra. H<sub>3</sub>R antagonists modulate the neurotransmitters involved in cognition such as histamine, acetylcholine and serotonin. H<sub>3</sub>R antagonists mediated cognitive-enhancing effects in animal models have generated considerable interest in their development for the treatment of cognitive deficits which involves disruption of multiple neurotransmitters.

we have designed and synthesized a novel series of 4,5,6,7-Tetrahydro-thiazolo[5,4-c]pyridine derivatives as H<sub>3</sub>R antagonists with high affinity at H<sub>3</sub>R and selectivity over closely related receptor subtypes. The lead compound from this series dose dependently antagonized the dipsogenia induced by (R)-alpha-methylhistamine confirming its functional antagonism at H<sub>3</sub>R. It has adequate oral exposure and favorable half-life in both rat and dog pharmacokinetic studies. The compound demonstrated high receptor occupancy (ED<sub>50</sub> = < 0.1 mg/kg), robust efficacy in rat time induced novel object recognition task (active at 1, to 10 mg/kg p. o.). In microdialysis assay, it showed dose dependent increase in acetylcholine levels. Details of chemistry, structure activity relationship, ADME and efficacy data will be presented in the poster.

#### **MEDI 385**

##### **Design, synthesis, and pharmacological characterization of novel carboxamides as 5-HT<sub>4</sub> receptor agonists**

**Rajesh K. Badange**, *rajesh@suven.com*, PRAMOD K. ACHANTA, Kiran K. Kandukuri, Venugopalarao Bhatta, Veena Reballi, Venkat R. Mekala, Gopinadh Bhyrapuneni, Vijay Benade, Ramakrishna Nirogi. Suven Life Sciences Ltd, Hyderabad, India

Alzheimer's disease (AD) is a neurodegenerative disorder, which usually develops slowly and can get worse over time primarily affecting new memory formation as well as retrieval of previously acquired memories. The drawbacks of currently approved therapies are modest efficacy and adverse side effects and their effects on cognitive functions are not sustained over the time. Therapies currently in clinical development may either offer symptomatic relief or provide pure disease modifications. There remains an urgent need for therapeutic agents that provide both improved symptomatic treatment and attenuate disease progression in patients with Alzheimer's disease (AD). 5-HT<sub>4</sub> receptor agonists may be of benefit for both the symptomatic and disease-modifying treatment of cognitive disorders via augmentation of neuronal acetylcholine (ACh) release as well as modulation of levels of the amyloid precursor protein (APP) derived peptides, amyloid beta (A $\beta$ ) and soluble amyloid precursor protein alpha (sAPP $\alpha$ ). Based on the literature precedence and scaffold hopping approaches we have designed and synthesized carboxamide based 5-HT<sub>4</sub> agonist compounds. The series in general has potent in vitro affinity at 5-HT<sub>4</sub> receptor (<10 nM). The lead compound from this series is a highly potent, selective and brain penetrant 5-HT<sub>4</sub> agonist. It demonstrated dose dependent receptor occupancy in rat brain. Animal models of efficacy confirms both symptomatic (activity in time induced novel object recognition model) and disease modifying potential (modulates cortical sAPP $\alpha$  level in mice brain) of the lead compound. The poster presentation will cover design, chemistry, SAR, ADME and animal efficacy studies.