Division of Medicinal Chemistry
Scientific Abstracts
for the
258th National Meeting and Exposition

August 25-29, 2019
San Diego, CA
**MEDI**

**Division of Medicinal Chemistry**

J. Schwarz, *Program Chair*

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**SUNDAY MORNING**

Section A

San Diego Convention Center
Room 6C

**Machine Learning in Medicinal Chemistry**

S. Patel, J. Stec, *Organizers, Presiding*

**8:15 MEDI 1.** NCATS ASPIRE: Synergizing engineering, synthetic chemistry, machine learning/AI, and biology to advance drug development. **D. Rudnicki,** K. Duncan, D.A. Tagle


**9:35 MEDI 3.** Machine learning for hit discovery: Recent work in virtual screening and *de novo* drug design. **R.E. Amaro,** C. Parks, Z. Gaieb

**10:15** Intermission.

**10:30 MEDI 4.** Designing for developability: Machine learning in data-driven drug discovery. **J. Karpiak**

**11:10 MEDI 5.** Withdrawn.

**11:50** Panel Discussion.
San Diego Convention Center  
Room 6D

General Orals

J. B. Schwarz, Organizer  
S. K. Cyr, Presiding


8:50 MEDI 7. Where do recent candidate drugs come from? J. Boström, D.G. Brown


10:10 MEDI 11. 4,6-Disubstutituted quinazolines as MEK5 inhibitors. P.T. Flaherty, S. Patel, A. Bhatt, T. Wright, J. Cavanaugh, M.E. Burow


11:10 MEDI 14. Selective ARTD8 inhibitors to better the understanding of metastatic cancers. **S.S. Schweiker**, A.L. Tauber, C. Kam, S.M. Levonis


**Origins & Future of Metabolite & Small Molecule Identification**

Sponsored by ANYL, Cosponsored by BIOL, BIOT and MEDI

**Measuring Protein Conformations & Folding Inside the Cell**

Sponsored by ANYL, Cosponsored by BIOL, BIOT and MEDI

**SUNDAY AFTERNOON**

San Diego Convention Center
Room 6C

**General Orals**

J. B. Schwarz, *Organizer, Presiding*


2:45 MEDI 20. Small molecule inhibitors of IRAK4. M.C. Bryan


3:35 MEDI 22. Asymmetric synthesis of aromatic lipoxin A4 analogues with upper chain modifications. A. Mahon, P.J. Guiry


San Diego Convention Center
Room 6D

Disease Modifying Approaches for the Treatment of Neurodegeneration

E. F. DiMauro, Organizer
H. Zhang, Organizer, Presiding
E. DiMauro, Presiding

1:30 Introductory Remarks.


3:20 Intermission.


5:20 Concluding Remarks.
Origins & Future of Metabolite & Small Molecule Identification

Sponsored by ANYL, Cosponsored by BIOL, BIOT and MEDI

SUNDAY EVENING

San Diego Convention Center
TBD

General Posters

J. B. Schwarz, Organizer

7:00 - 9:00

MEDI 31. Therapeutic potential of the caspase 1 inhibitors for the treatment of inflammatory disease. K. Kim, M. Iyer, R. Cinar, G. Kunos


MEDI 34. Discovery and structural optimization of small molecule inhibitors that regulate the wnt signaling pathway. W. Zhang


MEDI 36. Syntheses, characterizations, and a preliminary comparative cytotoxicity study of berenil-platinum complexes. A. Bielawska, R. Czarnomysy, K. Bielawski, A. Gornowicz, A. Muszynska


**MEDI 41.** Scaffold repurposing of a serotonin 2C agonist led to the discovery of highly selective dopamine D3 antagonists. L. Tan, J. Cheng


**MEDI 43.** Theoretical elucidation of the nucleophosmin enzyme inhibition by synthetic, natural, and designed new ligands: Molecular docking and molecular dynamic. N. NEDJINI, A. Ghomri, N. Missoum, S. Bouchentouf, S. Ghalem

**MEDI 44.** Synthesis and evaluation of new enantiopure pyridine-based arylaminoalcohols as antimalarial drugs. E. Pair, A. Dassonville-Klimpt, G. Bentzinger, P. LOUPIAS, A. Bouchut, C. Mullié, P. Agnamey, P. Sonnet

**MEDI 45.** Exploration of *Mycobacterium tuberculosis* RNA polymerase's putative ppGpp binding site as a potential therapeutic target. K. Guild, M.A. Stefan, G. Garcia
MEDI 46. Why is reversed-phase flash chromatography use increasing? **J.R. Bickler**

MEDI 47. Thiadiazole analogues as potent, liver selective glucokinase activators. 


MEDI 50. New 2-heteroaryl-4-quinolones as potential antibiotics targeting multi-drug resistant ESKAPEE pathogen communication systems. M. Duplantier, **P. Loupias**, E. Lohou, P. Sonnet

MEDI 51. Synthesis and study of new aminoquinolinemethanols as potential antibacterial drugs. P. Laumaillé, A. Dassonville-Klimpt, F. Peltier, **P. Loupias**, C. Mullié, C. Andréjak, S. Castelain, P. Sonnet

MEDI 52. Efflux pumps in *Acinetobacter baumannii*: Molecular characterization and study of new 1-(1-naphthylmethyl)-piperazine analogs as potential inhibitors. M. Choquet, **P. Loupias**, E. Lohou, C. Mullié, P. Sonnet


**MEDI 56.** Design, synthesis, and structure activity relationship of novel pyrazolo-pyrimidine muscarinic 1 positive allosteric modulators (M\(_1\) PAM). S. Gagganapally, D. Kancharla, M. Dasoju, N. Rao, R. Subramanian, R.V. Nirogi

**MEDI 57.** Design, synthesis, and structure activity relationship of novel 1,2,4-triazine-3-one: Derivatives as multimodal compounds intended to treat schizophrenia. V.R. Middekadi, B. Narasimha, A.R. Mohammed, D. Sisodaya, V. Mekala, S. Petlu, R. Nirogi

**MEDI 58.** Synthesis and biological evaluation of optimized analogues of the NPFF antagonist, MES304. K. Galal, C.R. McCurdy


**MEDI 60.** Development of novel sphingosine kinase inhibitors through structure-activity relationship study on jaspine B derivatives. S. Inuki, T. Miyagawa, S. Oishi, H. Ohno

**MEDI 61.** Halogen bond and its application in drug design. Z. Xu, W. Zhu


**MEDI 64.** Synthesis and anti-neuroinflammatory activity of N-heterocyclic analogs based on natural biphenyl-neolignan honokiol. S. Lee, Y. Yuan, S. Kwon, J. Lee, S. Seo
**MEDI 65.** Enantioselective synthesis of homoisoflavanones by asymmetric transfer hydrogenation and their biological evaluation for antiangiogenic activity. S. Kwon, M. Heo, B. Lee, S. Lee, J. Lee, S. Seo

**MEDI 66.** Enantioselective synthesis and absolute configuration determination of hydroxywilfordic acid in sesquiterpene pyridine alkaloids. J. Lee, Y. Yuan, S. Lee, S. Kwon, S. Seo


**MEDI 70.** MOEsacic: Application of matched molecular pair analysis to SAR exploration. G. Fortin, A. Ajamian

**MEDI 71.** Protocol for validating small-molecule structure assignment using calculated 13C NMR chemical shifts with quantum mechanics and MOE. A. Ajamian

**MEDI 72.** Scaffold replacement and 3D ligand optimization applied to the discovery of tyrosine kinase inhibitors. A. Ajamian

**MEDI 73.** Structure-based predictions of CYP selectivity, reactivity, and regioselectivity. A. Ajamian

MEDI 75. Novel glycolysis inhibitor improves the therapeutic regimen for triple negative breast cancer under hyperglycemic condition. D. Tailor, V. Kumar, A. Resendez, C. Going, S. Pitteri, S.V. Malhotra

MEDI 76. Examining ligand-HIV protease dissociation: Pathway, energy, flexibility, and comparison with association processes. J. Sun, M. Raymundo, Y.M. Huang, C. Chang


MEDI 78. Discovery of novel 4-alkylamino-2-(arylpiperazin)methylbenzonitrile derivatives as virus entry inhibitors for treatment of HCV infection. X. Jiang, J. Tan, Y. Wang, J. Li, J. Jin, X. Shi, Y. Quan, Y. Li, Z. Peng, Z. Li

MEDI 79. Discovery of carbazole carboxamides as novel RORγt agonists. M. Yu, N. Sun, Y. Huang, Y. Yan, C. Zhu, Q. Xie, Y. Wang


MEDI 83. Rational design and synthesis of novel inhibitors specific for interleukin-33. Y. Kim, J. Han, J. Pack, K. Kim, S. Park, D. Choi, S. Son, S. Son, K. Lee, K. Lee, Y. Jung, Y. Jeon, Y. Byun

MEDI 85. Design and synthesis of non-peptide analogs as novel hepsin inhibitors. **H. Kwon**, H. Ha, S. Nam, S. Son, Y. Byun

MEDI 86. Design and synthesis of trisubstituted pyridines as AKT inhibitors. **D.L. Prado Romero**, A. Hernandez Campos, R. Castillo-Bocanegra

MEDI 87. Discovery of small molecules that interact with Rpn-6 and are toxic to hematological cancers. **W. Tian**, D.J. Trader


MEDI 90. Establish cell-based assays for small molecules evaluation toward mucopolysaccharidosis type II. **C. Yu-Hsin**, W. Cheng


MEDI 94. Novel synthesis of chiral 2-trifluoromethylmorpholine. **J. Li**, L. Qi


MEDI 98. Natural products as source to find potential inhibitors from methicillin-resistant *Staphylococcus aureus* shikimate kinase: *In silico* based screening. **Li**
Lozano, A. Téllez Valencia, M. Gómez Palacio, J. Cisneros-Martinez, C.I. Avitia Domínguez


MEDI 100. Synthesis and spectroscopic identification of analgesic prodrugs attached to polyvinyl alcohol or polyvinyl phenol. K. Mohamoud, H.D. Tabba


MEDI 102. Structural characterization of capillary morphogenesis gene 2 inhibitors. S. Soleimani, J.D. Moody

MEDI 103. New methodology for the synthesis of sirtinol analogues a Sirtuin 2 inhibitor as antichagasic candidates. E.F. Pereira, R.A. Gomes, H.A. Stefani, G.H. Trossini

MEDI 104. pro-Pyrrolobenzodiazepine (pro-PBD) bioconjugates, part 5: Design and synthesis of bis-pro-PBD conjugates containing a self-immolative linkers that release active drug via intramolecular diazepine-ring-closure. I.R. Vlahov, A.E. Felten, N. Zou, K. Wang, S. Hahn, J. Vaughn, C.P. Leamon

MEDI 105. Glycone manipulation as a general strategy of optimizing the drug properties of the phyllanthusmin class of natural products. B.K. Mize, A. Huntsman, A. Young, J.L. Woodard, H. Chai, Y. Ren, M.A. Phelps, A.D. Kinghorn, J.E. Burdette, J. Fuchs


MEDI 111. Scaffold hopping: Versatile approach to develop new ligands for Liver X Receptor. R. Komati, J. Miller, J. Sridhar, K. Riley


MEDI 116. Withdrawn.


MEDI 119. Leveraging atropisomerism to obtain a selective inhibitor of RET kinase with secondary activities towards EGFR mutants. S. Toenjes, V. Garcia, S.M. Maddox, G. Dawson, M.A. Ortiz, J. Piedrafita, J.L. Gustafson

MEDI 121. IODVA1, a di-pyridine derivative with in vivo activity against cancer models. G. Premnauth, E.J. Merino, N. Nassar


MEDI 123. Revised synthesis of TC007: Potent lead for SMA treatment. U. Pandey, Y.P. Subedi, C.T. Chang


MEDI 125. Design and synthesis of tri-aryl methyl amine compounds for biological evaluation as anti-infective agents. I. Bal, W. Hatcher, T. Van Laar, S. Maitra

MEDI 126. Design, synthesis, and evaluation of GUNW-3 as a brain-targeting agent. A. Najmi, S. Wang, Y. Huang, Y. Alqahtani, X. Guan


MEDI 128. Synthesis and evaluation of small molecule scaffolds as potential protein-protein interaction inhibitors to prevent gankyrin-MDM2 binding. S. Yoganathan, J. Kong, A. Muth

MEDI 129. Use of neomycin as a side chain for phenanthroline based G-quadruplex binding ligands and telomerase inhibitors. M. Singh, R. Hekman, C. Vierra, L. Xue

MEDI 130. In silico screening and synthesis of 2,5,6-trisubstituted benzimidazoles as a new class of antitubercular agents targeting FtsZ. S. Kim, K. Haranahalli, A. Panapakides, A. Taouil, M. Awwa, I. Ojima


MEDI 133. Atropisomerism and PROTACs as strategies towards increased potency and selectivity of analogs of common kinase inhibitors. **S. Toenjes**, **S. Albright**, **R. Hazin**, S. Vaidya, J.L. Gustafson


MEDI 135. Co-crystal structure-based drug design and synthesis of plinabulin derivatives. M. Ma, Z. Ding, S. Wang, L. Ma, Y. Wang, J. Yang, **W. Li**

MEDI 136. Selective bromodomain inhibition of BRD4-D1 using trisubstituted-imidazoles and triazoles. **A. Divakaran**, H. Cui, S. Henry, A. Carlson

MEDI 137. Withdrawn.

MEDI 138. Preparation of intermediate of asenapine. **x. tian**, J. Ding, R. Zhang

MEDI 139. Withdrawn.


MEDI 141. Significance of chirality in drug design and synthesis of bitopic ligands as **D₃R** selective agonists. **A. Bonifazi**, F. Battiti, S. Cemaj, A.M. Guerrero, A. Shaik, A.H. Newman


MEDI 143. Discovery of pyrrolo[3,2-d]pyrimidine-containing compounds as inhibitors of NIK kinase. **Y. Zhao**, Z. Li, Z. Yan, X. Lv

MEDI 144. Discovery of ‘all-in-one’ nitric oxide-donor cephalosporin-3’-diazeniumdiolates with dual-antibacterial and antibiofilm properties. **M.J. Kelso**

MEDI 146. Ester bioisostere analogues of Astemizole as potential antiplasmodium agents. D. Mambwe, K. Chibale

MEDI 147. Modification of lactoferrin by peroxynitrite reduces its antibacterial activity and changes protein structure. A.Y. Alhalwani, R.L. Davey, N. Kaul, s.A. barbee, J.A. Huffman


MEDI 149. Phosphoramidate derivates as controlled-release prodrugs of L-Dopa. F.P. Olatunji, B.N. Kesic, C.J. Choy, C.E. Berkman


MEDI 152. Microwave-assisted expeditious and efficient synthesis of novel quinolin-4-ylmethoxychromen-2- and -4-ones catalyzed by YbCl$_3$ under a solvent free one-pot three component domino reaction and their antimicrobial activity. S. Kumar, A. Patel, N. Ahmed


MEDI 155. Design of GSK9742, a chemical probe for the TAF1/TAF1L bromodomains. M. Clegg, N. Theodoulou, G. Liwicki, R. Prinjha, N. Tomkinson, P. Humphreys

MEDI 157. Combatting the opioid and benzodiazepine epidemic by the synthesis of novel safer drugs designed to be functionally selective for α5- or α6-containing GABA\textsubscript{A} receptors. **D.E. Knutson**, G. Li, T. Prevot, L. Arnold, L. Chiou, M. Ernst, M. Mihovilovic, M. Savic, W. Sieghart, E. Sibille, J.M. Cook


MEDI 159. Solvent-free biogels for mechanobiology. **F. Fahimipour**, E. Dashtimoghadam, M. Vantankhah-Varnosfaderani, S. Sheyko


MEDI 162. New rhodium(I) NHC complex targeting TrxR inhibits hepatocellular carcinoma *in vivo*. **w. liu**


MEDI 166. Development of bioactive γ-AA peptides based peptidomimetics to control angiogenesis. **S.A. Abdulkadir**, P. Sang, C. Li, J. Cai


MEDI 169. Approaches to demonstrate pharmaceutical equivalence of Ibrutinib cocrystal complex for the follow-on generic drugs. W. Jiang, W. Liu, Y. Xu, B. Lim, D. Skanchy, R. Randad


Biosensing: New Strategies & Latest Development

Sponsored by ANYL, Cosponsored by BIOL, BIOT and MEDI

MONDAY MORNING

San Diego Convention Center
Room 6C

Rising Stars: Women in Medicinal Chemistry

Cosponsored by WCC
A. L. Garner, Organizer, Presiding

8:30 Introductory Remarks.


9:05 MEDI 172. Fragment to lead: Discovery and optimization of a novel bromodomain inhibitor. A. Adams

9:35 MEDI 173. Chemical targeting of deubiquitinating enzymes. S. Buhrlage
10:05 Intermission.


10:50 MEDI 175. Generating new synthetic transformations and unique heterocycles to drive anti-infective agent discovery and development. J.E. Golden

11:20 MEDI 176. Enabling medicinal chemistry as a process chemist. J. McCabe Dunn

11:50 Concluding Remarks.

Section B

San Diego Convention Center
Room 6D

Catastrophic Epilepsies: How Medicinal Chemists can Help

Financially supported by Sage Therapeutics
M. Blanco, Organizer, Presiding

9:00 Introductory Remarks.

9:05 MEDI 177. Overview of current drug discovery approaches for childhood epilepsies. A. Mingorance


10:40 Intermission.

11:30 MEDI 180. Novel synthetic neurosteroids to reduce seizure burden and improve survival in preclinical models of catastrophic epilepsies. **M. Blanco**

12:05 Concluding Remarks.

**Future of Biomacromolecules at a Crossroads of Polymer Science & Biology**

**Synthetic Cells**

Sponsored by POLY, Cosponsored by BIOL, CARB, CELL, COLL, ENVR, MEDI, PHYS and PMSE‡

**Recent Advances in Kinase Drug Discovery: A Joint Venture Between Medicinal, Biological & Computational Chemists**

Sponsored by COMP, Cosponsored by MEDI

**2019 ACS International Award for Research in Agrochemicals: Advances in the Physiology & Biochemistry of Insect Control**

Sponsored by AGRO, Cosponsored by AGFD, BIOL, MEDI, POLY‡ and PROF‡

**MONDAY AFTERNOON**

San Diego Convention Center
Room 6C

**Optimizing Brain Penetration**

A. B. Dounay, **Organizer, Presiding**
1:30 MEDI 181. Probabilistic MPO (pMPO) and its application in CNS drug discovery. **H. Gunaydin**

2:00 MEDI 182. Harnessing preclinical data as a predictive tool for human brain tissue targeting. **N. Patel**

2:30 MEDI 183. BBB organoid platform for modeling therapeutic delivery to the brain. C. Cho, J. Wolfe, C.M. Fadzen, D. Calligaris, K. Hornburg, **E. Chiocca**, N. Agar, B.L. Pentelute, S. Lawler

3:00 Intermission.

3:15 MEDI 184. Use of a CSF cannulated dog model in development of BACE1 inhibitors. **S. Monk**

3:45 MEDI 185. Considerations for optimizing CNS penetration and successful programs. **C.W. Lindsley**

4:15 MEDI 186. Optimization and identification of brain penetrant, M4 subtype-selective muscarinic receptor positive allosteric modulator (M4 PAM) clinical candidate. **C. Butler**

Section B

San Diego Convention Center
Room 6D

**No Linker Required: Non-PROTAC Degraders**

G. Wang, *Organizer*
J. Liang, *Organizer, Presiding*

1:00 MEDI 187. Cyclic peptide ternatin-4 promotes degradation of the translation elongation factor, EF1A. **J.W. Taunton**

1:40 MEDI 188. Small-molecule estrogen receptor degraders (SERDs): Chemical exploration and optimisation at AstraZeneca. **J.S. Scott**

2:20 MEDI 189. Small molecules that catalyze the degradation of splicing factors. **D. Nijhawan**

3:40 MEDI 191. ASTX660, a small molecule antagonist and degrader of cellular inhibitor of apoptosis proteins in phase I/II clinical trials. R. Holvey


2019 ACS International Award for Research in Agrochemicals: Advances in the Physiology & Biochemistry of Insect Control

Sponsored by AGRO, Cosponsored by AGFD, BIOL, MEDI and PROF

Future of Biomacromolecules at a Crossroads of Polymer Science & Biology

Tissue Engineering

Sponsored by POLY, Cosponsored by BIOL, CARB, CELL, COLL, ENVR, MEDI, PHYS and PMSE‡

Recent Advances in Kinase Drug Discovery: A Joint Venture Between Medicinal, Biological & Computational Chemists

Sponsored by COMP, Cosponsored by MEDI

MONDAY EVENING
San Diego Convention Center
TBD
Sci-Mix

J. B. Schwarz, *Organizer*

8:00 - 10:00


TUESDAY MORNING

San Diego Convention Center
Room 6AB

MEDI Awards Symposium

J. B. Schwarz, *Organizer*
A. Stamford, *Presiding*

9:00 MEDI 193. Translational chemistry. **P.S. Baran**

9:45 MEDI 194. Progress in the discovery of kinase inhibitors for treatment of parasitic diseases. **D.P. Rotella**

10:55 MEDI 196. How I spent my summer vacation: Insights from a 30-year career in drug discovery (and molecules that have broken my heart). J.E. Macor

San Diego Convention Center
Room 6D

Drug Discovery Beyond the Rule of 5

D. A. Degoe, Organizer, Presiding

8:30 Introductory Remarks.

8:35 MEDI 197. Property-based drug design: bRo5. P.B. Cox

9:05 MEDI 198. Onward, beyond the rule of 5! Understanding and controlling cell permeability in macrocyclic peptides. S. Lokey


10:35 MEDI 201. Design of orally bioavailable proteolysis targeting chimera (PROTAC) small-molecule degraders. S. Wang

11:05 MEDI 202. Chemical induced dimerization for targeted protein degradation. J. Bradner

11:45 Concluding Remarks.

Recent Developments in Structural Biology

Sponsored by BIOL, Cosponsored by MEDI
2019 ACS International Award for Research in Agrochemicals: Advances in the Physiology & Biochemistry of Insect Control

Sponsored by AGRO, Cosponsored by AGFD, BIOL, MEDI and PROF

Global Health: Biology & Chemistry of Waterborne Diseases

Sponsored by BIOL, Cosponsored by MEDI

Mass Spectrometry of Biomolecular Assemblies

Sponsored by ANYL, Cosponsored by BIOT, BMGT and MEDI

Biostimulants in Agriculture: Chemistry & Regulatory Aspects

Sponsored by AGRO, Cosponsored by BIOL, MEDI and TOXI

Recent Advances in Kinase Drug Discovery: A Joint Venture Between Medicinal, Biological & Computational Chemists

Sponsored by COMP, Cosponsored by MEDI

TUESDAY AFTERNOON

San Diego Convention Center
Room 6AB

MEDI Awards Symposium
J. B. Schwarz, Organizer
A. Stamford, Presiding

2:00 MEDI 203. Targeted small molecule degradation of a hypoxia-associated non-coding RNA enhances the selectivity of an RNA targeted small molecule. M.G. Costales, B. Suresh, M.D. Disney


3:40 MEDI 207. Adventures in allosteric drug discovery. C.W. Lindsley


Section B

San Diego Convention Center
Room 6D

Privileged & Underprivileged Functional Groups in Drug Design

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

2:00 Introductory Remarks.

2:05 MEDI 209. Natural product derived privileged scaffolds in drug discovery. M. Brimble, E. Davison
2:35 MEDI 210. Leveraging the necessary nitrogen atom in chemical biology and drug discovery. L.D. Pennington

3:05 MEDI 211. Geminal diheteroatomic motifs in drug design: Applications of acetals, ketals, and their sulfur and nitrogen homologues in medicinal chemistry. Y. Wu, N.A. Meanwell

3:35 MEDI 212. Design of ligands targeting carbohydrate binding sites: Galectin 3. F. Zetterberg

4:05 MEDI 213. Sulfoximines in drug discovery revisited: What has happened since 2013? U.T. Luecking


ACS Infectious Diseases Young Investigators Award Symposium
Sponsored by BIOL, Cosponsored by MEDI

Mass Spectrometry of Biomolecular Assemblies
Sponsored by ANYL, Cosponsored by BIOL, BIOT and MEDI

Biosensing: New Strategies & Latest Development
Sponsored by ANYL, Cosponsored by BIOL, BIOT and MEDI

Biostimulants in Agriculture: Chemistry & Regulatory Aspects
Sponsored by AGRO, Cosponsored by BIOL, MEDI and TOXI
TUESDAY EVENING

Future of Biomacromolecules at a Crossroads of Polymer Science & Biology

Sponsored by POLY, Cosponsored by BIOL, CARB, CELL, COLL, ENVR, MEDI, PHYS and PMSE

WEDNESDAY MORNING

Section A

San Diego Convention Center
Room 6AB

First Time Disclosure of Clinical Candidates

E. DiMauro, Organizer, Presiding

8:15 Introductory Remarks.


8:50 MEDI 216. Discovery of SAR439859, an orally bioavailable Selective Estrogen Receptor Degrader (SERD) to treat ER+ breast cancers. Y. Elahmad


9:50 Intermission.

10:05 MEDI 218. Discovery of AB928, a potent first-in-class dual A2a and A2b receptor antagonist for cancer immunotherapy. M.R. Leleti, J. Jeffrey, E.U.


12:05 Concluding Remarks.

Section B

San Diego Convention Center
Room 6D

Emerging Targets for Drug Abuse Therapy

C. R. Hopkins, Organizer, Presiding

9:00 Introductory Remarks.

9:10 MEDI 222. Issues in the evaluation and validation of targets for substance use disorder medication development. J. Acri


10:10 MEDI 224. Discovery of VMAT2 modulators as potential treatments for methamphetamine use disorders. G. Zheng
10:40 MEDI 225. Design, synthesis, and preclinical characterization of small molecule group II metabotropic glutamate receptor positive allosteric modulators. N.D. Cosford


Future of Biomacromolecules at a Crossroads of Polymer Science & Biology

Delivery Systems

Sponsored by POLY, Cosponsored by BIOL, CARB, CELL, COLL, ENVR, MEDI, PHYS and PMSE‡

Development of Novel Vector Control Technologies

Sponsored by AGRO, Cosponsored by MEDI

Biosensing: New Strategies & Latest Development

Sponsored by ANYL, Cosponsored by BIOL, BIOT and MEDI

Biostimulants in Agriculture: Chemistry & Regulatory Aspects

Sponsored by AGRO, Cosponsored by BIOL, MEDI and TOXI

Development of Novel Vector Control Technologies
Sponsored by AGRO, Cosponsored by MEDI

WEDNESDAY AFTERNOON

San Diego Convention Center
Room 6AB

Pharma Leaders Symposium

K. Briner, Organizer, Presiding


2:40 MEDI 228. DNA-encoded libraries at GSK. K.B. Goodman


4:10 MEDI 231. DNA-encoded chemical space: Widening the scope of DNA compatible chemistry. F. Berst, Y. Ruff, R. Martinez

Section B

General Orals
J. B. Schwarz, Organizer
M. Lu, Presiding


2:10 MEDI 234. Experimental identification of protein-ligand interactions in fragment-based drug discovery with high-throughput protein crystallography screening of fragment libraries. D. Das

2:30 MEDI 235. Structure-based design of potent and selective CGRP receptor antagonists for the treatment of migraine. I.M. Bell


Section C

San Diego Convention Center
Room 6C

Discovery of Therapeutic Agents for Chronic HBV Infection

M. Mish, H. Shen, Organizers, Presiding

2:00 Introductory Remarks.

2:05 MEDI 244. Discovery and development of a novel, class I Core protein Assembly Modulator (CpAM) for the treatment of chronic HBV infection. W. Zhu

2:35 MEDI 245. Discovery of RG7834 and target identification: First-in-class selective and orally bioavailable small molecule HBV expression inhibitor with a novel mechanism of action. S. Yang

3:05 MEDI 246. SB 9200 (inarigivir), a selective oral immuno-modulator for chronic hepatitis B. R. Iyer

3:35 Intermission.
3:50 MEDI 247. Hit to lead optimization of toll-like receptor agonists toward the treatment of hepatitis B virus. **D.C. McGowan**


4:50 Concluding Remarks.

**Covalent & Non-Covalent Dimers as Therapeutic Agents in Drug Discovery**

Sponsored by BIOL, Cosponsored by MEDI and ORGN

**Future of Biomacromolecules at a Crossroads of Polymer Science & Biology**

**Biomaterials**

Sponsored by POLY, Cosponsored by BIOL, CARB, CELL, COLL, ENVR, MEDI, PHYS and PMSE‡

**Study of Circulating, Cell-Free Biomarkers with Analytical Tools**

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**Development of Novel Vector Control Technologies**

Sponsored by AGRO, Cosponsored by MEDI
Biosensing: New Strategies & Latest Development

Sponsored by ANYL, Cosponsored by BIOL, BIOT and MEDI

WEDNESDAY EVENING

San Diego Convention Center
TBD

General Posters

J. B. Schwarz, Organizer

7:00 - 9:00

MEDI 249. Hidden bias in the dataset leads to misleading performance of deep learning in structure-based virtual screening. E. Chen, A. Cruz, S. Ramsey, V. Hornak, D. Koes, T. Kurtzman


MEDI 251. Discovery of a C-8 hydroxychromene as a potent inhibitor of estrogen receptor alpha with improved rat oral exposure over GDC-0927. S.S. Labadie


MEDI 255. Efficacy of 4-oxo-4,5-dihydrothieno[3,2-c]quinoline CDK5 inhibitors as modulators of adipogenic insulin/metabolic pathways. A. Chatterjee, S. Mukherjee, M. Chakraborty, A. Chakraborty

MEDI 256. Dual-acting compounds targeting the adenosine 2A receptor (A2AR) and histone deacetylases (HDACs) for cancer immunotherapy. W. Yan, R. Liu, J. Cheng


MEDI 258. Design, synthesis, and evaluation of O5 modified apramycin derivatives. V. Sarpe, A. Sonousi, J.C. Quirke, P. Rajasekaran, A. Vasella, E. Böttger, D. Crich


MEDI 261. Synthetic and biological studies of benzazepine derivatives as dopamine receptor ligands. R. Giri, W.W. Harding


MEDI 264. Developing chemical probes against falcilysin, an essential malarial metalloprotease. N. Maslov

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**MEDI 271.** Development of novel ecto-5'-nucleotidase inhibitor with non-competitive mechanism. W. Sun, Y. Lee, M. Kuo, C. Huang, S. Chen, C. Liu


**MEDI 273.** Planar catechin conjugated with DTPA as a promising antioxidant triggered by Fe$^{3+}$ coordination. K. Fukuhara, K. Imai, I. Nakamichi, K. Matsumoto, A. Ohno

**MEDI 274.** Drug development and production for cardiovascular diseases & arrest (CDA/CDD) (Oxonitrogenic). S.N. Olatunji


**MEDI 277.** Compound selectivity evaluation in PPAR family using machine learning modelling. **O.B. Scott**, R. Chen Xu, D. Ni, A.E. Chan

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MEDI 315. Combinatorial approach for synthesis of novel 1,3,5-triazine-2,4-diamines with potent and selective anti-proliferative activity. A. Junaid, C. Lay Hong, A.V. Dolzhenko

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NCATS ASPIRE: Synergizing engineering, synthetic chemistry, machine learning/AI, and biology to advance drug development

Dobrila Doda Rudnicki, dobrila.rudnicki@nih.gov, Katharine Duncan, Danilo A. Tagle. Special Initiatives, Office of The Director, NCATS, NIH, Bethesda, Maryland, United States

Recent innovations in automated chemical synthesis technologies, high-throughput biological screening, automation engineering, and machine learning/artificial intelligence (AI) indicate that now is the time to converge these technologies and advance our understanding of the relationship between chemical and biological space. While symbiosis of the above technologies has tremendous potential to advance drug development, with the input of the scientific community, funders, publishers and other interested stakeholders, NCATS has identified a number of challenges that surround the application of machine learning to drug development. These challenges include but are not limited to lack of standardization in chemistry; insufficient quality, variety and quantity of data in databases; lack of user-friendly electronic laboratory notebooks to provide better quality and quantity of day-to-day data and be accessible for machine learning; and limitations of biological assays that are currently used to identify and validate promising drug candidates. To address some of these issues and help catalyse the discovery and development of novel, safe, and effective treatments, while at the same time making the process faster and more cost-effective, NCATS is supporting the development of A Specialized Platform for Innovative Research Exploration (ASPIRE). ASPIRE aims to ignite development of innovative algorithms to predict and synthesize novel structures capable of interacting with specific targets; enable small-scale synthesis of the predicted molecules; and incorporate in-line, rapid biological testing of the molecules. If successful, this concerted and collaborative effort will revolutionize drug discovery and development. ASPIRE’s ultimate goal is to bring the promise of science to those in need of new or improved safe and effective treatments.

Lessons from the world’s largest prospective application of machine learning to hit discovery

Sara Omlid, Kong T. Nguyen, Andrea Lee, Denzil Bernard, Christian Laggner, Adrian Stecula, Niel M. Henriksen, terrence o'brien, Jeff M. Warrington, Mostafa H. Ahmed, Izhar Wallach, Abe Heifets, abe@atomwise.com, Han Lim. Atomwise, San Francisco, California, United States

Machine Learning tools promise to revolutionize drug discovery, greatly expand the set of druggable targets, and have shown unbelievably good performance on benchmarks for Medicinal Chemistry tasks. Unfortunately, recent analyses imply that such apparently-encouraging algorithmic performance are likely to be an artifact of
weaknesses in the design of these benchmarks. Therefore, we are running the largest assessment of machine learning for hit discovery in history, comprising over 350 projects on 238 targets with 112 universities in 19 countries. We present the first results from this broad experiment, and report on lessons learned and best practices for medicinal chemists considering artificial intelligence tools and for academic researchers embarking on translational research.

MEDI 3

Machine learning for hit discovery: Recent work in virtual screening and de novo drug design

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The pharmaceutical pipeline is challenged at the preclinical and clinical stages by costly, high attrition rates that impede the development of new therapies for many diseases. Machine learning based drug discovery approaches can help reduce such attrition by learning from previous successes and failures in a data driven fashion. Herein, we discuss some of the recent machine learning work in the Amaro lab pertaining to the critical hit discovery and hit-to-lead optimization phases of drug discovery. Firstly, we introduce recent proteochemometric machine learning virtual screening technologies that overcome many of the limitations of conventional docking and ligand based approaches such as (1) sensitivity to x-ray crystallographic structure, (2) lack of transferability to new targets with little or no prior data, and (3) no well-defined applicability domain. Secondly, we discuss recent success in coupling generative LSTM models with reinforcement learning for the design of multi-target inhibitors de novo aimed to help address the poor efficacy of clinical oncology candidates.

MEDI 4

Designing for developability: Machine learning in data-driven drug discovery

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The ‘design, make, test’ cycle is central to medicinal chemistry. While effective, the iterative nature of this cycle can drive inefficiency and protracted optimization timelines. Coupled with evolving multi-parameter optimization needs, the medicinal chemist is challenged to assimilate a large quantity of diverse data and to find solutions to diverse problems. Instead, a ‘design, predict, make, test’ cycle could drive greater efficiency and shorten timelines by focusing on collecting the necessary data to make the next set of informed predictions. This requires a new data-driven decision-making culture, ensuring that tools, processes, and people all have modelling and analytics available as a key
component from the beginning. This talk will explore how machine learning has been applied to all stages of the design-predict-make-test cycle, leveraging historical data to generate synthetically tractable molecules at pace that mitigate ADMET and scalability risks. We will also discuss design platforms that encourage the incorporation of predictive methods and democratization of these models to all chemists, with the limitations and lessons learned from deploying these approaches on real projects.

MEDI 5

Making big sense of big data by read-across of toxic properties of chemicals

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The European REACH regulation has made big data available in safety sciences – the challenge is now to make big sense of these data. The ECHA warehouses the largest dataset of \textit{in vivo} tests. This data was extracted using linguistic search engines into a structured, machine readable and searchable database, with 9,801 unique substances– including 3,609 unique study descriptions and a total of 816,048 study documents. This data can be used to explore toxicological data on a scale not previously seen.

Read-across, i.e. the local similarity-based intrapolation of properties, is gaining momentum with increasing data availability and consensus on how to process and report it. It is applied to \textit{in vivo} test data as a gap-filling approach, but can similarly complement other incomplete datasets. Big data are first of all repositories for finding similar substances and ensure that the available data is fully exploited. Substance similarity analysis was used to determine clustering of substances with similar hazard labels. Here, a new web-based tool under development called read-across-based structure activity relationship (RASAR), which aims to support and automate structure-based read-across, is presented.

In collaboration with Underwriters Laboratories (UL), the database has expanded to more than 10 million chemical structures, more than 300,000 of which are annotated with biological and chemicophysical data and 50,000 with animal data. It took an Amazon cloud server two days to analyze the similarities and differences between the 10 million chemicals to place them on a map, where similar chemicals are put close to each other, dissimilar ones distant. Making use of 74 properties in a data fusion approach, random forest machine learning was applied in a five-fold cross-validation. Applying this to 190,000 classified chemicals based on animal tests, 87% of the time the computer was correct. Notably, each prediction comes with an expression of certainty based on the constellation of data available. The software was even better for finding toxic than non-toxic substances with 89% success—exceeding the 70% probability of animal tests to find a toxic substance again in a repeat animal test, shown in a parallel analysis of the database. The software (the UL Cheminformatics Tool Kit) at this stage predicts nine different hazard classifications, traditional testing for which consumes 57% of all animals in safety testing in Europe, or about 600,000 animals per year.
MEDI 6

Synthesis and evaluation of near-IR boron-dipyrromethene (BODIPY) bioconjugates selectively targeting cancers overexpressing epidermal growth factor receptor (EGFR)

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For this work, five boron dipyrromethene (BODIPY) bioconjugates were synthesized to incorporate the epidermal growth factor receptor (EGFR)-targeting peptide 3PEG-LARLLT and/or a glucose or biotin ethylene diamine monomer for the purpose of imaging colon cancers overexpressing EGFR. These bioconjugates were then evaluated to determine their photophysical properties and binding affinities for the extracellular domain (ECD) of EGFR using fluorescence microscopy, surface plasmon resonance (SPR), molecular modeling, competitive binding assays, in vitro and in vivo studies. BODIPY bioconjugates containing the EGFR-targeting peptide 3PEG-LARLLT were found to bind specifically to EGFR ECD whereas those bioconjugates without peptide were found to bind non-specifically or weakly. All BODIPY bioconjugates were determined to have low dark- and phototoxicity (IC₅₀ > 94 μM) in human HT-29 cells. In vivo studies using nude mice with subcutaneously implanted human HT-29 xenografts revealed that BODIPY bioconjugates with the EGFR-targeting peptide localized within the tumor xenografts within 24 h of intravenous injection. The results presented will illustrate that BODIPY bioconjugates containing the EGFR-targeting peptide 3PEG-LARLLT are promising candidates for use as near-IR fluorescent imaging agents for colon cancers overexpressing EGFR.

MEDI 7

Where do recent candidate drugs come from?

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Choosing lead generation strategy is one of the most important decisions in drug discovery projects. An overview of what strategies have been successful in identifying small molecule candidate drugs will be presented. To find this information (a set of clinical candidates and their respective original hit), recent Journal of Medicinal Chemistry articles were scrutinized. We observe that most candidate drugs come from known starting points (43%). For targets, where there’s little information, it is reassuring to be able to show that HTS delivers (29%). The remainder of approaches included focused screening, structure-based drug design, fragment-based lead generation, and
DNA-encoded library screening. It is clear that regardless of the hit-finding strategy, the final clinical candidate is a much-improved compound compared to the initial hit. Significant effort and time in chemistry is often required which adds to MW and complexity of scaffolds. In conclusion, this study provides a retrospective analysis of past trends that have led to successful clinical candidates and hopefully provides the framework for the exploitation of future opportunities.

MEDI 8

Discovery of lipid prodrugs of tenofovir with improved metabolic properties

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Tenofovir (TFV) is an acyclic nucleoside reverse transcriptase inhibitor (NRTI) employed globally in first-line regimens for the treatment of HIV-1. However, due to the negative charges on the phosphonate at physiological pH, TFV exhibits poor oral bioavailability and low cellular uptake. As a result TFV is typically administered as the phosphonate diester and phosphoramidate prodrugs, TFV disoproxil fumarate (TDF) and TFV alafenamide (TAF) respectively. Prodrugs of TFV mask the phosphonate and, therefore, dramatically improve oral bioavailability and cell membrane permeability. The principal drawbacks to TDF and TAF are the organ-specific toxicities that result from cleavage in the liver and, in the case of TDF in plasma, resulting in accumulation of TFV in bone and the kidney. CMX157, another potent orally bioavailable TFV prodrug, was developed to address these limitations. CMX157, which disguises the acyclic nucleoside phosphonate as a partially metabolized phospholipid, is stable in plasma and is predominantly cleaved by phospholipase C intracellularly. Unfortunately, CMX157 is susceptible to cytochrome P450 mediated ω-oxidation at the terminal methyl group on the lipid chain. We have sought to overcome this shortcoming by designing novel lipid prodrug analogues of TFV that resist hepatic ω-oxidation while maintaining the efficacy exhibited by CMX157. Herein, we report several novel CMX157 analogues with improved metabolic stability, which are expected to decrease levels of TFV in the liver and plasma, thereby mitigating organ-specific toxicities typically associated with current TFV prodrugs. In addition to long term safety and tolerability, this strategy has the potential to extend the duration of action of these prodrugs which, in the long-term, could improve patient compliance and limit the quantity of drug required in the treatment of HIV-1.

MEDI 9

Discovery of small molecule antagonists of the toll-like receptors TLR7/8/9 for the treatment of lupus
Within the innate immune system, key components include several families of pattern recognition receptors (PRRs), including the Toll-Like Receptor (TLR) family. These PRRs recognize pathogen-associated molecular patterns (PAMPs) from microbial sources, and danger-associated molecular patterns (DAMPs) from stressed, damaged, or necrotic host cells. Endosomally localized TLR7, 8 and 9 respond to single-stranded (ss)RNA (TLR7/8) or unmethylated ssDNA (TLR9) and their aberrant activation by self-RNA/DNA contributes to the disease pathophysiology of systemic lupus erythematosus (SLE) and related autoimmune diseases by the production of cytokines (e.g. IL-6, IL-12, TNFα, IFNα) and B-cell activation. Inhibition of this undesired TLR7/8/9 activation is anticipated to offer therapeutic benefit for SLE patients. High throughput screening (HTS) of a compound collection led to the identification of a series of antagonists of TLR7/8/9 based on an indole template. This presentation will detail the in vitro and in vivo optimization of this series leading to the identification of compounds with excellent on-target potency and high efficacy in rodent models of lupus and other autoimmune disorders.

MEDI 10

Discovery and disclosure of GLPG1205, a first in class GPR84 negative allosteric modulator in phase II clinical trial

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GPR84 is a member of the metabolic G protein-coupled receptor family mainly expressed in immune cells and upregulated under inflammatory conditions. It plays an important role in driving chemotaxis of several leukocyte subtypes upon activation by medium chain fatty acid type ligands. In this presentation, the identification of potent dihydropyrimidino-isoquinolinones acting as GPR84 functional antagonists will be described. The set-up of the biological cascade and the optimization of the in vitro potency and ADME/PK properties of the Hit series leading to the identification of GLPG1205 will be addressed. The chemical structure of GLPG1205 will be disclosed. In addition, studies establishing the particular binding mode of GLPG1205 and its close analogues as negative allosteric modulators will be documented. The effect of GLPG1205 on neutrophil and macrophage chemotaxis assays, its efficacy in a chronic
mouse colitis model as well as pharmacological data supporting current progression of GLPG1205 in a phase IIa clinical trial in IPF (NCT03725852) will be presented.

**MEDI 11**

4,6-Disubstituted quinazolines as MEK5 inhibitors

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The MAPK signaling cascade mediates internal cell responses including growth and movement to external and internal stressors. This cascade consists of a 3-tiered protein phosphorylation sequence with a MEK member as the most restrictive member in these signaling cascades. Of the 8 known human MEK isoforms, MEK5 is significantly upregulated in breast cancer and correlates with decreased patient survival and increased patient morbidity. Identification of lead compound 1 in the BindingDatabase as a compound with collateral MEK5 inhibition suggested exploration of 4- and 6-position structural variants on the quinazoline core to optimize MEK5 activity and selectivity. The computational design, docking, synthesis, and biological testing for a series of 4-alkyl, aryl, and hetaryl derivatives along with 6-aryl variations will be presented.
Azetidinyl diamides as potent reversible inhibitors of monoacylglycerol lipase (MAGL)

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The biological significance of the endocannabinoid system has been studied extensively in recent years. Several endogenous ligands (endocannabinoids) have been discovered to interact with cannabinoid receptors 1 and 2 (CB1 and CB2) and play important roles in regulating a wide range of physiological processes. The endocannabinoid 2-arachidonoyl glycerol (2-AG) is a full agonist of CB1 and CB2, and the principal endocannabinoid found in the brain. 2-AG is rapidly degraded to arachidonic acid (AA) and glycerol by the serine hydrolase monoacylglycerol lipase (MAGL). Inhibition of MAGL has the potential to elevate 2-AG levels which will boost endogenous cannabinoid activity and produce a variety of desirable therapeutic effects. Furthermore, MAGL-mediated 2-AG hydrolysis is an important source of brain AA, a precursor for prostaglandins that promote neuroinflammation and lead to neurodegeneration. Therefore, inhibiting MAGL offers a dual benefit in treating inflammatory disorders. Majority of the reported MAGL inhibitors are irreversible inhibitors. However, chronic inhibition of MAGL by an irreversible inhibitor or genetic deletion of MAGL has been shown to desensitize CB1, which eventually impairs the 2-AG mediated CB1-dependent beneficial effects. It is anticipated that the reversible inhibition mechanism will allow for more precise modulation of 2-AG levels in vivo with an improved therapeutic index. We report herein the discovery of a series of azetidinyl diamide compounds as potent reversible inhibitors of MAGL. Many analogs in this series possessed potent in vitro MAGL inhibitory activity in the enzyme assay and significantly increased 2-AG levels in homogenized rat brain tissue. The lead compound of the series exhibited potent and durable efficacy in a rat complete Freund’s adjuvant (CFA)-induced inflammatory pain model and a chronic constriction injury (CCI)-induced rat neuropathic pain model. Additionally, this lead compound demonstrated very good selectivity for MAGL, and its structure in complex with MAGL was obtained by X-ray crystallography.
(BET) family of bromodoms, which has led to the development of multiple small molecule inhibitors and an increasing number of clinical assets. Central to this flurry of research has been the ready availability of high quality BET chemical probes, in particular I-BET762 and (+)-JQ1. However, the BET family represents only eight reader domains of the bromodomain phylogenetic tree and the therapeutic potential of the remaining 53 bromodomains is comparatively less explored.

P300/CBP-associated factor (PCAF) and general control nonderepressible 5 (GCN5) are multi-domain proteins containing a highly homologous bromodomain and are reported to have a role in the production of inflammatory cytokines. To (in)validate PCAF/GCN5 bromodomains as tractable and disease relevant targets, GSK embarked on a knowledge-based screen against the PCAF bromodomain. Deconstruction of an unselective hit to a highly efficient fragment was followed by structure guided optimisation to deliver GSK4027, a high quality PCAF/GCN5 bromodomain chemical probe. However, bromodomain inhibition alone with GSK4027 was unable to recapitulate the diminished inflammatory response of PCAF-deficient immune cells. The knowledge gained during the development of GSK4027 was used to generate the first bifunctional PCAF/GCN5 proteolysis targeting chimera (PROTAC) GSK699 which selectively degraded PCAF/GCN5 efficiently to demonstrate profound modulation of multiple inflammatory mediators in LPS-stimulated macrophages and dendritic cells.

MEDI 14

Selective ARTD8 inhibitors to better the understanding of metastatic cancers
A protein known as ARTD8 has been shown to be over expressed in most cancer types and supports the metastases of cancer cells through enhancing tumour growth, accelerating the metabolism and promoting cell survival. Inhibition of ARTD8 has been shown to inhibit DNA repair mechanisms and selectively decrease the metabolism of tumour cells while not effecting the growth of normal non-cancerous cells. This makes ARTD8 an interesting target for selectively targeting metastatic cancers as these once-resistant cancers would be more susceptible to regular anti-cancer therapies.

Currently there is no selective ARTD8 inhibitors and the understanding of how ARTD8 functions has only been studied using knockdown models. To further our understanding of metastatic cancers and work towards developing a treatment more research is needed. Our research team aims to generate a selective inhibitor for ARTD8 to help develop the understanding of metastatic cancers. Work by our team used a de novo computational modelling method followed by organic synthesis of potential inhibitors. The ARTD8 inhibitors, once synthesised and structurally elucidated, were then analysed in chemiluminescence inhibition assays against both ARTD8 and ARTD1 to determine selectivity.

MEDI 15

Selective class I HDAC inhibitors based on aryl ketone zinc binding induce HIV-1 protein for clearance

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HIV persistence in latently infected, resting CD4+ T cells is broadly considered a barrier to eradicate HIV. Activation of provirus from latently infected cells using latency-reversing agents (LRAs) followed by immune-mediated clearance to purge reservoirs was confirmed to be promising therapeutic approaches. Histone deacetylases (HDACs) and histone acetyltransferases (HATs) control the acetylation level of lysine residues in histones to regulate the gene transcription. The deacetylation leads to a more condensed chromatin structure, reducing the gene transcription. Thus HDAC inhibitors can increase the gene transcription and several HDAC inhibitors (vorinostat and panobinostat) had been examined as LRAs which induced HIV protein expression on CD4+ T cells. In this presentation, we are going to report the discovery of a series of selective and potent class I HDAC inhibitors based on aryl ketone as zinc binding group. SAR led to the discovery of a highly selective class I HDAC inhibitor with excellent
potency in both enzymatic and cellular assays. This HDAC inhibitor also induces the expression of HIV gag P24 in the patient latent T cells.

**MEDI 16**

**Challenging the sensitivity of HDX/MS with a large heterodimeric protein receptor: Characterization of the binding interactions of new generation integrin α4β7 inhibitors**

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Integrins are heterodimeric receptor molecules that function in cell adhesion and signaling, with key roles in multiple sclerosis, inflammation and cancer, and as a result are important drug targets. Currently, 3 of the 24 known human integrins have emerged as attractive targets because the effect of their inactivation has been probed by monoclonal antibodies, peptides and small molecule potential integrin inhibitors. Highly effective new antibodies and peptides targeting α4β7 have been discovered and have shown significant pre-clinical efficacy for the treatment of inflammatory bowel diseases. A case in point are the monomeric/dimeric disulfide-linked cyclic peptides PTG-100, which have recently shown major benefits in human studies. Despite this relevant finding, the characterization of the binding epitope of these new generation integrin inhibitors on the α4β7 receptor is still elusive.

In this study, we report for the first time the molecular characterization of the binding interactions of clinical therapeutic disulfide-linked cyclic peptides PTG-100 against the integrin α4β7 receptor as probed by HDX/MS and computational approaches. The results of this study are of paramount importance to get a deeper insight into the involvement of α4β7 in autoimmune diseases and to guide the discovery of new chemotypes as inhibitors of this integrin receptor.

**MEDI 17**

**Discovery of a series of pyrimidine carboxamides as inhibitors of vanin-1 for the treatment of inflammatory conditions**

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Vanin-1 is a glycosylphosphatidylinositol-anchored, cell surface associated pantetheinase that catalyzes the hydrolysis of pantetheine to pantothenic acid (vitamin B5) and cysteamine. Vanin-1 has been implicated in inflammatory diseases with a large oxidative stress component including inflammatory bowel disease (IBD). Support for the role vanin-1 in this disease includes over-expression in patients with the main forms of IBD, ulcerative colitis and Crohn’s disease. In addition, protection of vanin-1 deficient mice against experimental colitis has been reported. Thus, inhibition of vanin-1 represents a novel approach for the treatment of IBD, as well as other inflammatory conditions.

An HTS was run to identify vanin-1 inhibitors leading to the discovery of a series of aminopyrimidines containing a diaryl ketone linker that remained as the mainstay of the early medicinal chemistry efforts. Concerns with our ability to advance a compound from this series as a candidate for human clinical trials due to its human pharmacokinetic prediction and potential complications during development caused by the presence of the diaryl ketone moiety led us to look for ketone replacements. This presentation will describe the successful replacement of the ketone moiety with an amide leading to the discovery of a series of pyrimidine carboxamides. The rapid optimization of this series to deliver (2-((pyrazin-2-ylmethyl)amino)pyrimidin-5-yl)(8-oxa-2-azaspiro[4.5]decan-2-yl)methanone as a potent, selective, and orally bioavailable vanin-1 inhibitor suitable for progression as a preclinical candidate for the treatment of inflammatory conditions will be presented.

**MEDI 18**

**Discovery and development of novel diazeniumdiolate derivatives as nitric oxide donors**

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Nitric oxide (NO) and nitroxyl (HNO) are implicated in cardiovascular, nervous and immune system responses. However, therapeutic applications have lagged due to the metastability of both NO and HNO which requires that either be generated in situ by HNO or NO donors. Diazeniumdilates have proven to be valuable NO donors as they are stable as sodium salts but will release NO (or HNO) under physiological conditions. O²-alkylation or –arylation of these stable zwitterionic salts form stable pro-drugs which have found application in hypertension, cancer or as anti-microbials.
The synthesis of diazeniumdiolates (DAZDs) was demonstrated in 1960 by Drago et al., however this method has proven challenging due to high N₂O concentrations and flammable solvents which can lead to detonation. Merck Process Research developed a safer and scalable method, which has expanded the scope of DAZDs into sterically hindered dialkylamines and primary amines. Modification of the amine moiety on the diazeniumdiolate has enabled tuning of the NO release rate and enabled varying of the NO/HNO ratios for primary amine DAZDs. This presentation will describe the next generation synthesis of dialkylamine and primary amine diazeniumdiolates, the kinetics of decomposition and the NO/HNO pathways, and address the challenges of NO donors as therapeutic agents.

MEDI 19

Glycopeptide drugs from endogenous peptides violate all of Lipinski’s rules and penetrate the BBB

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Glycosylation has proven to be an effective method to convert endogenous peptide neurotransmitters (highly amphipathic peptides that interact with GPCRs) into glycopeptide drugs capable of "membrane hopping" and penetration of the blood-brain barrier (BBB). Generally speaking, these are WYSIWYG drugs—the binding affinities of the original peptides are mirrored by the glycopeptides, but the PK/PD properties have been greatly altered. Several examples will be presented, ranging from small peptides such as enkephalins and angiotensins (6-mers, 7-mers), to much larger peptides such as endorphins, dynorphins (18-mers), PACAP and VIP (27-mers, 28mers), as well as cyclic peptides. All of the resulting glycopeptide drug candidates have potent central activity in mice and/or rats. Quantification of the glycopeptides in vivo, and factors affecting stability and BBB penetration will be discussed. The increased lifetime and BBB penetration of the glycosides show great promise for the world of pharmaceutical development.

Glycopeptides with M.W.’s over 3,500 penetrate the BBB

**MEDI 20**

**Small molecule inhibitors of IRAK4**

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Introduction: The innate immune response enables cells to quickly respond to inflammatory cytokines by mounting the initial protective response through the activation and downstream function of the interleukin-1 receptor activated kinase (IRAK) family.
Small molecule kinase inhibitors of IRAK4 have long been sought to block this response in auto-inflammatory diseases such as lupus.

Methods: In an effort to block disease progression, several scaffolds of IRAK4 small molecule inhibitors were explored using structure-based drug design. The discovery and development of our lead scaffold along with how it was influenced by other scaffolds will be presented including structural understanding of the binding site and in vivo PK and PD.

Results: Through medicinal chemistry efforts including structure-based drug design, analysis of physicochemical properties and application of drug development principles, a series of potent and selective IRAK4 inhibitors were discovered. These molecules proved stable across species and showed compelling activity in in vivo models for inflammation.

Discussion: The discovery, development and in vivo profile of our lead IRAK4 small molecule inhibitors will be disclosed for the first time.

MEDI 21

**Novel, potent small-molecule inhibitors modulating immune-oncology targets CD73 and A$_{2A}$/A$_{2B}$ adenosine receptors discovered via DNA-encoded library screening**

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Tumors utilize many different escape mechanisms to evade anti-tumor immune responses. Xios Therapeutics has screened X-Chem’s proprietary 200-billion molecule DNA-encoded library against several immuno-oncology (IO) targets addressing T-cell centric, myeloid immunity and onco-metabolite pathways. Adenosine, for example, is a potent immunosuppressive metabolite, and the ecto-5-nucleotidase (a.k.a.CD73), which catalyzes the conversion of AMP to adenosine, is the rate limiting enzyme for the production of extracellular adenosine in the tumor microenvironment. Hence, pharmacological inhibition of CD73 and/or the downstream adenosine receptors are considered attractive targets for IO drug discovery. Here, we exemplify and enumerate the diversity, selectivity and physiochemical properties of selected hit-to-lead compounds identified from our DNA-encoded library screens of CD73 and the adenosine A$_{2A}$ receptor.

In the context of the immune-suppressive purinergic pathway, we have integrated
structural biology, medicinal chemistry and clinical pathology evaluation of target expression across tumor types and developed both $A_{2A}$ selective and dual $A_{2A}/A_{2B}$ selective receptor antagonists. Furthermore, we have compared the ability of equipotent $A_{2A}$ and dual $A_{2A}/A_{2B}$ adenosine receptor antagonists to reverse the effect of NECA, a nonhydrolyzable analog of adenosine, on the maturation and activation of dendritic cells (DC). Starting with the differentiation of human immature DC, we demonstrate the added benefit of dual $A_{2A}/A_{2B}$ inhibitors vs $A_{2A}$ selective inhibitors on relieving immunosuppression of myeloid cells. As a second node for intervention, we have performed a DNA-encoded library screen on CD73, resulting in the identification of novel sub-micromolar ligands, which bind to CD73 in an ‘open conformation’ revealed by the co-crystal structure of X6034 ($EC_{50} = 310 \text{ nM}$) in complex with CD73. In conclusion, the combination of all these data, together with the productivity of the DNA-encoded library screens for identifying novel, drug like chemical matter on challenging targets, provide a unique opportunity for potentially harnessing the full power of immunotherapy for cancer.

MEDI 22

Asymmetric synthesis of aromatic lipoxin A$_4$ analogues with upper chain modifications

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Lipoxins are a group of bioactive compounds enzymatically derived from arachidonic acid by a family of lipoxygenase enzymes, which were first isolated from human leukocytes by Serhan and Samuelsson in 1984.[1] The two naturally occurring Lipoxins, Lipoxin A$_4$(LXA$_4$) (1) and Lipoxin B$_4$ (LXB$_4$) (2) are trihydroxytetraene-containing eicosanoids. Lipoxins regulate components of both the innate and adaptive immune systems to initiate the resolution of inflammation by activating the FPR2/ALX receptor.[2,3] Although a healthy bodily response, the effective resolution of inflammation is essential to maintain normal tissue homeostasis and the prevention of chronic inflammatory diseases. The major obstacle associated with using Lipoxins to treat diseases caused by chronic inflammation is the rapid metabolism observed in vivo, which is characteristic of all autacoids. These LX metabolites exhibit dramatically decreased biological activity and are considered inactive metabolites, rendering them poor potential pharmacological agents.[4] Within our research group the rapid metabolic inactivation has been overcome by synthesising aromatic and heteroaromatic analogues of LXA$_4$ increasing the potency over 1,000 fold.[5] The focus of this project is to synthesise a wide range of LXA$_4$ analogues specifically designed to overcome the rapid metabolic deactivation, in particular the β-oxidation of the upper chain of which is known to be another source of metabolic instability in LXA$_4$. The research involves both advanced asymmetric synthesis and biological assays on THP-1 LUCIA monocyte cells.
Discovery of BMS-211, a self-immolative prodrug as an orally active imidazo[2,1-f][1,2,4]triazinepan-CK2 inhibitor for the treatment of cancer


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CK2 is a small family of serine/threonine kinases (CK2A1, CK2A2) with nearly identical sequence differing only in C-terminus. Phosphorylation of its substrates occurs by utilizing either ATP or GTP as a phosphate donor. CK2 is reported to phosphorylate and modulate the activity of several oncogenic transcription factors, including CREB, Myc, Max, Jun, Fos and Myb. Aggressiveness of several cancer types such as HNSCC, SqNSCLC, prostate cancer and AML correlates with higher levels of CK2A1 and is associated with poor prognosis. Also, dysregulation of the enzymes has been shown...
to promote and maintain a malignant phenotype through mechanisms that affect anti-apoptotic and pro-proliferative signaling pathways. Further, CK2 inhibition or knockdown with RNAi results in growth suppression and/or apoptosis of both solid and hematologic cancer cell lines. This presentation will focus on the SAR studies leading to the discovery of a highly potent, ATPcompetitive pan-CK2 inhibitor, BMS-699 with a commensurate level of cellular potency. Upon oral dosing, BMS-699 demonstrated durable PK/PD response and robust, anti-tumor efficacy in CK2-driven models. The presentation will also discuss further optimization to identify an orally bioavailable self-immolative prodrug, BMS-211 with improved pharmaceutical properties for future development.

**MEDI 24**

**Design, synthesis, and evaluation of novel heterocyclic warheads for cysteine targeting covalent inhibitors**

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The success of drugs such as ibrutinib and osimertinib has led to renewed interest in irreversible inhibitors that form covalent bonds with cysteine or other nucleophilic amino acids. Irreversible inhibitors have several potential advantages including high potency and specificity, and prolonged pharmacodynamics. Despite significant effort, the simple acrylamide Michael acceptor remains ‘state of the art’ in terms of cysteine capture, due to its ease of synthesis, acceptable reactivity window and DMPK compatibility. Acrylamide reactivity is greatly influenced by the nature of its connection to the non-covalent binding element of such potential drugs, which in turn, is dictated by the SAR for binding to the chosen target. Therefore, there remains a significant need for additional cysteine reactive warheads with tuneable properties and reactivity profiles which present attachment vectors not accessible with acrylamides. We report here our work on the synthesis, reactivity and application of novel vinyl- and alkynyl-substituted heterocycles (both aromatic and non-aromatic) as alternative electrophilic warheads for chemical biological probes and drug molecules. These heterocycles are capable of covalent bond formation with cysteines and present novel binding and attachment vectors. Exploration of electronic and steric effects on varying scaffolds has revealed unique reactivity profiles, differentiating the novel heterocycles further from the traditional acrylamide motif. Moreover, we have demonstrated that suitable examples of these novel covalent binding warheads can be incorporated into known drug scaffolds, retaining potency and good pharmacological properties. Additionally, current effort is directed towards application of these new warheads to target previously ‘undruggable’ cysteines and extend the scope of current covalent cysteine targeting.

**MEDI 25**
Discovery of small molecule inhibitors of neutral sphingomyelinase 2 for the treatment of neurodegenerative diseases

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Extracellular vesicles (EVs) are constitutively shed from cells and released in response to various stimuli. Their protein and RNA cargo are modified by the stimulus, and in disease conditions EVs can carry pathological cargo involved in disease progression. Neutral sphingomyelinase2 (nSMase2) is a major regulator of at least one of several independent routes of EV biogenesis and its inhibition is a promising new therapeutic approach for neurological disorders. Unfortunately, known nSMase2 inhibitors exhibit μM potency, poor physicochemical properties, and/or limited brain penetration. The purpose of this work has been to identify a drug-like inhibitor of nSMase2. We conducted a human nSMase2 high throughput screening campaign employing over 365,000 compounds. Selected hits were optimized focusing on potency, selectivity, metabolic stability, pharmacokinetics and ability to inhibit EV release in vitro and in vivo. Optimization of one of the selected hits led to the identification of phenyl(R)-(1-(3-(3,4-dimethoxyphenyl)-2,6-dimethylimidazo[1,2-b]pyridazin-8-yl)pyrrolidin-3-yl)-carbamate (PDDC), a potent (IC$_{50}$ = 0.30 μM) and selective non-competitive inhibitor of nSMase2. PDDC was metabolically stable, with excellent oral bioavailability (%F=88), and brain penetration (AUC$_{brain}$/AUC$_{plasma}$=0.60). PDDC dose-dependently (EC$_{50}$ = 0.5 μM) inhibited the release of astrocyte-derived-extracellular-vesicles (ADEV). In an in vivo inflammatory brain injury model, PDDC robustly inhibited ADEV release and the associated peripheral immunological response. A closely related inactive structural analog of PDDC showed no effect. In summary, PDDC is a structurally novel, potent, orally available, and brain penetrant inhibitor of nSMase2. PDDC inhibits the release of ADEVs in tissue culture and in vivo. PDDC is actively being tested in animal models of neurological disease and along with closely related analogs, it is being considered for clinical translation.

MEDI 26

Molecular insights into effects of Alzheimer’s disease risk-variant R47H TREM2
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Triggering receptor expressed on myeloid cells-2 (TREM2) is an immune receptor expressed on the surface of microglia, macrophages, dendritic cells, and osteoclasts. The TREM2-R47H variant is a significant risk factor for late-onset Alzheimer's disease (AD), and the molecular basis of TREM2-R47H loss-of-function is an emerging area of TREM2 biology. Here, we report three high-resolution structures of the extracellular ligand-binding domains (ECD) of TREM2-R47H, apo wild-type (WT), and phosphatidylserine (PS)-bound WT TREM2 at 1.8 Å, 2.2 Å, and 2.2 Å resolutions, respectively. The structures revealed that Arg-47 plays a critical role in maintaining the structural fold of the complementarity-determining region 2 (CDR2) loop and the putative positive ligand–interacting surface (PLIS) in conformations capable of ligand interaction. This was exemplified in the PS-bound structure, in which the CDR2 loop and PLIS drove critical interactions with PS via surfaces that are disrupted in the variant. Together with *in vitro* and *in vivo* characterization, our structural findings elucidate the molecular mechanism underlying loss of ligand binding, putative oligomerization, and functional activity of TREM2-R47H. They also help unravel how decreased *in vitro* and *in vivo* stability of TREM2 contribute to loss of function in disease.

**MEDI 27**

Design, synthesis, and identification of novel, orally bioavailable non-covalent NRF2 activators

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Nrf2 is a transcription factor regulating expression of the Phase II Antioxidant Response. Nrf2 plays an important role in neuroprotection and detoxification. Nrf2 activation is inhibited by interaction with Keap1. Covalent Keap1 inhibitors such as dimethyl fumarate (DMF) and RTA-408 are either on the market or in late stage clinical trials which implies potential benefit of Nrf2 activation. Activation of Nrf2 by disrupting Nrf2-Keap1 interaction through a non-covalent small molecule is an attractive approach with the promise of greater selectivity. However, there are no known non-covalent Nrf2 activators with acceptable pharmacokinetic properties to test the hypothesis in vivo. Based on our early reported work, using structural-based design, followed by extensive SAR exploration, we have identified a novel series of non-covalent Nrf2 activators with acceptable pharmacokinetic properties to test the hypothesis in vivo. Representative analog shows excellent oral PK and good Nrf2-dependent gene inductions in kidney. These results provide a peripheral in vivo tool compound to validate the biology of non-covalent activation of Nrf2.
Discovery and development of potent, selective, and brain-penetrant LRRK2 kinase inhibitors for Parkinson's disease

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Parkinson's disease (PD) is a debilitating neurodegenerative disease defined by a characteristic tremor, rigidity, and slowing of movement in afflicted patients. Mutations in Leucine-rich repeat kinase 2 (LRRK2) have been associated with familial and sporadic PD. The association between LRRK2 and neurodegeneration was first identified in studies of several families that presented with an autosomal dominant, late onset form of PD. LRRK2 pathogenic variants generally increase kinase activity. For example, the most common G2019S substitution in the activation loop increases the kinase activity, likely by stabilizing the active conformation. Modulation of kinase activity by interfering with the ATP-binding in the kinase domain can be achieved with small molecule kinase inhibitors. This talk will describe the discovery of potent, selective and brain-penetrant LRRK2 kinase inhibitors and approaches towards development candidate molecules.

CD33: From Alzheimer's disease GWAS to therapeutic target

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Genome-wide association studies have identified and validated several genes, such as CD33, associated with AD susceptibility that directly implicate the innate immune system. CD33 is a sialic acid binding protein expressed on the surface of myeloid cells, and higher CD33 expression levels in the brain have been associated with more advanced cognitive decline and AD. We demonstrated that individuals with the Alzheimer's disease associated rs3865444CC risk genotype have increased expression of full-length CD33, the isoform containing the sialic acid binding domain, on the surface of their monocytes compared to those with the rs3865444AA protective genotype. The risk allele is also associated with diminished internalization of amyloid-β1-42 peptide, accumulation of neuritic amyloid pathology and fibrillar amyloid on in vivo imaging, and increased numbers of human microglia with small, thick processes, and a rounded
morphology. Using a crosslinking strategy combined with mass spectrometry we identified immune cell specific sialic acid-dependent and independent CD33 binding partners. Using proximity ligation assays, we have validated these results in vitro as well as in situ. For one of the binding partners, we confirmed that the CD33 ITIM domain was also involved in the interaction. Using a known inhibitor for the binding partner, we can disrupt the interaction. In conclusion, we have identified and validated the functional relevance of CD33 binding partners that are specific to the sialic acid binding domain of CD33, the domain that is modulated by the Alzheimer’s disease association.

MEDI 30

CoREST complex-selective HDAC inhibitors promote pro-synaptic effects and represent promising therapies for multiple neurodegenerative diseases

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Synaptic dysfunction is a pathological feature in many neurodegenerative disorders, including Alzheimer’s disease, and synaptic loss correlates closely with cognitive decline. Histone deacetylase enzymes (HDACs) are involved in chromatin remodeling and gene expression, and have been shown to regulate synaptogenesis and synaptic plasticity, thus providing an attractive drug discovery target for promoting synaptic growth and function. Historically, HDAC inhibitor compounds with pro-synaptic effects have been plagued by known HDAC dose-limiting hematological toxicities, precluding their application to treating chronic neurologic conditions. We identified a series of novel HDAC inhibitor compounds that selectively inhibit the HDAC-CoREST complex while minimizing hematological side effects. HDAC1 and HDAC2 associate with multiple co-repressor complexes including CoREST, which regulates neuronal gene expression. We show that selectively targeting the CoREST co-repressor complex results in increased spine density and synaptic proteins, and improved long term potentiation in a mouse model at doses which provide a substantial safety margin that would enable chronic treatment. This approach represents a promising therapeutic strategy in targeting synaptic pathology involved in multiple neurologic disorders.

MEDI 31

Therapeutic potential of the caspase 1 inhibitors for the treatment of inflammatory disease

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Caspase-1 is an endogenous cysteine protease formed as an inactive pro-caspase-1
and activated by dimerization and auto proteolysis within multiprotein complexes including adaptor ASC and nod-like receptor family such as NLRP3 called inflammasomes by linking microbial and endogenous danger signals to caspase-1 activation. Activated caspase-1 is required for IL-1β and IL-18 release, cell death, and plays a key role in inflammation. Several diseases are associated with the dysregulated activation of caspase-1 and IL-1β secretion. Targeting proteases and specifically caspases via small molecule therapeutics is an active area of research. Herein, we present our strategy for the design and synthesis of small molecule inhibitors of the caspase 1 as a therapeutic potential for the treatment of inflammatory disease. Inhibitors were screened with fluorometric method. The level of inhibition of caspase-1 activity has been analyzed by comparing with and without testing inhibitors.

MEDI 32

Discovery of BCL-X\textsubscript{L} degraders as potent and platelet-sparing anticancer agents

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BCL-X\textsubscript{L} is a well-validated therapeutic target for cancer. However, inhibition of BCL-X\textsubscript{L} could cause severe thrombocytopenia which prevents the clinical use of BCL-X\textsubscript{L} inhibitors. Traditional structural modifications are unlikely to address the platelet toxicity issue associated with the inhibition of BCL-X\textsubscript{L} since it is an on-target toxicity. Herein we report the utilization of an emerging technology in drug discovery, known as Proteolysis Targeting Chimera (PROTAC), to design small molecules that can recruit BCL-X\textsubscript{L} protein to an E3 ubiquitin ligase for induced degradation. Our PROTACs are based on ABT263, a potent inhibitor of both BCL-X\textsubscript{L} and BCL-2. The solvent exposed morpholine ring of ABT263 was replaced by a piperazine ring in order to make it ready for linker connection. The linker unit that connects ABT263 and E3 ligase ligands, as well as the linkage unit between the linker and the piperazine ring, were systematically modified. Several ABT263-based PROTACs showed improved antiproliferative activity against MOLT-4 cells that depend on BCL-X\textsubscript{L} for survival when compared with ABT263. Protein degradation assay confirmed that those conjugates were able to degrade BCL-X\textsubscript{L} but not BCL-2 in MOLT-4 cells. The best PROTACs in each series have been screened for \textit{in vitro} platelets toxicity. Human platelets were more tolerant to these ABT263-based PROTACs treatment whereas none of the conventional BCL-X\textsubscript{L} inhibitors including ABT263 showed selectivity for MOLT-4 cells over platelets. Overall, our study demonstrates a novel strategy to reduce on-target toxicity by conversion of an inhibitor into a PROTAC.

MEDI 33

Homology modeling of DNMT isoforms: Towards the identification of selective inhibitors in food chemicals
DNA methyltransferases (DNMT) comprise a set of enzymes that have a central role in epigenetic regulation. They are promising targets for the treatment of different types of cancer and other diseases. To be able to design drugs with selective inhibition towards the different isoforms of DNMTs, homology modeling of the isoforms whose crystallographic information is not available was done. Herein, we report the results of homology models of the catalytic and PWWP domains which have a so-called “aromatic box” cavity. Based on the crystallographic information available and the homology models, it was determined what are the isoforms of DNMTs with most likely selective inhibition by a small molecule. We also discuss the results of a consensus docking study to determine the degree of selectivity of five DNMT inhibitors found in foods towards the different isoforms of DNMT.

**MEDI 34**

**Discovery and structural optimization of small molecule inhibitors that regulate the wnt signaling pathway**

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The Wnt family is an important cellular signaling molecule that plays an important role in cell proliferation, differentiation, migration, and embryogenesis. Studies have shown that dysregulation of the Wnt signaling pathway leads to a range of diseases such as tumors, degenerative diseases, endocrine disorders, metabolic diseases, inflammation and fibrosis. Therefore, research and development of small molecule drugs with regulatory Wnt signaling pathways are of great significance for the treatment of these diseases. We have found that cyclohexenyl dimethimide-aromatic amine compounds exhibit significant activity in regulating the wnt signaling pathway in the L-Wnt3A cell luciferase reporter assay. When the number of carbon atoms in the linker between the cyclohexenyl dimethimide and aromatic amine fragment is four, such compounds show a significant inhibition of the wnt signaling pathway (IC\(_{50}\) = 30 nM). When the number of carbon atoms in the linker is three, the biological activity is significantly reduced. When the number of atoms is two, the compounds exhibit a better activation of the wnt signaling pathway (EC\(_{50}\) = 5 µM). Subsequent studies have shown that the target of this type of compound is Porcupine (PORCN), which affects the secretion process of wnt protein.

**MEDI 35**
As a part of our ongoing effort to develop isoquinoline antitumor agents, we recently synthesized a new group of compounds starting from \((L)\)-tartaric acid applying our own methodology. The evaluations of their bioactivity disclosed, that these compounds inhibit topoisomerase type I and II. We synthesized derivatives in both optical forms bearing a variety of substituents as presented on structure A. The impact of substitution pattern and absolute configuration on bioactivity was analyzed to contribute to the rational design of more selective drugs to target topoisomerase proteins.

New isoquinoline derivatives were tested for their anticancer potential in vitro against three different human cell lines, including MCF-7 and MDA-MB-231 breast cells, and AGS-CRL-1739 gastric cells. The results from experiments were compared with effects obtained after incubation in the presence of camptothecin and etoposide. Cell cycle analysis and apoptosis assay were performed by standard flow cytometric method. Confocal microscopy bioimaging was used to demonstrate the expression of pivotal proteins engaged in apoptosis (caspase-8, caspase-3, p53) and cell signaling (AKT, ERK1/2). The cytotoxic and antiproliferative effects of the novel compounds were associated with the induction of apoptosis. We demonstrated the higher activity of caspases 3, 8, 9, and 10, which confirmed that induction of apoptosis is associated with external and internal cell death pathway. The novel isoquinoline derivatives decreased the expression of AKT and ERK1/2. Their mechanism was associated with p53-mediated apoptosis, accumulation of cells in the G2/M phase of cell cycle and inhibition of topoisomerase type I and II.
Syntheses, characterizations, and a preliminary comparative cytotoxicity study of berenil-platinum complexes

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We synthesized a new group of pyrazole noncovalent berenil-platinum complexes and demonstrate that the synthesized compounds triggered a proapoptotic cascade in breast cancer cells. The novel platinum complexes were obtained by two-step synthesis. Since it is known that berenil, having functional and triazene groups, may bind to metals as linear monodentate, chelating bidentate, and in bridging bidentate modes, we have performed IR, ¹H-, and ¹³C-NMR spectra of the synthesized compounds to determine the mode of metal-berenil bonding. The spectra show that binding of the metal to the amidino-group of the ligand does not occur since the frequencies attributed to the amidino-moiety, v(CN) 1686-1687 cm⁻¹ (for free berenil 1668 cm⁻¹) as well as the signal in ¹³C-NMR of the carbon from the amidine group remain unaltered relative to the free ligand, 165.2 ppm. The presence of three bands at 1606-1607, 1257-1259, 1173-1175 cm⁻¹ in the IR spectrum shows, on the other hand, that the triazene group coordinates in linear or bridging modes. The ¹H- and ¹³C-NMR spectra further support this mode of binding. Thus, the spectra and the micronalytical data suggest that the compounds are dimers where Pt binds to the nitrogen atoms of two triazene groups in a bridging mode.

Our biological studies demonstrated that the novel platinum complexes can modulate both the apoptotic pathways and activate initiator as well executioner caspases. Additionally, the dinuclear platinum complexes increase the expression of NF-κB and decrease the expression of Akt, which leads to increased apoptosis. Moreover, although the structure-activity relationship observed on the reaction level of the tested pyrazole platinum complexes in vitro does not entirely explain the mechanism of their cytotoxic action, our results suggest that the presence of the methyl substituent at the N3 position of the pyrazole ring is an advantageous feature for the pyrazole platinum complex’s DNA crosslinking activity. Moreover, results from the our studies suggest that both ancillary ligand and intercalative ligand influence the degree of binding of these complexes to DNA as a result of which the majority of the complexes possessed antiproliferative activities against cancer cell lines.

Synthesis and anti-endoplasmic reticulum stress activity of 2-arylcarbonylhydrazinecarbothioamides

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Misfolded or unfolded proteins are accumulated in lumen of endoplasmic reticulum (ER) in ER stress condition. It has been implicated in many pathological conditions such as Alzheimer’s disease, diabetic retinopathy, atherosclerosis, b-cell apoptosis and lung inflammation. A high throughput screen to identify compounds which reduce ER stress identified a series of \(N\)-substituted-2-arylcarbonylhydrazinecarbothioamides to potently decrease ER stress signal, showing up to almost two orders of magnitude better activity than salicylate and hydroxynaphthoic acids as chemical chaperone. Structure-activity relationship (SAR) study showed that 2-arylcarbonyl moiety is critical for the activity of the hydrazinecarbothioamide analogues and side chains on thioamide moiety were relatively insensitive to the activity. Some analogues were found to consistently exert the potency under more physiologically relevant condition where ER stress was induced by palmittic acid. ER stress markers such as CHOP and phosphorylation of eIF2a and PERK were decreased in western blotting upon treatment of compound 4h.

**MEDI 38**

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

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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 metastasis. 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 metabolomic changes are not seen in cells treated with ON 123300 in non-ARK5 expressing 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 metabolomic 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 39

Optimization of quinazolinone-based covalent inhibitors of KRAS\textsuperscript{G12C} in the discovery of AMG 510


KRAS\textsuperscript{G12C}, the protein product of the oncogenic KRAS p.G12C mutation, has emerged as a promising target in the treatment of lung adenocarcinoma, colorectal cancer, and pancreatic cancer. We have recently reported novel quinazolinone-based covalent inhibitors of KRAS\textsuperscript{G12C} that leverage a previously unexploited cryptic pocket on the surface of GDP-KRAS\textsuperscript{G12C} to enhance binding to the switch II pocket (S-IIP) of KRAS\textsuperscript{G12C}, locking KRAS\textsuperscript{G12C} into its inactive, GDP-bound state. Herein, we report details of the optimization of early phthalazine-based inhibitors of KRAS\textsuperscript{G12C}, leading to the identification of quinazolinone-based leads. We also describe the structural and biophysical optimization of the resulting leads, culminating in the identification of AMG 510, a highly potent, selective, and well-tolerated KRAS\textsuperscript{G12C} inhibitor currently in Phase I clinical trials in subjects with solid tumors harboring the KRAS p.G12C mutation (NCT03600883).

MEDI 40

Synthesis and structure–activity relationships of pyrazine-2-carboxamide derivatives as novel echinoderm microtubule-associated protein-like 4 (EML4)–anaplastic lymphoma kinase (ALK) inhibitors

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Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase, and echinoderm microtubule-associated protein-like 4 (EML4)–ALK oncogenic fusion kinase is currently considered a validated therapeutic target for the treatment of EML4–ALK-positive non-small cell lung cancer (NSCLC). We previously reported ASP3026, a 1,3,5-triazine derivative, as a novel EML4–ALK inhibitor. Our next objective was to prepare another potent EML4–ALK inhibitor with a different chemical structure from that of ASP3026. In-house library screening and subsequent preliminary structure–activity relationship (SAR) exploration identified 1, a pyrazine-2-carboxamide derivative. Structural optimization of 1 led to the discovery of 2 as a novel and potent EML4–ALK inhibitor. Oral administration of 2 demonstrated potent antitumor activity in mice xenografted with 3T3 cells expressing EML4–ALK. The synthesis and biological evaluation of pyrazine-2-carboxamide derivatives will be presented, together with studies on their SAR using computational modeling.

MEDI 41

Scaffold repurposing of a serotonin 2C agonist led to the discovery of highly selective dopamine D3 antagonists

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The dopamine D3 receptor (D3R) has long been a target of interest in CNS disorders such as drug addiction. Most D3R ligands share a typical linear scaffold “aryl head-basic nitrogen-spacer-amide-aryl tail”, in which the “aryl head-basic nitrogen” binds to the orthosteric pocket of the receptor while the “amide-aryl tail” moiety binds to the extended binding pocket (EBP). Based on this model and the structural differences between D3R and homologous D2R, highly selective D3R antagonists could be
discovered through the optimization of the spacer and the tail aryl groups. In our previous work, 2-phenylcyclopropylmethylamines (PCPMAs) have been discovered as selective serotonin 2C (5-HT2C) agonists, and some of those compounds showed moderate dopamine D3R binding affinity. We anticipated that PCPMA binds to the orthosteric pocket of both 5-HT2C and D3R, and the introduction of a proper spacer and a tail group could generate novel compounds that are selective for D3R. A novel series of PCPMA derivatives have been therefore designed and synthesized, and a number of D3R ligands with high affinity and binding selectivity have been discovered. Among them, compound **IHCH-4075** binds to the human D3R with a Kᵢ value of 1.1 nM and displays a selectivity of >2000 against the human D2R. These findings would expand the chemical types of D3R antagonists and provide highly selective D3R ligands as potential drug candidates.

![Chemical structure of PCPMA](image)

**5-HT2C agonist**

D3R Kᵢ = 811 nM

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**D3R ligands**

<table>
<thead>
<tr>
<th>Compd</th>
<th>Kᵢ, nM</th>
<th>D2R/D3R</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHCH-4075</td>
<td>2362</td>
<td>1.1</td>
</tr>
<tr>
<td>IHCH-4076</td>
<td>2105</td>
<td>2.5</td>
</tr>
<tr>
<td>IHCH-4077</td>
<td>1502</td>
<td>2.3</td>
</tr>
</tbody>
</table>

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**MEDI 42**

**Discovery of BMS-986160 as a second-generation inhibitor of the hepatitis C virus NS3/4A with pan-genotypic antiviral activity**

Previously, we reported a second-generation inhibitor of the hepatitis C virus NS3/4A protease: the discovery of BMS-986144 with pan-genotypic antiviral activity. As part of our continuous effort in search of a structurally differentiated backup to BMS-986144, we conducted computational molecular modeling studies that led to a specific focus around the P2* region. In this presentation, we will describe the discovery of BMS-986160, a potent HCV NS3 protease inhibitor that demonstrates superior pan-genotypic antiviral activity and excellent coverage of the highly resistant variants in vitro. The structure-activity relationship that led to the discovery of BMS-986160 will be described in detail along with preclinical characteristics.

MEDI 43

Theoretical elucidation of the nucleophosmin enzyme inhibition by synthetic, natural, and designed new ligands: Molecular docking and molecular dynamic

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Inhibition of Nucleophosmin enzyme is considered as a key in type cancer treatment actually a significant number of synthetics inhibitors of this enzyme was studied. However, NSC348884 synthetic inhibitors and tripeptids were identified as the most efficient ones. In this work we present a comparative theoretical study of nucleophosmin enzyme inhibitors by NSC348884 synthetic inhibitors, natural and tripeptids compared with a series of our designed inhibitors by means of molecular docking and molecular dynamics approaches. Theoretical calculation was done using MOE software. The interactions between the studied inhibitors and our enzyme were elucidated through molecular docking and molecular dynamics simulations. A number of key residues and specific interactions at the binding site of nucleophosmin was identified. We note in particularity the implication of the TYR 29 amino acid and also the presence of aromatic interactions. Obtained results by molecular Docking and molecular dynamics both leads to the same conclusion and predict that Gnemonol B is the best inhibitor between the studied systems.

MEDI 44

Synthesis and evaluation of new enantiopure pyridine-based arylaminoalcohols as antimalarial drugs

Etienne Pair, Alexandra Dassonville-Klimpt, Guillaume Bentzinger, Pauline Loupias, pauline.loupias@etud.u-picardie.fr, Anne Bouchut, Catherine Mullié, Patrice Aghamey, Pascal Sonnet. AGIR, Amiens, France
In 2017, around 219 million cases of malaria were reported worldwide and led to 435,000 deaths, 61% of them children. Since 2014, investments in malaria control raised from 2.5 to 3.1 billion dollars. However, the World Health Organization (WHO) highlighted that no significant progress in reducing malaria cases has been made in the same time. One of the major drawbacks in fighting malaria is the emergence of drug resistance. In all regions of the world, *Anopheles* mosquitos, the vector of malaria, is resistant to at least one of the four most common insecticide. *Plasmodium* parasites, and particularly the most virulent *P. falciparum*, have also shown a great adaptive potential. Since 2002, to limit the apparition of resistances towards the newly developed artemisinin treatments, the WHO recommends the use of artemisinin-based combination therapies (ACT) with arylaminoalcohols such as mefloquine (MQ) or lumefantrine (LM). Unfortunately, in 2009, the first signs of artemisinin resistance have been spotted in the Great Mekong region. In this context, there is a crucial need for new drugs designed for their efficiency against *P. falciparum*.

LM and MQ have been selected for ACTs because of their pharmacokinetics parameters. More particularly, their slow clearance compensates the one-hour half-life of artemisinin. However, it has recently been found that one enantiomer of MQ was more potent and less susceptible to pass the blood-brain barrier. In light of these results and despite the serious neurological side effects, MQ is still used as a racemic mixture, like the other arylaminoalcohols. Yet, several arylaminoalcohols with similar potential have not been completely explored. For example, clinical trials of enpiroline, a pyridine-based arylaminoalcohol, have never been concluded despite promising activities, low toxicity and good pharmacokinetics.

With that in mind, our team has been working for years on the enantioselective syntheses of various arylaminoalcohols and the evaluation of their antibacterial and antiplasmodial potential. We herein describe the synthesis and *in vitro* evaluation of new pyridine-based arylaminoalcohols. Our stereoselective and divergent approach allows us to access both enantiomers with good ee and to introduce various amine substituents. The *in vitro* efficiencies against *Plasmodium falciparum* (3D7 and W2) and the structure-activity relationships will be discussed.

**MEDI 45**

**Exploration of Mycobacterium tuberculosis RNA polymerase's putative ppGpp binding site as a potential therapeutic target**

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Rifamycins (Rifs) are highly potent antibiotics that treat tuberculosis by targeting the causative pathogen’s, *Mycobacterium tuberculosis* (*Mtb*), RNA polymerase (RNAP). Rifamycin resistance has become a major issue that is caused by single point mutations in the Rif binding site. The drug resistant mutations also cause fitness defects for the bacterium; however, secondary mutations occur that compensate for the fitness defects. These compensatory mutations primarily occur adjacent to or in the putative guanosine tetraphosphate (ppGpp) binding site. ppGpp is an alarmone that is produced during the
stress response of many bacteria, including *Mtb*. In *Escherichia coli*, ppGpp has been shown to have many different effects on the cell; one of them is binding to and inhibiting RNAP. Using *E. coli* as a model for *Mtb*, our lab has been working under the hypothesis that ppGpp binds to *Mtb* RNAP in the analogous site to that in the *E. coli* RNAP and that the compensatory mutations were disrupting ppGpp’s binding. There has been evidence that ppGpp is necessary for *Mtb* to become latent. We hope to utilize this and design a molecule to block ppGpp binding thus bacteria will stay active and be much easier to kill. I have performed both cross-linking and kinetics studies that confirm the binding and reduction of activity of the *E. coli* RNAP by ppGpp; however, the *Mtb* RNAP does not bind or respond to ppGpp.

**MEDI 46**

**Why is reversed-phase flash chromatography use increasing?**

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

Flash chromatography is the primary tool used by medicinal chemists for reaction mixture purification. Over the past 10 or so years, the use of reversed-phase flash chromatography for reaction mixture purification has increased dramatically due to both chromatographic and non-chromatographic reasons.

In this poster, we will show examples of why chemists are increasingly using reversed-phase flash chromatography for routine intermediate and final compound purification.

**MEDI 47**

**Thiadiazole analogues as potent, liver selective glucokinase activators**

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The intracellular enzyme glucokinase (GK) is expressed primarily in liver and pancreas. GK facilitates the conversion of glucose to glucose-6-phosphate – the first step in glucose metabolism – and is a key regulator of glucose homeostasis. Small molecule allosteric activators of GK have been demonstrated in numerous animal models and clinical trials to lower glucose levels – thereby showing therapeutic promise for the treatment glucose metabolism disorders. However, it has been postulated that GK
activation in pancreatic beta-cells, even at low glucose concentrations, may result in excessive insulin secretion and ultimately, mechanism-based hypoglycemia. To ameliorate the potential for hypoglycemia, hepatocentric GK activators based on 5-amido-1,2,4-thiadiazoles have been developed. Described herein is the design and SAR of several potent, liver-centric GK activators with excellent oral exposure and liver selectivity in mouse PK studies. Despite achieving high drug liver concentrations and having suitable protein free fraction, these GK activators did not show efficacy in mouse PD studies. Efforts are ongoing to understand this PK / PD disconnect.

MEDI 48

Synthesis and structure–activity relationship (SAR) studies of novel pyrazolopyridine derivatives as inhibitors of enterovirus replication

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Enteroviruses are small, non-enveloped RNA viruses responsible for poliomyelitis, encephalitis, acute heart failure or severe hepatitis in newborns. In the United States recent outbreaks of coxsackievirus B1 (CVB1) infections and coxsackievirus A6 served as reminders of the ongoing threat raised by these pathogens. No antiviral agents are currently approved to treat enterovirus infections. Extensive studies in pursuit of candidate antiviral agents have targeted the viral capsid, the virus-encoded RNA polymerase and proteases, and other viral proteins involved in replication.

By applying a rapid, live virus assay to identify enterovirus inhibitors from nearly 86,000 compounds, a novel group of antienteroviral compounds: 1H-pyrazolo[3,4-b]pyridine-4-carboxamides were identified. The target of these compounds was identified as the viral 2C protein, which plays a role in RNA replication. In order to establish a good structure–activity relationship (SAR) and identify the most ‘druglike’ members of this pharmacophore, a series of novel pyrazolopyridine compounds have been designed and prepared by a general synthetic route. Their activities against the replication of poliovirus-1, EV-A71, and CV-B3 enteroviruses were evaluated. The comprehensive understanding of the SAR was obtained by utilizing the variation of four positions, namely, N1, C6, C4, and linker unit. From the screened analogues, the inhibitors with the highest selectivity indices at 50% inhibition of viral replication (SI50) were those with isopropyl at the N1 position and thiophenyl-2-yl unit at C6 position. Furthermore, the C4 position offered the greatest potential for improvement because many different N-aryl groups had better antiviral activities and compatibilities than the lead compound JX001.

For example, JX040 with a 2-pyridyl group was the analogue with the most potent activity against non-polio enteroviruses, and JX025, possessing a 3-sulfamoylphenyl moiety, had the best activity against polioviruses. In addition, analogue JX037, possessing a novel pyrazolopyridine heterocycle, was also shown to have good
antienteroviral activity, which further enlarges the compound space for antienteroviral drug design.

Tested Pharmacophores and Structures of JX001, JX040, JX025 and JX037.

MEDI 49

Synthesis of new FDI-6 derivatives as inhibitors and radiotracers of FOXM1

César S. Huerta García¹, huerta_garcia@hotmail.com, Alicia Hernandez Campos¹, Carlos A. Velazquez², Rafael Castillo-Bocanegra¹. (1) Departamento de Farmacia, Facultad de Química - Universidad Nacional Autónoma de México, Mexico, Mexico, Mexico (2) 2-142L Katz Ctr for Pharm Health Research, University of Alberta, Edmonton, Alberta, Canada

The Forkhead box M1 protein (FOXM1) belongs to a family of evolutively conserved transcription regulators, which controls a broad range of normal biologically essential functions such as DNA damage repair, cellular proliferation, cell cycle progression, cellular renovation, cellular differentiation, cellular migration and angiogenesis. As a transcription factor FOXM1 expression is frequently overregulated in practically all types of cancer. Additionally, it has been observed that the in vitro inhibition of the transcriptional FOXM1 activity is associated with a decrease in cellular proliferation for many different types of cancer cells; thus, this transcription factor is considered a good target for fighting this disease with utility both as a radiotracer for diagnosis and as a drug for therapy.

Carlos Velásquez group, in University of Alberta, Canada, previously reported a series of docking and molecular dynamic studies, in which an important interaction between the Forkhead Domain Inhibitor-6 (FDI-6) and the Arg297 residue inside the FOXM1-DNA binding domain (DBD) was observed. In order to prove the importance of this interaction, in this work we synthesized a series of new FDI-6 derivatives possessing a 4-iodophenyl with different substituents at position 2 of the phenyl group, whose
anticancerogenic activity will be determined. Additionally, an easily accessible methodology to substitute the iodine for a fluorine atom \(^{(19)F}\) in the newly synthesized compounds is being studied. This methodology could be used with radioactive fluorine \(^{(18)F}\) and the radioactive compounds can be assessed as radiotracers.

To support the experimental observations a complementary docking studies between the compounds and one of the FOXM1 protein domains were carried out in order to know more about the need of the different substituents at positions 2 and 4, of the phenyl moiety, of FDI drugs.

Progresses of these studies are presented in this work.

**MEDI 50**

**New 2-heteroaryl-4-quinolones as potential antibiotics targeting multi-drug resistant ESKAPEE pathogen communication systems**

*Marine Duplantier, Pauline Loupias, pauline.loupias@etud.u-picardie.fr, Elodie Lohou, Pascal Sonnet. AGIR, Amiens, France*

ESKAPEE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp. and Escherichia coli*) responsible for various nosocomial infections, constitute an important group of multi-drug resistant bacteria. To overcome this serious threat to public health, the development of antimicrobial molecules active towards new pharmacological targets appears as a promising strategy. For this purpose, bacterial communication systems, called Quorum Sensing (QS), could be interrupt to disturb the expression of virulence factors, the multiplication of bacteria and/or the development of biofilms in response to environmental factors.

The *pqs* system, one of the three main QS circuits of *P. aeruginosa*, is based on two small signalling molecules, the *Pseudomonas* quinolone signal (PQS) and its precursor 2-heptyl-4(1H)-quinolone (HHQ). *P. aeruginosa* internalizes extracellular PQS synthesized by neighboring bacterial cells. High cellular concentration of PQS then activates the transcriptional regulator PqsR which triggers the synthesis of enzymes involved in the metabolic HHQ/PQS pathway. During this process, HHQ is converted into PQS and leads to the regulation of *P. aeruginosa* medium. Furthermore, *P. aeruginosa* produces a secondary metabolite through this PQS pathway, the 2-heptyl-4-hydroxyquinoline-N-oxide (HQNO), which is toxic for various competing microorganisms such as *S. aureus*. In fact, HQNO disrupts the respiratory chain of many bacteria at the cytochrome bc1 complex what provokes reactive oxygen species accumulation and finally apoptosis. Recently, the interest of quinolone scaffold in the design of QS and respiratory chain inhibitors has emerged. HHQ analogues such as 6-nitro-HHQ-3-carboxamide have been described as PqsR antagonists and 2-phenyl or pyridinyl-4-quinolone series have been respectively identified as *Mycobacterium tuberculosis* and *Plasmodium falciparum* type II NADH/quinone oxidoreductase (NDH-2) inhibitors.
Taking these studies into account, we aim to develop a new 2-heteroaryl-4-quinolone family with potential antibacterial properties. In the poster, the synthesis of first expected derivatives carrying out metal-catalyzed C-C or C-N coupling reactions from 2-bromo-4-chloroquinoline precursors is presented.

MEDI 51

Synthesis and study of new aminoquinolinemethanols as potential antibacterial drugs

Pierre Laumaillé, Alexandra Dassonville-Klimpt, François Peltier, Pauline Loupias, pauline.loupias@etud.u-picardie.fr, Catherine Mullié, Claire Andréjak, Sandrine Castelain, Pascal Sonnet. AGIR, Amiens, France

Infectious diseases are the second most frequent cause of death worldwide. Among them, tuberculosis and nosocomial infections are particularly worrying. Tuberculosis is a bacterial infection caused by some bacteria from the genus *Mycobacterium*, such as *Mycobacterium tuberculosis*. The majority of the nosocomial infections involves the ESKAPE pathogens.

Mycobacteria and ES KA PE bacteria can become resistant to most current antibiotic treatments. In the case of tuberculosis, the treatment of drug-resistant or multi drug-resistant mycobacteria is more complex and requires combination chemotherapy. Since 1970, only five antibiotics with new mechanism of action were marketed. Consequently, there is a necessity to set up new strategies to prevent the spread of antibiotic resistant bacteria.

The quinoline core is found in anti-infectious drugs such as mefloquine (MQ) or bedaquiline (BQ). MQ is an aminoquinolinemethanol antimalarial drug that possesses also antibacterial activity against Gram-positive bacteria and most mycobacterial strains. Bedaquiline (BQ) is a diarylquinoline, recently marketed as antitubercular compound, which acts against latent mycobacteria by binding selectively to the mycobacterial F0F1-ATP synthase, a novel bacterial target. Some studies reported also that MQ was able to inhibit the F0F1-ATP synthase of *Streptococcus pneumoniae*.

During the antibacterial screening of new aminoquinolinemethanols synthesized in the AGIR’s team, we have identified a promising compound with good activities against *S. aureus* (MIC = 8 µg/mL), *E. faecalis* (MIC = 8 µg/mL) and *E. coli* (MIC = 16 µg/mL) and a very strong activity against *M. tuberculosis* (MIC = 1 µM).

The objectives of this work are to design, to synthesize and to evaluate the antibacterial activity of new enantiopure aminoquinolinemethanols expecting to target the F0F1-ATP synthase. Currently, more than twenty compounds have been synthesized through an asymmetric synthetic route in 5 steps with a yield ranging from 14 and 47%. This synthesis and the antibacterial evaluation against two strains of mycobacteria and four ES KA PE pathogens will be presented.
MEDI 52

Efflux pumps in *Acinetobacter baumannii*: Molecular characterization and study of new 1-(1-naphthylmethyl)-piperazine analogs as potential inhibitors

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Over the past few decades, the emergence of antibacterial resistance has become a major public health issue. The ESKAPEE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter spp.* and *Escherichia coli*) have been identified as the leading cause of multi-drug resistant nosocomial infections as a result of intensive use of broad-spectrum antibiotics to treat these infections. Moreover, overexpression of multi-drug efflux transport systems has been described as one of the most critical resistance mechanisms. As various families of efflux pumps co-exist in *A. baumannii* like Resistance-Nodulation-Division (RND) tripartite systems and Major Facilitator Superfamily (MFS) proteins, the development of efflux pump inhibitors to help restoring antibiotic activity on resistant strains could be key to new effective treatments. 1-(1-NaphthylMethyl)-Piperazine (NMP) and Phenylalanine-Arginine-β-Naphthylamide (PAβN), already described as efflux pump inhibitors, have been tested on 134 ciprofloxacin resistant strains of *A. baumannii* collected from clinical isolates in Amiens University Hospital (Amiens, France). An efflux driven mechanism of resistance has been phenotypically detected in 35 strains measuring ciprofloxacin MICs with and without NMP or PAβN. Quantification of mRNA will be performed on these isolates to characterize the overexpressed pumps and identify the origin of this resistance in our local clinical environment. Meanwhile, the synthesis of new NMP analogs has been undertaken. These promising compounds will then be evaluated as efflux pump inhibitors on the 35 isolates of our collection displaying an efflux driven resistance to ciprofloxacin.

MEDI 53

Optimization of 4-hydroxy-3-(heteroaryl)pyridine-2-one APJ receptor agonists for potency and oral PK profile

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Apelin-13 is an endogenous peptidic agonist of the APJ receptor which has demonstrated increased cardiac function in heart failure patients. The low plasma stability of apelin-13 has precluded both oral administration and chronic dosing.
therefore we focused on identification of a small molecule agonist to address these
limitations. We report optimization of a HTS lead including detailed SAR of heterocyclic
linkers (and substitution thereof) at the C3 position of the 4-hydroxypyridine-2-one core
and for the phenyl ring at the C5 position. Incorporation of polar groups at the C6
position to improve physicochemical properties and increase bioavailability, re-
opimization for potency and discovery of efficient synthetic methods will be described
which enabled identification of our clinical candidate.

MEDI 54

Design and synthesis of a targeted covalent inhibitor of poly(ADP-ribose)
glycohydrolase (PARG)

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Targeting DNA damage repair enzymes offers a promising approach for the
development of new selective therapeutics for cancer. The enzyme Poly(ADP-ribose)
glycohydrolase (PARG) plays an important role during this DNA damage repair process
through hydrolysis of poly(ADP-ribose) (PAR) chains. Protein poly ADP-ribosylation
(PARylation) is a post-translational modification of DNA lesions with PAR chains,
catalyzed by poly(ADP-ribose) polymerases (PARPs), and has been a significant small
molecule target in BRCA1/2 mutant cancer cells. Critical for the PARP/PARG pathway,
X-ray repair cross-complementing protein 1 (XRCC1) is a scaffolding protein involved in
the repair of DNA single-strand breaks. Depletion of XRCC1 sensitizes cancer cells to
PARG inhibition, establishing a synthetic lethal relationship between XRCC1 and
PARG. Here we describe the design and synthesis of potent small molecule, covalent
inhibitors of PARG targeting a cysteine in the binding pocket, identified through use of
X-ray crystallography.

MEDI 55

“First principle” concept in designing small molecules for targeting RNA
expansion repeats

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The massive of the genome sequencing data has established a clear connection
between several neurological and neuromuscular disorders, and expansions of short
nucleotide repeats. To name few, these maladies include Myotonic Muscular Dystrophy,
instances it was demonstrated that the small organic molecules therapeutic strategy – a
well-proven tool of modern medicine – also can be utilized for treatment these, otherwise non-curable, disorders by targeting specific RNA sequences of the overexpressed expansions repeats. The ligand-target mechanism when the RNA expansion repeats are targeted with small molecules has been shown working in multiple research studies including animal models. However, one of the limiting obstacles for finding new high-quality lead molecules is that most of the commercial high-throughput screening (HTS) libraries are biased towards the protein affinity chemical space. The unique distinction of the RNA affinity chemical space requires different weight factors that contribute to physicochemical interactions of a ligand-target ensemble in the RNA chemical space vs in the protein one. One of the most advantageous approaches is to target RNA’s with designer macrocyclic compounds. The use of macrocycles for therapeutic RNA targeting is especially alluring as selective G-Quadruplex RNA (as well as DNA) ligands. As a back-end selectivity reinforcement approach, we propose the 3D shape and electrostatic field similarity virtual screening method using the complimentary trinucleotide sequences as reference training sets.

MEDI 56

Design, synthesis, and structure activity relationship of novel pyrazolo-pyrimidine muscarinic 1 positive allosteric modulators (M1 PAM)

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Positive allosteric modulation (PAM) of the muscarinic acetylcholine receptor subtype 1 (M₁) 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 M₁ 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 M₁ 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, invitro potencies and pharmacokinetic studies of pyrazolo-pyrimidine carboxamides will be disclosed in this poster presentation.

**MEDI 57**

**Design, synthesis, and structure activity relationship of novel 1,2,4-triazine-3-one: Derivatives as multimodal compounds intended to treat schizophrenia**

**Vanajareddy R. Middekadi**, vanajareddy1412@gmail.com, Bogaraju Narasimha, Abdul R. Mohammed, Dharmendra Singh Sisodaya, Venkat R. Mekala, Surendra Petlu, Ramakrishna Nirogi. Medicinal chemistry, suven life sciences, 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-HT₂A, 5-HT₁A receptors, serotonin transporter SERT and dopamine receptor D₂. 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, invitro potencies and pharmacokinetic studies of 1,2,4-triazine-3-one derivatives will be disclosed in this poster presentation.

**MEDI 58**

**Synthesis and biological evaluation of optimized analogues of the NPFF antagonist, MES304**

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Neuropeptide FF receptors (NPFFR-1 and NPFFR-2) are G-protein coupled receptors which, along with their endogenous peptidic ligand NPFF(SQAFLFQPQRFa), are linked
to modulation of opioid induced tolerance and hyperalgesia. Further understanding of the NPFFR system can aid in delineating its role in the modulation of opioid activity, and eventually can lead to developing safer analgesics. Currently, there exists a limited number of small molecule ligands that are used to investigate the pharmacology of the NPFF system. However, most of these molecules lack the desired level of affinity and/or selectivity. Our lead compound, MES304, showed one of highest affinity values at NPFFRs within the benzylpiperidine series, and four-fold selectivity between the two receptor subtypes. In the present work, we report the synthesis of an optimized series of compounds and some preliminary pharmacological characterization. Our investigation focused on maintaining the guanidino-piperidine core of MES304, while introducing structural diversity at the N-benzyl position. This was achieved through a divergent synthesis revolving around a reductive amination step with various aromatic and aliphatic aldehydes. In addition, due to the structural similarity between our analogues and some synthetic opioid molecules, we investigated the off-target binding affinity of these molecules at the different opioid receptors.

MEDI 59

Discovery of a bromodomain and extraterminal (BET) inhibitor with a low predicted human dose derived from an encoded library technology hit
The bromodomain and extra-terminal domain (BET) family of bromodomain-containing proteins (BCPs) are important regulators of the epigenome through their ability to recognise acetylated lysine post-translational modifications on histone tails. These interactions have been implicated in a variety of disease states and, consequently, disruption of BET-KAc binding has emerged as an attractive therapeutic strategy with several small molecule inhibitors now under investigation in the clinic. However, until the utility of these advanced candidates is fully assessed by these trials, there remains scope for the discovery of inhibitors from new chemotypes with alternative physicochemical, pharmacokinetic and pharmacodynamic profiles. Accordingly, this poster describes the development of the potent benzimidazole dimethylpyridinone BET inhibitor 2 (Figure 1) which exhibits favorable pharmacokinetic properties and a low predicted human efficacious dose. This compound originated from Encoded Library Technology (ELT) hit dimethylphenol benzimidazole 1 (Figure 1), which was modified to an improved dimethylpyridinone benzimidazole series using structure-based design. Subsequent optimisation of activity, BCP selectivity and pharmacokinetic properties was carried out leading to benzimidazole dimethylpyridinone 2.

Figure 1. Optimisation of dimethylphenol benzimidazole ELT hit 1 to benzimidazole dimethylpyridinone 2.

MEDI 60
Development of novel sphingosine kinase inhibitors through structure-activity relationship study on jaspine B derivatives

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Sphingosine kinases (SphKs) are key enzymes that regulate sphingosine 1-phosphate production levels, and are involved in a range of cellular processes. SphKs exist in two isoforms in mammals: SphK1 and SphK2, serving the same catalytic reaction, but displaying different cellular localizations. SphK1 is located mainly in the cytosol. The overexpression of SphK1 is observed in various tumors and is involved in the severity of malignancy. On the other hand, SphK2 functions in various cellular organelles. Several studies have revealed that the functions of SphK2 are associated with autoimmune and inflammatory diseases. We have focused on a naturally occurring sphingosine analog, jaspine B, as a promising lead for the development of novel SphK inhibitors. Our previous SAR study revealed that 4-epi isomer of jaspine B (4-epi-jaspine B) displayed the potent inhibitory activity towards SphKs.

In this study, we focused on the modification of the lipid tail of 4-epi-jaspine B, and designed a new series of derivatives containing various functional group in the lipid tail. The synthesis of the designed derivatives has been accomplished based on a late stage cross metathesis reaction that facilitates the introduction of various lipid side chains to the tetrahydrofuran head group. A biological evaluation revealed that the replacement of one methylene at the lipid tail with ether oxygen affected the inhibitory activity of 4-epi-jaspine B, leading to the identification of a selective SphK2 inhibitor. Our results could contribute to the understanding of molecular recognition of sphingolipids by SphKs and aid further development of novel potent ligands via modifications of lipid substrates.

Halogen bond and its application in drug design

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Around one quarter of chemical drugs are organohalogens. Theoretical and experimental studies revealed that there might be a net attraction between heavy halogen atoms of organohalogen drugs and the heavy atoms of proteins, which are called halogen bond (XB). The bond is an attraction between a positively charged region, called sigma hole, on heavy halogen atoms of organohalogen (XB donor) and the nucleophilic regions of protein residues or peptide bonds (XB acceptor). With quantum chemistry calculations, we demonstrated that all XBs could be stable regardless of the charged states of both XB donor and acceptor. Thus, 9 differently charged XB could be designed and applied in drug design. However, there is a challenge for the application of XB in drug design as classic modeling approaches is unable to treat sigma hole properly. We developed new scoring functions that can take XB into calculation for molecular docking and virtual screening. With the functions, we repositioned two organohalogens as B-Raf V600E inhibitors, which showed both in vitro and in vivo activities against multiple myeloma cell lines. We also successfully optimized a series of highly efficient PDE5 inhibitors via halogenation. The designed halogen bonds between the new organohalogens and PDE5 were confirmed by both quantum chemistry calculation and x-ray crystallization (Figure 1), demonstrated that XB has great application potential for drug design and development.

![Figure 1. Predicted and X-ray diffracted parameters of the designed halogen bonds of organofluorine (a) and (d), organochlorine (b) and (e), organobromine (c) and (f); and predicted and determined bioactivities (g).](image)

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MEDI 62

Design, synthesis, and pharmacological characterization of novel carboxamides as 5-HT4 receptor agonists
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-HT4 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 (Aβ) and soluble amyloid precursor protein alpha (sAPPα). Based on the literature precedence and scaffold hopping approaches we have designed and synthesized carboxamide based 5-HT4 agonist compounds. The series in general has potent in vitro affinity at 5-HT4 receptor (<10 nM). The lead compound from this series is a highly potent, selective and brain penetrant 5-HT4 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 sAPPα level in mice brain) of the lead compound. The poster presentation will cover design, chemistry, SAR, ADME and animal efficacy studies.

MEDI 63

Design, synthesis, and pharmacological characterization of novel series of 4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine derivatives as H3 receptor antagonists

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H3 receptors (H3R) are autoreceptors which regulate the release of histamine in the brain, particularly in the cortex, striatum, hippocampus, amygdala and substantia nigra. H3R antagonists modulate the neurotransmitters involved in cognition such as histamine, acetylcholine and serotonin. H3R 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 H3R antagonists with high affinity at H3R 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 H3R. It has adequate oral exposure and favorable half-life in both rat and dog pharmacokinetic studies. The compound demonstrated high receptor occupancy (ED50 = < 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 64**

**Synthesis and anti-neuroinflammatory activity of N-heterocyclic analogs based on natural biphenyl-neolignan honokiol**

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Novel isoxazole and pyrazole analogs based on natural biphenyl-neolignan honokiol were synthesized and evaluated for their inhibitory activities against nitric oxide production in lipopolysaccharide-activated BV-2 microglial cells. The isoxazole skeleton was constructed via nitrile oxide cycloaddition from oxime 3 and pyrazole was generated by condensation of 4-chromone and alkyl hydrazine. Following, we synthesized a series of 17 isoxazole and 18 pyrazole derivatives and evaluated their inhibitory effects on NO production in LPS-activated BV-2 cells. Among the prepared compounds, 13b and 14a inhibited NO production in LPS-activated BV-2 cells by suppressing iNOS and COX-2 expression. The pyrazole analog 14a was the most potent inhibitor. These findings provide insight into the structural features influencing biological activities of this class of compounds and provide a foundation for further studies of analog design. Recently, retinoid X receptor was studied as the only binding protein of honokiol derivatives, although the various biological activities of honokiol were well known. Our synthetic and medicinal chemistry work would be exploited to design photoaffinity probes for target identification using a forward chemical genetic approach. Further analysis of the mode of action and biological activity in vivo of these pyrazole analogs as well as their potential as novel drug candidates is under way.

**MEDI 65**

**Enantioselective synthesis of homoisoflavanones by asymmetric transfer hydrogenation and their biological evaluation for antiangiogenic activity**

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Neovascular eye diseases are a major cause of blindness. Excessive angiogenesis is a feature of several conditions, including wet age-related macular degeneration, proliferative diabetic retinopathy, and retinopathy of prematurity. Development of novel
anti-angiogenic small molecules for the treatment of neovascular eye disease pipeline for these diseases. We have previously reported the therapeutic potential of antiangiogenic homoisoflavanone derivatives with efficacy in retinal and choroidal neovascularization models, although these are due to racemic compounds due to the C3-stereogenic center in the molecules. This work presents asymmetric synthesis and structural determination of anti-angiogenic homoisoflavanones and pharmacological characterization of the stereoisomers. We describe an enantioselective synthesis of homoisoflavanones by virtue of ruthenium-catalyzed asymmetric transfer hydrogenation with dynamic kinetic resolution, providing a basis for further development of these compounds into novel experimental therapeutics for neovascular eye diseases.

MEDI 66

Enantioselective synthesis and absolute configuration determination of hydroxywilfordic acid in sesquiterpene pyridine alkaloids

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Those containing tertiary hydroxy groups exhibit potent anti-HIV activity in the sesquiterpyridine alkaloids. A novel enantioselective strategy for the synthesis of the diester derivative of hydroxywilfordic acid, a key fragment of anti-HIV sesquiterpene pyridine alkaloids, was developed. Asymmetric cyanation using Jacobsen’s (R,R)-aminothiourea and hydrolysis were performed to afford chiral α-hydroxy-α-methyl acid as the (S)-isomer. Naturally derived hydroxywilfordate prepared by methanolysis of wilfortrine was found to be the (R)-isomer upon comparison with the synthetic compound. Asymmetric cyanosilylation of the α,β-unsaturated ketone using Jacobsen’s (R,R)-amino-thiourea was performed to synthesize the (S)-isomer. The stereochemistry of the tertiary alcohol in naturally occurring hydroxywilfordic acid could be assigned as the (R)-configuration. Currently, synthetic strategies for regioselective/chemoselective esters or amide formation from hydroxywilfordic acid are under investigation as a means to obtaining simplified analogs of sesquiterpene pyridine alkaloids and evaluating the biological activities of their derivatives.

MEDI 67

Discovery of an advanced dual chitinase inhibitors OAT-870: New potential therapeutic in therapy of lung diseases

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Acidic mammalian chitinase (AMCase) and chitotriosidase 1 (CHIT1) are the enzymatically active chitinases, which have been shown to be involved in various lung pathologies including idiopathic pulmonary fibrosis (IPF), sarcoidosis, chronic obstructive pulmonary disease (COPD) and asthma. Elevated CHIT1 levels and activity were found in the plasma and bronchoalveolar lavage (BAL) fluids from patients with interstitial lung diseases (IPF and sarcoidosis). AMCase is activated during type 2 inflammatory responses in both murine models of airway inflammation and in asthma patients.

Herein we present design and synthesis of a series of potent dual AMCase and CHIT1 inhibitors. Rational optimization of OAT-177 led us to discovery of a new advanced lead compound OAT-870 with good in vitro activity for both human and murine chitinases. In vitro structure-activity relationship data, ADME, pharmacokinetic properties as well as in vivo data showing strong anti-inflammatory effects of compound OAT-870 in house dust mite (HDM) induced airway inflammation model are reported.
Chitinase-3-like protein 1 (CHI3L1, YKL-40) is a carbohydrate-binding protein that unlike other members of 18-glycosylhydrolase family, including chitotriosidase (CHIT1) and acidic mammalian chitinase (AMCase) does not possess chitinase activity. YKL-40 has been shown to bind short chitin oligomers and it has been suggested to bind heparin. Elevated serum YKL-40 level has been correlated with poor prognosis and shorter survival of patients with cancer. The protein has been proposed to act through IL13Ra2 and Syndecan-1 receptors via respectively chitin-binding and heparin-binding domains but its detailed biological functions are still poorly understood.

Herein, we demonstrate carbohydrate-binding properties of YKL-40, chitooligosaccharides binding, heparins/heparan sulphates binding, and the interplay between both types of these interactions. In this regard, we also present the screening cascade of small molecule compounds capable of interfering with YKL-40 binding chitooligosaccharide ligands alone (compound 1) or chitooligosaccharide and heparin/heparan sulphate ligands (compound 2) concurrently. Low nanomolar activities have been identified among both groups of compounds. Parallel optimization of ADME and pharmacokinetic properties of compounds is underway. Similarly, \textit{in vitro} cellular assays, as well as \textit{in vivo} models to study compounds’ anti-cancer effects are under development.
Discovery of OAT-1441: Highly active, selective, and orally bioavailable inhibitor of human AMCase

Gleb Andryianau, g.andryianau@gmail.com, Michal L. Kowalski, Michal Piotrowicz, Barbara Dymek, Magdalena Salamon, Agnieszka Zagozdzon, Aleksandra Rymaszewska, Marcin Mazurkiewicz, Szymon Klossowski, Piotr Sklepiewicz, Marzena Mazur, Sylwia Olejniczak, Robert Koralewski, Krzysztof Matyszewski, Bartlomiej Borek, Wojciech Czestkowski, Piotr Niedziejko, Agnieszka Bartoszewicz, Elzbieta Pluta, Mariusz M. Gruza, Karolina Dzwonek, Filip Stefaniak, Jacek Olczak, Adam Golebiowski. OncoArendi Therapeutics SA, Warsaw, Poland

Acidic Mammalian Chitinase (AMCase) is a representative of GH18 glycoside hydrolases family and is one of two proteins in mammals with chitinolytic activity preserved throughout the evolution (together with chitotriosidase - CHIT1). Elevated AMCase levels in lungs have been correlated with type 2 inflammation development in the animal models of asthma. Our recent studies demonstrated that selective AMCase inhibition by OAT-177 exhibits strong anti-inflammatory effect in House Dust Mite (HDM)-induced asthma model in mice. Moreover, increased amounts of AMCase have been found in the samples from allergic patients. Herein, we report our SAR studies based on structure-guided scaffold hopping and lead optimization that resulted in the discovery of an improved compound. OAT-1441 is a single nanomolar inhibitor of human AMCase, which displays excellent hAMCase/hCHIT1 as well as hAMCase/hERG selectivity. In comparison to previously reported data for allosamidin, Wyeth-1, bisdionin F and argifin, OAT-1441 shows improved drug-like properties and pharmacokinetic parameters in rats, which make it suitable for oral administration.
MOEsaic: Application of matched molecular pair analysis to SAR exploration

Guillaume Fortin, gfortin@chemcomp.com, Alain Ajamian. Chemical Computing Group, Montreal, Quebec, Canada

SAR analysis can be 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. Other typical workflows are shown below.

- 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.

Protocol for validating small-molecule structure assignment using calculated 13C 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 13C chemical shifts of close structurally related compounds. The calculated chemical shifts are then compared with experimental 13C 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 13C chemical shifts, 5) compare the calculated 13C NMR chemical shifts of multiple compound candidates with experimentally derived 13C values to identify the best match using the NMR Spectral Analysis application in MOE.
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 BRC-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 73**

Structure-based predictions of CYP selectivity, reactivity, and regioselectivity

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

Cytochrome P450 oxidases (CYPs) are heme-containing enzymes responsible for clearing drug molecules through oxidative metabolism. Understanding the interactions between drug molecules and CYPs is critical for evaluating drug efficacy, clearance, toxicity, and drug-drug interactions. Although dozens of crystal structures of the five predominant CYP isoforms have been solved, most of the modeling tools that predict drug-CYP interactions completely neglect this structural information. In this work, both 2D methods and 3D methods are used to predict the isoform selectivity, small molecule reactivity, and regioselectivity of CYPs.

**MEDI 74**

Synthesis and evaluation of racemic [\(^{11}\text{C}\)]BLZ945: Candidate radioligand for PET imaging of brain macrophage colony-stimulating factor 1 receptor

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Neuroinflammation is associated with many neuropsychiatric disorders. In neuroinflammation, there is a generally greater expression of colony-stimulating factor 1 receptor (CSF1R) on microglia than in healthy brain. This suggests that CSF1R can be a target for studying neuroinflammation with positron emission tomography (PET). BLZ945 (4-((2-(((1R,2R)-2-hydroxycyclohexyl)amino)benzo[d]thiazol-6-yl)oxy)-N-methylpicolinamide) is a potent (IC\(_{50} = 1 \text{nM}\)) and selective inhibitor of CSF1R. We envisaged that BLZ945 could be labeled with carbon-11 (t\(_{1/2} = 20 \text{ min}\)) and thereby
provide a candidate PET radioligand for CSF1R. Racemic $[^{11}\text{C}]\text{BLZ945}$ was produced in two-steps (Figure). Thus, the prepared racemic picolinamide, $\text{Ps}a97$ (~1.8 µmol), was treated with $[^{11}\text{C}]\text{MeI}$ in DMSO (0.4 mL) in the presence of TBAOH (1 M, 2 eq.) at 100 °C for 5 min, and then with excess TBAF (12 eq.) at 100 °C for 5 min. Racemic $[^{11}\text{C}]\text{BLZ945}$ was purified with HPLC and formulated for intravenous injection. The whole radiosynthesis required 49 min and gave formulated radioligand in 6.5% yield. Evaluation of racemic $[^{11}\text{C}]\text{BLZ945}$ in non-human primates and rodents with PET showed low brain uptake ($\text{SUV} = 0.7$). Further investigation showed that this radioligand was a substrate for two efflux pumps, P-glycoprotein 1 (Pg-P) and breast cancer resistance protein (BCRP) at the blood-brain barrier. The unexpected efflux transporter liability of racemic $[^{11}\text{C}]\text{BLZ945}$ renders this radioligand (and by inference the single homochiral $(R,R$)-eutomer) as ineffective.

**Figure:** Synthesis of racemic $[^{11}\text{C}]\text{BLZ945}$ (shown for the $(R,R$)-enantiomer only).

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**MEDI 75**

**Novel glycolysis inhibitor improves the therapeutic regimen for triple negative breast cancer under hyperglycemic condition**

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Hyperglycemic and hyper insulin condition is the signature symptoms for type two diabetes which is the most favorable condition for the development of a cancer. Women with type two diabetes (T2D) have 20-27% higher risk to develop breast cancer, including triple negative breast cancer (TNBC). Hyperglycemic and/or hyper insulin condition leads to the therapy resistance, and according to ‘Warburg’s effect’ cancer cells consume high amount of glucose as compared to normal cells, via aerobic glycolysis process. To combat this condition currently several clinical studies are underway, with the combination therapy of T2D and chemotherapy drugs e.g., metformin and erlotinib. The major drawback of such T2D drugs is that they do not affect cancer cells under hyperglycemic and hyper insulin conditions. These T2D drugs including metformin, work via AMP-activated protein kinase (AMPK) activation to switch aerobic glycolysis to oxidative
phosphorylation. To address this challenge, we have developed a novel AMPK activator (SU-18) which selectively induces an oxidative phosphorylation in TNBC cells, and glycolysis in normal cells. We found that SU-18 induces G2/M phase arrest, mitochondrial stress and apoptosis in TNBC cells similar to metformin, but at 1000 of the concentration. This drug selectively reduces the glucose consumption, lactate and ATP reduction in TNBC cells, whereas the normal cells act opposite to this. We found that SU-18 acts through AMPK activation, which otherwise gets eliminated in the presence of AMPK inhibitor (compound c). It also improves the blood glucose level in hyperglycemic mice, and inhibits the tumor growth and progression. Comparative studies with metformin suggest that SU-18 works irrespective of hyperglycemic and insulin conditions, whereas metformin is ineffective under these conditions. FDG-PET analysis further supports our findings that treatment with SU-18 reduces the FDG accumulation in tumor cells. Overall, our study provides strong basis for clinical development of SU-18 for TNBC patients.

MEDI 76

Examining ligand-HIV protease dissociation: Pathway, energy, flexibility, and comparison with association processes

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Due to the high mutation rate caused by reverse transcription and rapid replication process, cross drug resistance has been a key obstacle in drug development for human immunodeficiency virus (HIV). HIV protease (HIVp) plays an integral role in its life cycle which makes it a prime target for drug therapy and compounds bind with longer residence time to HIVp may help to prevent drug resistance because pharmacological activity upholds when a drug is in bound-state with the target protein. Fully understanding the factors that govern a long or short residence time can assist us design drugs with desired binding kinetics. Here, we investigated ligand dissociation process for a slow binder, ritonavir, and a fast binder, xk263, by using unbiased all-atom accelerated molecular dynamics (aMD) simulation with reseeding approach and an explicit solvent model. Using ritonavir-HIVp and xk263-HIVp ligand-protein system as cases, we observed that these two ligands preferred same unbinding route. Moreover, ritonavir required larger HIVp motion to dissociate compared to xk263 dissociation process since xk263 can leave binding pocket without observable conformational change of HIVp. In addition, ritonavir formed more hydrogen bonds with multiple residues of HIVp. In contrast, hydrogen bonding between xk263 and HIVp was majorly restricted to Asp25, Asp124, Ile50 and Ile149. K-mean clustering on combined trajectory of ligand-protein association and dissociation revealed common HIVp conformations.
during ligand binding and unbinding. This study deepens our understanding of the dynamic process of ligand dissociation and provides insights into ligand-protein interaction and drug discovery.

MEDI 77

Novel imidazopyrimidine binders to embryonic ectoderm development (EED) protein that inhibit polycomb repressive complex 2 (PRC2) activity

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The cellular epigenetic machinery (writers, erasers and readers) contribute to the transcriptional control of genes without affecting the underlying DNA sequence. Epigenetic marks imparted by the writers (methyl and acetyl transferases) can lead to the transcription or repression of genes. When these events are aberrant they can lead to cancer progression and may be targeted with disease-modifying inhibitors. The validity of multiple epigenetic oncology targets has been established in clinical trials [histone deacetylase (HDAC) and DNA-methyl transferase (DNMT) inhibitors] and several additional targets are under investigation (PRC2, DOT1L and BET). The polycomb repressive complex 2 (PRC2) comprises five core components and is responsible for the methylation of histone 3 at lysine 27 (H3K27). Trimethylation of histone 3 (H3K27Me3) silences the transcription of various tumor suppressor genes, which in turn, regulates cellular growth and differentiation in a tightly regulated manner. The dysregulation of PRC2 by mutation of its components or alteration of chromatin remodeling pathways (e.g., SWI/SNF) can result in malignant transformation of certain cell types. There are several studies underway that examine inhibition of the catalytic site housed within the enhancer of zeste homolog 2 (EZH2) subunit of the PRC2 complex. More recently, an allosteric inhibition site within the PRC2 EED subunit has been explored. We will describe a structure-based approach toward an early lead molecule designed to interact with a unique binding conformation of lysine 211 within the EED protein. The initial imidazopyrimidine lead compound was neither highly soluble nor metabolically stable in vitro. Here, we illustrate the discovery of that lead compound and its optimization to provide a selective and orally efficacious EED-binding inhibitor of the PRC2 complex.

MEDI 78

Discovery of novel 4-alkylamino-2-(arylpiperazin)methylbenzonitrile derivatives as virus entry inhibitors for treatment of HCV infection

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Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, which may develop into chronic liver cirrhosis and even hepatocellular carcinoma. Although the directed antiviral agents (DAAs) are successfully developed, the high cost and resistance-associated variants are still challenging. In this study, a new series of 4-alkylamino-2-(arylpiperazin)methylbenzonitrile derivatives was synthesized and evaluated for their antiviral activity in HCV-infected Huh7.5 cell cultures. SAR study confirmed a new antiviral chemotype for treatment of HCV infection, also identified compound L0909 as a potent HCV inhibitor with IC50 value at low nanomolar level and with superior therapeutic index (TI) value above 3000. Meanwhile, L0909 displayed the similar efficacy against multiple clinical resistance-associated variants as well as the wild type virus in vitro. However, no antiviral activity was observed for L0909 treatment at concentration of micromole in HCV replicons assay. Time-of-addition experiment indicated that L0909 inhibited HCV replication by acting on the entry stage of HCV viral cycle. The synergic effect was also observed for combination treatment of L0909 with the available DAAs, such as sofosbuvir, telaprevir or simeprevir, in HCV-infected cell culture. Moreover, pharmaceutical evaluations revealed that L0909 is oral available to both rats and beagle dogs with the bioavailability above 40% and less toxic with the maximum tolerable dosage of 1200 mg/kg after oral treatment for mice. Current results supported further preclinical investigation on L0909 as a promising candidate for HCV therapeutics backup.

MEDI 79

Discovery of carbazole carboxamides as novel RORγt agonists

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Retinoic acid receptor-related orphan receptor gamma-t (RORγt) is a promising target for the treatment of autoimmune diseases and cancers. As a key transcriptional factor, RORγt drives the development and function of CD4+ Th17 and CD8+ Tc17 cells. With the first RORγt agonist LYC55716 entered clinical trials for solid tumors, the development of RORγt agonists as small molecule therapeutics for cancer immunotherapy has attracted great attentions. Starting from the RORγt inverse agonists GSK805 (1) and Takeda’s compound (2), Wang and colleagues discovered a novel series of RORγt inverse agonists such as carbazole carboxamide 3 using a molecule hybridization strategy followed by optimization, which exhibited better physicochemical properties (e.g., lower MW and cLogP) compared with the parent compounds. Further exploration of structure-activity relationship (SAR) by introducing different substituents on the carbazole ring of 3 led to discovery of the functionally switchable RORγt modulators. Docking studies showed that both 6-substituents (A-series) and 9-substituents (B-series) on the carbazole ring can stabilize the AF2 domain, thus making
the corresponding compounds RORγt agonists (Figure 1). It was found that with the size of the 6- or 9-substituents getting bigger, the max activation increased initially then reduced. Two representative RORγt agonists A-4 and B-3 showed good agonist activities with EC$_{50}$ values of 9.8 nM and 50.9 nM, achieving max activation of 85.8% and 86.3% in RORγ dual FRET assay, respectively. Furthermore, A-4 and B-3 showed good agonists activities in Gal4 cell reporter assay with EC$_{50}$ values of 85 nM and 161 nM, respectively. These compounds provided nice chemical starting points for further optimization of the carbazole-based RORγt agonists.

![Diagram of RORγt agonists](image)

Figure 1. Discovery of novel series of RORγt agonists

**MEDI 80**

**Focused gradient generation: Easy method development for normal phase preparative chromatography**

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A technique was developed to easily create optimized chromatography methods for reversed phase flash chromatography from analytical HPLC/UHPLC runs. This has now been extended to normal phase preparative High Performance Chromatography. Time-on-Target uses a model compound to set a desired retention time on the chromatography system that is 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 an
efficient focused gradient. The determined gradient is fast, saving solvent and reducing waste. After the initial calibration, method development for preparative chromatography is faster than that using TLC for normal phase.

**MEDI 81**

**Design and synthesis of folate receptor targeted self-immolative tris-payload conjugates**


Folate-receptor (FR) targeted small molecule drug conjugates (SMDCs) are designed to deliver highly potent agents to cancer cells and activated macrophages which express high levels of the folate receptor.

In an effort to increase the dose of active agent to the tumor, we have synthesized several FR targeted triple drug conjugates. The conjugates link folic acid to three drug payloads, either MMAE or tubulysin B hydrazide, through either a reductively or enzymatically labile linker system. A key feature of each of the syntheses is the introduction of all three of the combined linker-drug constructs onto the conjugate’s backbone by either three simultaneous copper-free Huisgen cycloaddition reactions (click chemistry) or by three simultaneous peptide bond forming condensation reactions.

**MEDI 82**

**Synthesis of targeted small molecule drug conjugates employing a self-immolative disulfide/quaternary ammonium-based linker system**


Small molecule drug conjugates (SMDCs), compounds comprised of a cytotoxin conjugated to a targeting moiety through a linker and spacer, have the potential to greatly improve cancer therapy by allowing for the delivery of active agents at dosages that would have been previously impossible due to their systemic toxicity. Each of the constituent parts of the SMDC plays an important role. The linker, for example, must be sufficiently stable as to allow for circulation and delivery of the conjugate to the tumor site, but be sufficiently labile in the tumor micro-environment or within the tumor itself so as to assure effective release and subsequent delivery of the toxin. Many groups, including our own, have utilized disulfide-based linker systems since the environment in internalized endosomes and around the tumor is reductive. Once the disulfide bond is reduced, the ease with which the linker remnant eliminates from the cytotoxin is a
critical factor affecting the utility of the SMDC. Herein, we report the synthesis of SMDCs utilizing a self-immolative disulfanylethyl ammonium linker system. This linker allows for the conjugation of drug payloads which possess tertiary amines to the SMDC system. Folate-receptor or prostate specific membrane antigen (PSMA) targeted conjugates utilizing a microtubule interacting agent such as vinblastine, a tubulysin, or dolastatin 10 were synthesized to demonstrate the utility of this methodology. Chemical release studies on these conjugates demonstrated that under reductive conditions the disulfide bond was reduced and the remaining thioethyl moiety was quickly expelled, allowing for the release of free drug within minutes. Selected in vitro and in vivo biological results will also be reported.

MEDI 83

Rational design and synthesis of novel inhibitors specific for interleukin-33

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Interleukin-33 (IL-33) is a member of the IL-1 superfamily that plays an important role in immune-mediated diseases such as asthma, atopic dermatitis, and rheumatoid arthritis. IL-33 drives the expression of Th2 cytokines and regulates immune responses by binding to ST2 receptor, an orphan receptor of the IL-1 receptor family. Although IL-33 was identified as a ligand for ST2, no small molecule inhibitors to block the interaction of IL-33 and ST2 have been reported. We previously reported that 2-phenyl-5H-[1,3]oxazolo[4,5-c]quinolin-4-one binds to the hydrophobic pocket of IL-33 at 2D NMR studies, thus, might block the interaction between IL-33 and ST2. Novel fifteen oxazolo[4,5-c]quinolin-4-one analogs were synthesized in 6 steps with 9% overall yield. Alkylation at the final step provided a mixture of O- and N-alkylated products. Most of the final compounds interacted with the amino acid residues in the interface region of IL-33 with ST2 at the 2D NMR studies. The O-alkylated analog 7c was the most potent one with an IC$_{50}$ value of 70 nM at cell-based ELISA assay. It also reduced eosinophil recruitment to the lung at in vivo experiment with ovalbumin-challenged mouse model. To improve synthetic yield for 7c, we established an alternative route which provided the final compound (~16% overall yield) with exclusive O-alkylation. Compound 7c can
be utilized as a template compound for structural optimization and as a tool compound for investigating the IL-33/ST2 signaling pathway.

MEDI 84

Discovery of biphenylflavone analogs as novel TSLP Inhibitors

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Thymic stromal lymphopoietin (TSLP) plays an important role in the development of Th2-mediated immune response, resulting in progression of allergic inflammation in the lung or skin. Modulation of TSLP/TSLPR signaling by soluble TSLPR fragment fused to Fc fragment of immunoglobulin (TSLPR-Ig) or anti-TSLP antibody have proven that inhibition of TSLP/TSLPR pathway may reduce eosinophilic airway inflammation and allergen-induced bronchoconstriction. Low molecular weight (M.W.) drugs possess several advantages over biologic drugs such as facile oral formulation, better tissue penetration, and low cost.

As an effort to identify small molecules to block TSLP/TSLPR signaling pathway, we screened in-house natural product library. One of flavonoid analogs was found to be a mode rate inhibitor of TSLP signaling from in vitro ELISA assay. Therefore, we synthesized a number of flavonoid derivatives in 5 steps (aldol condensation, cyclization, Suzuki coupling, demethylation, hydrogenation) with overall yields of 2.8% to 22.6%. According to structure-activity relationship (SAR) studies, at least two hydroxyl groups are required for TSLP inhibition in A ring of flavonoid. Introduction of the biphenyl group in B ring enhanced TSLP-affinity. In addition, reduction of flavone to flavanone in C ring resulted in improved water solubility with affecting TSLP-inhibitory activities. SAR studies identified that the biphenyl flavanone analog was the most potent in this series and can be utilized as a prototype molecule for structural modification in the discovery of low M.W. TSLP inhibitors.

MEDI 85

Design and synthesis of non-peptide analogs as novel hepsin inhibitors

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Hepsin, a type II transmembrane serine protease, is predominantly expressed in prostate cancer (PCa) and plays a crucial role in the promotion of progression and metastasis in PCAs. As it is highly up-regulated in PCa over benign prostatic hyperplasia or normal state and its active site is located in the cell surface region, hepsin has emerged as an attractive biomarker for PCa diagnosis and therapy.
Previously, Leu-Arg (LR) dipeptides conjugated with ketobenzothiazole (kbt) or ketothiazole ring were reported, exhibiting strong inhibition against hepsin in the nanomolar $K_i$ range. The guanidine group of these analogs was the key moiety for binding to hepsin. However, the cyclized by-products were observed in the synthesis of dipeptide analogs due to the flexibility of side chain in the Arg. With an aim to improve drug-like properties of LR-kbt, cylic ring structures such as phenylguanidine and cyclohexylguanidine were introduced at the side chain of Arg. Novel twelve non-peptidic analogs were prepared in 28% overall yield over 7 steps. Among the final compounds, the phenylguanidine analog (KB734) exhibited hepsin-inhibitory activity in the $K_i$ value of 91 nM and 50-fold hepsin selectivity over matriptase. *In silico* docking study of KB734 with hepsin demonstrated that the phenylguanidine moiety formed a salt bridge with the carboxylate group of Asp189 similar to the guanidine of Ac-LR-kbt. KB734 has a potential to be used for further structural optimization in the development of novel non-peptidic hepsin inhibitors.

**MEDI 86**

**Design and synthesis of trisubstituted pyridines as AKT inhibitors**

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Protein kinase B, also known as AKT, is a key enzyme for many cellular processes. AKT isoforms are involved in cell cycle regulation, growth factors signaling, angiogenesis, tumorigenesis, etc. These means that the three known AKT isoforms are involved in cancer. Hyperactivation of each isoform is associated with certain types of that disease. Therefore, AKT was cataloged as a promising target for the development of novel anticancer drugs. Previously, a novel 2,4,6-trisubstituted pyridine was identified as an AKT pan-inhibitor. The new hit was optimized through structure-based design. Large series of compounds were designed and synthesized with symmetrical substitution at positions 2 and 6. However, the observed solubility of the obtained compounds was limited. This fact made the biological assays more difficult. Consequently, new asymmetrical molecules were designed. These new series had similar score values with the symmetric compounds when the docking studies were performed. Asymmetric pyridines had better solubility than their symmetric counterparts, leading to the development of more selective molecules.

**MEDI 87**

**Discovery of small molecules that interact with Rpn-6 and are toxic to hematological cancers**

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Since discovered in last century, the proteasome has become an exciting research field for developing drugs that inhibit the protease subunits to halt proteasomal function, which can lead to apoptosis. However, resistance has been observed with those inhibitors which makes developing new molecules targeting different subunits on proteasome an urgent task. A considerable number of subunits in proteasome processes no protein degradation function yet they are crucial for proteasome stability. One example is Rpn-6, it is required to associate the regulatory particle with the core particle to form the full 26S proteasome. We have discovered a peptoid molecule named TXS-8 that possesses moderate binding affinity towards Rpn-6 in vitro and it has toxicity towards some hematological cancer cell lines. Our further experimental data suggests that the cell death caused by dosing TXS-8 is unrelated to proteasome malfunction or deteriorated structural integrity so we suspect that Rpn-6 may serve more than being a subunit of the proteasome. Moreover, we discovered that TXS-8 is selective towards Rpn-6 through a pull-down assay which makes TXS-8 a promising molecule for further research. Future work includes studies to determine what other role Rpn-6 plays in hematological cancers.

MEDI 88

Synthesis and in vitro anticancer evaluation of novel 2,4,6-trisubstituted pyridines designed as AKT inhibitors

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In the present work the synthesis, characterization, docking studies and biological evaluation of nine pyridine derivatives is reported. These were designed as serine-threonine kinase B (AKT) inhibitors. The compounds presented interesting results of cell growth inhibition percentages on five cancer lines (DU-145, PC-3, MCF-7, MDA-MB-231, HCT-15). Besides, some compounds presented selectivity on certain cancer lines without affecting the control line (COS-7). Finally, the docking studies revealed important information about the pyridine scaffold substitution useful for the design of AKT inhibitors.

MEDI 89

Pharmacophore-based tailoring of new fused thiophenes for JNK inhibition as potential anticancer agents

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c-Jun N-terminal kinases (JNKs) are members of mitogen-activated protein kinase (MAPK) family that respond to stress stimuli and mediate key cellular activities in cancer initiation and progression. N-(3-cyano-4,5,6,7-tetrahydro-1-benzothien-2-yl)1-naphthamide was reported as a potent JNK inhibitor with pIC$_{50}$ values of 6.5 and 6.7 for JNK2 and JNK3, respectively. In this study, series of 3-cyano-4,5,6,7-tetrahydro-1-benzothiophene with 2-benzamides; 2-benzylamines or 2-urea moieties were designed as potential anticancer agents through inhibition of JNKs. The preliminary in-vitro anticancer screening using MTS assay against A549 cell line showed that benzyl urea (1), 3-bromobenzamide (2) and 4-bromobenzylamine (3) are the most active members among the ureas, benzamides and benzylamines, with IC$_{50}$ values of 1.6, 7.6 and 2.7 μM, respectively. Current direction of this research is examining the inhibitory activity of the synthesized compounds against JNK2 and JNK3. The outcome of this study would enable structure-based design of selective JNK inhibitors as potential anticancer agents.

![Chemical structures](image)

**IC$_{50}$ values:**
- (1) 1.6 μM
- (2) 7.6 μM
- (3) 2.7 μM

**MEDI 90**

Establish cell-based assays for small molecules evaluation toward mucopolysaccharidosis type II

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Mucopolysaccharidosis type II (MPS II), or Hunter syndrome, is an X-linked lysosomal storage disease caused by genetic deficiency of the enzyme iduronate-2-sulfatase (IDS), required for the step-wise degradation and recycling of complex glycosaminoglycans (GAGs). Loss of IDS activity results in abnormal accumulation of GAGs (i.e., heparan and dermatan sulfates) in multiple tissues and organs, resulting in progressive cellular and multi-organ dysfunction. Currently, the protein drug is highly expensive for enzyme replacement therapy (ERT) of MPS II. In order to cost down and have a better life quality of patients, it is necessary to
discover a new approach by using small molecules for treating this GAG metabolic
disease. However, because of the structural complication of GAGs, convenient
evaluation platforms for small molecule screening toward MPSII remain to be explored.
Herein, we would like to establish a series of analytical platforms including enzyme-
based, cell-based assays for small molecules evaluation. Through our effort, several
analytic parameters have been examined to establish these accessible systems. With
these assays in hand, a small molecule library screening will be performed soon.

MEDI 91

Synthesis of nucleotide-based inhibitors against bacterial cell wall translocase MraY

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The rise of antibiotic-resistant bacteria has posed a serious threat to public health.
MraY, one of essential enzymes in peptidoglycan biosynthesis, is a promising target for
new antibiotics development. MraY is an integral membrane protein that catalyzes the
transfer of the monophospho-MurNAc-pentapeptide moiety from Park's nucleotide
(UDP-MurNAc-pentapeptide) onto the undecaprenyl phosphate, to give Lipid I with
concomitant release of UMP. In addition, several naturally occurring nucleotide
antibiotics have been found to target this bacterial translocase, which allows scientists
take advantage of them for scaffold design and structural modification. Taken together,
MraY is considered as an attractive and accessible antibacterial druggable target, and
without a eukaryotic counterpart.

In our previous work of MraY inhibitor discovery, systematical structural modifications of
MraY substrate Park's nucleotide, were performed to investigate the interactions
between moieties of Park nucleotide and MraY enzyme residues. Unexpectedly, one of
analogues becomes an inhibitor in an enzyme-based MraY functional assay. However,
its MIC value does not show a promising result; presumably, its hydrophilic
pyrophosphate moiety might affect its penetration through the bacterial cytoplasmic
membrane. In contrast, naturally occurring nucleotide antibiotics don’t contain a
pyrophosphate moiety and they might inspire scientists for initial scaffold design, though
their complex structures and multi chiral centers might limit their structural diversity and
preparation efficiency.

Herein, we would like to develop a flexible synthetic approach to prepare nucleoside
derivatives with simplified structures for our MraY inhibition study and antibacterial
activity study.

MEDI 92

Exploring Zafirlukast as a novel West Nile virus NS2B-NS3 protease inhibitor

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The West Nile virus (WNV) is a neurovirulent mosquito borne pathogen that is prevalent worldwide. Upon infection, the viral genome is translated by host ribosomes into a genomic polyprotein containing all protein elements necessary for viral replication. The genomic polyprotein is cleaved by the viral NS2B-NS3 protease. The NS2B is a cofactor that binds to the NS3 to provide the proteolytic activity needed for viral replication. The protease is an integral component of the WNV life cycle and therefore an attractive therapeutic target for WNV infection. Zafirlukast, an FDA approved Asthma alleviant has been discovered as a novel allosteric inhibitor for the NS2B-NS3 protease. Zafirlukast has shown promising inhibition against the NS2B-NS3 protease through disruption of the NS2B cofactor binding to the NS3 to form the active protease with an IC$_{50}$ value of 32 µM. The Zafirlukast scaffold consists of three components: a cyclopental carbamate, an o-toluic sulfonamide, and a methylated indole core. This research explores the synthesis of third-generation Zafirlukast derivatives by creating analogs of the indole core. Altering the indole core modifies the angle and position of the phenyl carbamate and o-toluic sulfonamide within the allosteric site which would increase binding and inhibition. The third-generation molecules contained variations in the core by substituting it with quinolines, phthalimides, and triazoles. These core analog structures will be evaluated in an enzymatic assay to probe the allosteric binding site and lead to improved NS2B-NS3 protease inhibition. These third-generation compounds will expand our knowledge of the NS2B-NS3 protease inhibitor molecular scaffold.

MEDI 93

Synthesis and initial assessment of 6-aminopyridin-3-ol derivatives against inflammatory bowel disease in vitro and in vivo

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Inflammatory bowel disease (IBD) is a chronic inflammatory pathology including Crohn’s disease (CD) and ulcerative colitis (UC) occurring in gastrointestinal tract. Although several molecular targets have been proposed for IBD, TNF-α currently seems to be the most successful target. TNF-a-induced adhesion of immune cells to intestinal epithelium is considered as an initial event of inflammation in IBD. We have found some analogues of 6-aminopyridinol to significantly inhibit TNF-a-induced adhesion of monocytes to HT-29 human colonic epithelial cells. The best compounds showed almost five orders of magnitude better inhibition than 5-aminosalicylic acid (5-ASA, a.k.a. mesalazine), an active metabolite of sulfasalazine (SSZ) that is a clinically used for IBD. The best compounds showed a dramatic activity in 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colon inflammation in rat model(1 mg/kg, p.o.). Body and colon weights and myeloperoxidase (MPO) level were recovered in significant extent. The effects was similar to that of sulfasalazine (300 mg/kg), a prodrug of 5-ASA. Moreover, the compounds significantly suppressed the expression of pro-inflammatory cytokines such as TNF-a, IL-1β, and IL-
6 while increasing the level of IL-10, an anti-inflammatory cytokine. Also, they suppressed the expression of intercellular adhesion molecule-1 (ICAM-1) as well as chemokines such as monocyte chemoattractant protein 1 (MCP-1), which mechanistically supports the potential of the compound as a novel platform for anti-IBD drug discovery.

**MEDI 94**

**Novel synthesis of chiral 2-trifluoromethylmorpholine**

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Chiral 2-trifluoromethylmorpholine is a useful intermediate employed in the syntheses of RSV, IRAK4 inhibitors, AMPA receptor antagonist, GPR43 agonist and mGluR2 negative allosteric modulator etc. We developed a route to yield optically pure 2-trifluoromethylmorpholine without SFC separation. Our method has a number of attractive features, including readily available and inexpensive starting material 2-(trifluoromethyl)oxirane, mild reaction conditions and easy purification [Figure 1]. This new protocol was successfully used to generate 400 g of compound 1 with an overall yield of 36%.

Figure 1: Synthetic route to chiral 2-trifluoromethylmorpholine
Syntheses of 2-fluoropyridines

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2-Fluoropyridines are extensively used in drug discovery. Syntheses of these molecules usually involve diazotization of corresponding 2-aminopyridines. We are reporting a special synthetic approach to 2-fluoropyridines, with 2a-h prepared in 28-65% yields, using silver (II) fluoride as fluorination reagent. [Figure1]

![Figure 1. Synthetic route to 2-fluoropyridines](image)

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Figure 1. Synthetic route to 2-fluoropyridines

**MEDI 96**

Improved synthesis of 4,4-disubstituted-2-aminomethyl oxetanes

**Huawen Lian**, lian_huawen@4RingChem.com, GuiHua Liu, ShanBao Yu, Minmin Yang. Department of Synthetic Chemistry, PharmaBlock Sciences (Nanjing), Inc., Nanjing Jiangsu, China
4,4-disubstituted-2-aminomethyl oxetanes are useful building blocks in medicinal chemistry. Previously they were prepared from the corresponding hydroxymethyl oxetanes in our lab, whose syntheses were plagued by use of organotin reagent and presence of tetrahydrofuran impurity. We have hence developed an improved synthesis of those compounds. In our approach, intermediate epoxide 3 was opened with dibenzylamine instead, and the resultant diol was then converted to oxetanes in good overall yield.

Figure 1: Syntheses of 4,4-disubstituted-2-aminomethyl oxetanes

MEDI 97

Syntheses of 2-fluoromethyl N-containing heterocycles

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We have developed a convenient synthetic method to convert 2-hydroxymethyl groups on some nitrogen-containing saturated rings, such as pyrrolidine, piperidine and piperazine, to 2-fluoromethyl groups with good to excellent yields. Formation of ring enlargement byproduct was not observed with our method, which is common with typical fluorination reagent such as DAST.
Methicillin-resistant Staphylococcus aureus (MRSA) is a major challenge facing public health around the world. The adverse effects of existing treatments and the appearance of strains resistant to them give rise to the urgent need to design new drugs against MRSA. To this end, one strategy is to obtain inhibitors of key enzymes for bacteria survival. In this context, the enzymes of shikimate pathway, a crucial route in bacterial metabolism but absent in humans, have been considered as good targets. Under this point of view, the aim of this work was to find potential inhibitors of shikimate kinase from MRSA (SaSK), an enzyme that catalyzes the conversion of shikimate to shikimate-3-phosphate in the shikimate pathway. To do this, a natural products database was studied applying virtual screening strategy using Autodock Vina software. The grid box was determined centering Arg120, an amino acid that participates in shikimate binding during enzyme catalysis. Additionally, physicochemical druglike properties and toxicological parameters were determined using DataWarrior software. The results showed that the five compounds with the best binding energy were Galic acid, Trans-
Caffeic acid, Salicylic acid, 3,4-Dihydroxybenzoic acid, Trans-Ferulic acid, and with values of -6.6, -6.6, -6.4, -6.2, and -6.2 Kcal/mol, respectively. Four of them made hydrogen bond interactions with residues that participates in enzyme catalysis, such as Asp37. Furthermore, the physicochemical evaluation indicated that these compounds supports the characteristics to be considered as potential drugs. However, according to the predicted toxicological analysis, all molecules presented a high mutagenicity potential, only Trans-Ferulic acid and Trans-Caffeic acid showed the possibility to be tumorigenic, Salicylic acid to be irritant, and Galic acid, Salicylic acid, and Trans-Ferulic acid, presented effects on reproduction. In conclusion, the natural products reported here have the potential to inhibit SaSK and can be considered as hits to design inhibitors that serve as leads to obtain new drugs against MRSA.

MEDI 99

Exploration of target space of electrophilic quinazolines

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One of the most critical aspects of drug discovery is to develop ligands that are not only potent but also selective for target proteins. We seek to utilize aspects of traditional medicinal chemistry methods in combination with an emerging chemical-proteomic method in order to selectively and covalently target proteins without prior knowledge of their binding site, affinity, phenotype, etc. Our approach involves designing probes containing an electrophilic “warhead” that resides on a heterocyclic scaffold known to be a pharmacophore. These probes are equipped with a “clickable” tag, often a terminal alkyne or an azide group. The electrophilic warhead is devised to target reactive, nucleophilic amino acid residues like cysteine for covalent protein labeling when introduced into the proteome, while the clickable tag can be subsequently conjugated with a fluorophore or biotin group with Cu catalyzed click-chemistry for target visualization or enrichment.

Our lab previously synthesized an electrophilic 4-anilinoquinazoline probe, Q01 (Fig. 1), that selectively and potently bound V-ATPase, a multisubunit enzyme responsible for regulating acidity of various vesicles such as endosomes and lysosomes in cells. It was the first covalent small-molecule modulator of V-ATPase to be reported, and because of our emerging method, we have been able to study what was once a poorly understood mechanism of action owing to the limitations of conventional methods. We have expanded our approach and synthesized a panel of analogous probes that contain different electrophiles at different positions around the 4-anilinoquinazoline core in order to investigate the dependence of target space on electrophilic position (Fig. 1). We have introduced our compounds into the proteome and identified the major targets of each probe. We are encouraged to observe that a few show distinct target profiles from that of Q01. We have continued to unveil more of the chemical nature of V-ATPase, and
with our method, anticipate being able to do the same with many more proteins in the future. We believe that our chemical proteomic approach will result in the elucidation of new mechanistic, physiological, and pathological information of diverse proteins. It is an exciting and novel endeavor with great potential and promise that will employ the inter-disciplinary methods of chemical biology, biochemistry, and organic synthesis, to ultimately contribute to the larger chemical biology interface effort.

MEDI 100

Synthesis and spectroscopic identification of analgesic prodrugs attached to polyvinyl alcohol or polyvinyl phenol

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Prodrug approach deals with chemical biotransformation or enzymatic conversion or involves inactive or less active bio-reversible derivatives of active drug molecules. They have to pass through enzymatic or chemical biotransformation before eliciting their pharmacological action. It is estimated that about 10% of the drugs approved worldwide can be classified as prodrugs. Prodrugs, which have no or poor biological activity, are chemically modified versions of a pharmacologically active agent, which must undergo bio-reversible transformation in vivo to release the active drug. They are designed in order to improve the physicochemical, biopharmaceutical and pharmacokinetic properties of pharmacologically potent compounds. Several carboxylic group-containing drugs are changed to the corresponding acid chlorides. The latter is then reacted with the alcoholic polymer; namely, polyvinyl alcohol or polyvinyl phenol. This resulted in an ester prodrug that is purified and fully identified using Infrared, Proton and Carbon-NMR Spectroscopy, and Mass Spectrometry.

MEDI 101

Pharmacophore-based virtual screening for finding potential inhibitors of shikimate kinase from methicillin-resistant Staphylococcus aureus

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Nosocomial infections are an important public health problem, they pose a major challenge for treatment and are associated with an increased morbidity and mortality. Methicillin-resistant Staphylococcus aureus (MRSA) is a major human pathogen and one of the most dangerous bacteria found in health care facilities. Due to adverse effects and resistance to the current treatments, it is necessary to develop new drugs against this bacterium. The enzymes of shikimate pathway, an important route for bacterial survival and absent in humans, such as shikimate kinase (SaSK), which catalyses the conversion of shikimate to shikimate-3-phosphate, are considered as
excellent targets to search new inhibitors that can help the development of new drugs. With the aim to find new potential SaSK inhibitors, a structure-based pharmacophore modeling approach was applied using LigandScout v4.3 software and the Sigma-Aldrich small molecules database. After pharmacophore filtering, a virtual screening was applied using Autodock Vina taking Arg 120 as the grid box center. Toxicological and druglike properties were also determined via DataWarrior software and Molsoft server (http://www.molsoft.com). The results showed that the top 5 molecules with the best binding energy were SR 1001, Uridine-5'-triphosphoric acid, Cytidine-5'-triphosphate, (S)-3-(Benzyloxy)-2-hydroxypropyl 4-methylbenzenesulfonate, and Inosine 5'-triphosphate with binding energies values that ranged from -7.2 to -6.6 kcal/mol. Hydrogen bonds and cation-π interactions were formed between these molecules and important residues like Asp37, Glu41, Arg120 and Arg138. Druglike properties predicted indicated that the selected compounds showed the characteristics to become potential drugs and the toxicological analysis revealed that most of the compounds had no risk for toxic effects, only SR 1001 presented a low risk for reproductive adverse effects. In conclusion, these molecules have the potential to inhibit SaSK and can be considered as hits to obtain new drugs against this bacterium.

MEDI 102

Structural characterization of capillary morphogenesis gene 2 inhibitors

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Capillary Morphogenesis Gene 2 (CMG2) plays a significant role in mediating angiogenesis. Competitive inhibition of CMG2 binding to its physiological ligands results in a substantial reduction of pathological angiogenesis versus the growth factors as observed in models of corneal neovascularization, endothelial tube formation, and endothelial cell migration. CMG2 is one of the proteins which is produced in cases of cancer. CMG2 overexpression is associated with increased tumor grade and poor patient survival. Peptides and small molecules have been developed which bind with CMG2 to block its functionalities in cancers. The ability to block the functionality of CMG2 will hopefully be used to treat the cancer. Atomic-level structures of CMG2 bound to the peptides will give us more insights about their binding modes. CMG2 will be purified by Affinity Chromatography and Size Exclusion Chromatography. Crystallization conditions are known and crystallization will be achieved using sitting drop Vapor diffusion. Then, the crystals will be inspected by X-Ray diffraction. The novelty of this research is to use structure-based drug design. Having pictures of CMG2 bound with peptides will allow us to modify the peptides to function better in blocking the CMG2 proteins.

MEDI 103

New methodology for the synthesis of sirtinol analogues a Sirtuin 2 inhibitor as antichagasic candidates
Neglected diseases are caused by infectious and parasitic agents. These diseases are prevalent in tropical and poor areas and in developing countries have been presenting medical relevance. Among the neglected diseases, Chagas disease is endemic in Latin America and has spread to other continents by migratory movements. The research of new antichagasic agents at the national and international levels and in the majority carried out academically, no therapeutic alternatives for the disease have been found yet, thus persisting the urgent need for the discovery and development of new antichagasic agents. The currently strategy in drug discovery involves the choice and selection of specific biochemistry target. In case, sirtuin 2 (silent information regulator 2 – Sir2) were shown to be essential for the in vitro growth of \textit{T. cruzi}. Sir2 inhibitors like sirtinol showed efficacy against \textit{T. cruzi} growth. This work presents a comparative of methodologies to synthesize EFsi1 – analogue of sirtinol as a potential antichagasic candidate. The reaction to obtain this product is performed in two stages and in this new proposal it is performed one-pot, using green chemistry principles (scheme 1).

For this purpose, a Microwave Synthesis Reactor - Monowave 300 – Anton Paar and ultrasonic cleaner 40 khz Biobase-UC-10A were used. The synthesis on the bench was also performed to establish a comparison. The best result was obtained in microwave with 64% yield in 40 min of the reaction than in the bench with 25% yield in 16 horas of the reaction.
**MEDI 104**

*pro*-Pyrrolobenzodiazepine (*pro*-PBD) bioconjugates, part 5: Design and synthesis of *bis*-pro-PBD conjugates containing a self-immolative linkers that release active drug via intramolecular diazepine-ring-closure

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Pyrrolo[2,1-c][1,4]benzodiazepines (PBDs) are a group of antitumor antibiotics produced by various actinomycetes bacteria which have emerged as some of the most potent chemotherapeutic compounds. PBD dimers (bis-PBDs) arrest DNA replication by selectively alkylating and crosslinking DNA at sequence specific sights found in the DNA minor groove. Due to their potent cytotoxicity and antitumor activity, PBDs have been widely utilized as payloads in antibody drug conjugates (ADCs). However, when used as stand-alone therapeutics or as the warhead for small molecule drug conjugates (SMDCs), the reactive imine functionality has the potential to cause off-target toxicities. As an elegant solution to this undesired effect, a diazepine-ring-opened conjugated prodrug was developed. Our *pro*-PBD employs an aromatic amine and an oxime ether in lieu of the reactive imine found in the active drug.

Our strategy utilizes either the *pre*-N-10 aromatic amines or alternatively the oxime-ethers as attachment points for reduction-sensitive self-immolative linkers to form *bis*-pro-PBD conjugates. By attaching a folic acid (FA) via a water-soluble spacer to a cleavable linker, we can direct our novel prodrug conjugates towards folate-receptor(FR)-over-expressing cancer cells. Once the prodrug (pro-PBD) conjugate binds to a targeted cell, the conjugate would be expected to experience FR-mediated endocytosis resulting in on-site-generation of bis-PBD which should passively diffusion into the cell. To improve the range of applications for this new class of latent DNA-alkylators, we modified their linkers to tailor the kinetics of prodrug release and drug formation. The design and synthesis of these warheads and linker systems utilized in a novel class of Small Molecule Drug Conjugates (SMDCs) for targeted cancer therapies will be discussed in the presented poster.

**MEDI 105**

Glycone manipulation as a general strategy of optimizing the drug properties of the phyllanthusmin class of natural products

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Natural products have proven to be useful lead compounds in part due to their densely functionalized cores and abundant chirality. For example, arylnaphthalene lignan lactone containing natural products have been recognized as an important class of compounds due to their cytotoxicity against an array of different human cancer cell lines and, therefore, have been the focus of a number of drug development studies. The phyllanthusmins represent a specific subclass of arylnaphthalene lignan lactones isolated from the plant *Phyllanthus poilanei*. These natural products and structurally related synthetic analogues show moderate to good antiproliferative activity against ovarian cancer cell lines and have previously displayed anticancer activity in colon cancer cell lines. Preliminary structure-activity relationship studies on this class of compounds focused on functionalization of the diphyllin portion of the phyllanthusmins. Our current research, however, has focused on selective functionalization of the glycone portion of the compound, specifically through further development of the galactose moiety of PHY-34, an analogue that has shown potent in vivo efficacy in an OVCAR-8 xenograft model.

**MEDI 106**

**Carbamate-benzoxaborole compounds as potent and broad-spectrum antifungal agents targeting protein prenylation**

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With the emergence of widespread fungicide-resistance in crop protection, and the increasing morbidity and mortality of fungal infections due to drug-resistance in human health, new antifungal agents with unexploited modes-of-action are urgently needed. To
address this need, we now report the discovery and characterization of a novel class of benzoxaboroles with carbamate substituents that demonstrate potent and broad-spectrum activity against both plant and human fungal pathogens. To define mechanism of action, two potent representative compounds, BN845 and BN880 were used to isolate and whole-genome sequence mutants in the genetically tractable model fungus, *Saccharomyces cerevisiae*. Haploinsufficiency sensitivity testing, and drug synergy assays were also performed. Resistant clones with mutations at the active sites of two enzymes in the protein prenylation pathway were identified and confirmed by gene-swapping. Molecular modeling analysis supports these enzymes as likely targets of this compound class and additionally suggests that the boron group plays an important role interacting with the catalytic metal ions at the active sites of the enzymes. This study showcases a novel mechanism for boron-containing antifungal compounds and demonstrates that carbamate-substituted benzoxaboroles have significant potential as antifungals for crop protection, and as novel therapeutic agents for human fungal infections.

MEDI 107

**Novel macrocyclic lipopeptides as serine protease inhibitors targeting *Escherichia coli* type I signal peptidase**

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In the fight against antibiotic resistance the search for novel drug targets is of high priority. Bacterial type I signal peptidase of *Escherichia coli*, known as LepB, is a potential target for the development of novel antibiotics. Recently, a set of cationic lipopeptides have been discovered that potently inhibited the LepB enzyme and showed good antimicrobial activity. However, the cytotoxicity and hemolytic profiles of these compounds were not optimal, suggesting that further optimization is needed to develop a promising lead compound. Therefore, we have developed novel macrocyclic lipopeptides, linking P2 and P1’ by a boronic ester warhead, capable of inhibiting *Escherichia coli* type I signal peptidase (*EcLepB*) and exhibiting good antibacterial activity. Structural modifications of the macrocyclic ring, the peptide sequence and the lipophilic tail led us to 14 novel macrocyclic boronic esters. Among the synthesized macrocycles, potent enzyme inhibitors in the low nanomolar range (e.g. compound 42f, *EcLepB* IC$_{50}$ = 29 nM) were identified also showing good antimicrobial activity (e.g. compound 42b, *E. coli* WT MIC = 16 µg/mL). The unique macrocyclic boronic esters described here were based on previously published linear lipopeptidic *EcLepB* inhibitors in an attempt to address cytotoxicity and hemolysis. We show herein that structural changes to the macrocyclic ring influence both the cytotoxicity and hemolytic activity suggesting that the P2 to P1’ linker provide means for optimizing off-target effects. However, for the present set of compounds we were not able to separate the antibacterial activity and cytotoxic effect.
MEDI 108

Development of a prodrug strategy for CNS delivery of nuclear receptor modulators

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Neurodegenerative CNS diseases remain challenging to target therapeutically due to the restriction of drug-like molecules from passing through the blood-brain barrier. Nuclear receptors are important drug targets in the CNS, however, many of their modulators contain polar functional groups like carboxylates for target engagement and thus are inhibited from crossing the blood-brain barrier. Additionally, isosteric replacement of these groups can improve brain penetration, but adverse peripheral effects mire their advancement in the clinic. Herein is described the development of a prodrug strategy which can successfully deliver more potent modulator to the brain while attenuating peripheral exposure by conversion of the parent carboxylic acid-containing drugs into amides. These amide prodrugs not only improve blood-brain barrier passage, but are substrates for a brain-residing amidase called fatty acid amide hydrolase (FAAH) while remaining masked in the periphery. FAAH cleavage of the prodrugs increases brain exposure and brain-to-serum ratios of the parent drugs up to ~100-fold compared to administration of the corresponding parent drug. Physicochemical properties, FAAH substrate validation, and comparisons of CNS vs peripheral drug action will be presented. Our results indicate this strategy can be extended to a variety of relevant carboxylic acid-containing drug structures.

MEDI 109

Synthesis and trypanocidal activity of new N-(1H-benzimidazole-2-yl)benzenesulfonamides
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Chaga’s disease, a neglected tropical disease caused by protozoan parasite Trypanosoma cruzi, is still a major public health burden in Latin America and is emerging in other countries through the world. Moreover, no vaccine or highly effective treatments are availed. Two drugs, benznidazole and nifurtimox, have been used as trypanocidal agents, but their serious side effects and lack of availability are still a problem. In order to find a good treatment for Chaga’s disease, many researchers have been working to find a cure for this parasitic infection. In Mexico, our research group at Facultad de Química, UNAM has found a hit molecule (a substituted $N$-(1$H$-benzimidazole-2-yl)-1$H$-benzimidazole carboxamide) that has important activity against triosephosphate isomerase enzyme of $T$. cruzi; also, this molecule presents in vitro activity against the protozoan parasite. However this molecule was very insoluble, therefore we made structural modifications and synthesized a series of eight new $N$-(1$H$-benzimidazole-2-yl)benzenesulfonamides. The synthesis and the biological evaluations of this last-mentioned molecules will be presented.

MEDI 110

Synthesis and evaluation of a series of analogues to the AT\textsubscript{2}R prototype antagonist C38

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The angiotensin II type 1 receptor (AT\textsubscript{1}R) has for a long time been a target for drug therapy due to its involvement in the pathogenesis of hypertension. Even though AT\textsubscript{1}R was for a long time thought to be the only target for its endogenous ligand angiotensin II (Ang II), Ang II is also a ligand for the angiotensin II type 2 receptor (AT\textsubscript{2}R). This receptor has gained interest as a potential target for therapeutics with two clinical trials being conducted for different indications; the AT\textsubscript{2}R antagonist EMA401 in phase II trials for treatment of peripheral neuropathic pain and the AT\textsubscript{2}R agonist C21 entering phase II clinical trials for idiopathic pulmonary fibrosis. The latter, which originates from our laboratory, can be converted by shifting of the methylene imidazole group from the \textit{para} to the \textit{meta} position of the phenyl ring to yield C38 which is an AT\textsubscript{2}R selective antagonist. In our work, we have used this compound as a prototype to yield two new series of compounds, expanding our knowledge of the factors impacting AT\textsubscript{2}R affinity.
The first series explores the effects on affinity, physical and biological parameters by minor alterations of the \textbf{C38} phenyl ring, while we in the second series investigate the replacement of the benzyl imidazole head group of \textbf{C38} with bicyclic amides. One compound in this second series showed a five-fold affinity improvement in comparison with \textbf{C38}. Data from the first series of compounds was also used to propose a new model for the binding mode of analogues to \textbf{C38} using the newly published \textbf{AT}_{2}\textbf{R} crystal structure.

\textbf{MEDI 111}

\textbf{Scaffold hopping: Versatile approach to develop new ligands for Liver X Receptor}

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The liver X receptor (LXR) is a ligand-activated receptor protein that is involved with metabolic processes and is responsible for maintaining cholesterol levels in the blood and in cells. This nuclear receptor has become the subject of intense investigation in the last few years because of its potential to serve as a target in efforts to lower cholesterol levels and to starve cancer cells of cholesterol, thus killing (or slowing the growth of) these cancer cells. We have been involved in research aiming to identify novel LXR ligands that bind to the receptor very strongly. We have carried out computational investigations in order to identify new ligands with strong potential to bind LXR. The main computational tools we have used are protein-ligand docking, scaffold replacement studies. To date, we have identified three ligands, along with several methylated derivatives, that show strong potential for LXR binding. We are currently in the process of determining the synthetic route that can be followed in order to synthesize these molecules. Once this has been determined, we will synthesize these ligands and do bioassay studies in order to determine how well these ligands bind to LXR.

\textbf{MEDI 112}

\textbf{Synthesis of 2-aminooxazole inhibitors of kinase STK-16}

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Protein kinases are a class of enzymes that transfer phosphate groups from ATP to specified substrates, resulting in structural and functional modifications to substrate activity. Cell division, signaling, and metabolism are all affected by the phosphorylation of proteins via post-translational modification by protein kinases. Within the past few decades, protein kinase research has emerged at the forefront of chemical biology as
one of the primary areas of interest in drug development. An estimated total of 500 protein kinases exist in the human kinome. However, only a small fraction of these have been subjected to studies regarding biological function and therapeutic targeting. The impetus to determine the functions of various kinases lies in the potential to modulate them and thus treat various ailments, particularly cancer.

A common practice in determining the function and mechanism of a protein kinase is the synthesis and utilization of small-molecule chemical probes. These inhibitors are targeted towards a specified protein and subsequently elucidate pathways in both healthy and diseased cells. From this verification, the probe can serve as a precursor to a therapeutic drug in combating the disease in question. Our project focuses on the inhibition of kinase STK-16, an understudied serine-threonine kinase. Our goal is to synthesize a library of small molecule chemical probes that are both potent and selective inhibitors of STK-16. Previously conducted research has found that kinase STK-16 inhibition has resulted in increased cell binucleation and reduced total cell number. Considering the relationship between cell binucleation and cancer, it is suspected that STK-16 is associated in some way with cancer cells. It is our hope that a potent inhibitor may possibly lead to a new chemotherapy agent.

MEDI 113

Synthesis of benzoxazole inhibitors of kinase CK2

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Protein Kinases are enzyme catalysts that allow the transfer of phosphate from ATP to serine, threonine, and tyrosine amino acids of their respective substrate proteins. Although a large number of kinases have been discovered, the biological roles of the majority of these kinases remain unknown. This along with the fact that kinase inactivity has been strongly correlated to a number of human diseases has propelled research into better understanding kinase activity and developing small molecules that target these proteins. Success in targeting kinases is underscored by the fact that the FDA has approved over 35 kinase inhibitor drugs within the last 18 years, and many studies have demonstrated that protein kinases are one of the most effective protein targets for drug therapeutics.

Despite the breakthroughs in recent years, kinase potential still remains largely untapped, and a number of calls for contribution have been made. To answer this call, a composition of a public library of kinase activity, called the kinase chemogenomic set (KCGS), was recently disclosed to accelerate the synthesis and screening of drugs targeting kinase activity. With public access to the KCGS, many researchers are leveraging this resource to study biological function and therapeutic potential of many understudied kinases. As a part of this public effort, our group has focused on the synthesis of a benzoxazole compound that targets the kinase protein CK2. In developing a procedure for the synthesis of drugs targeting this kinase, we hope to
develop a library of potent and selective compounds that can later be screened as potential treatments for human diseases and added to the comprehensive public library of kinase inhibitors.

MEDI 114

Synthesis of cathepsin B inhibitors as a treatment targeting anthrax and ebola

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Targeting the proteins of pathogenic invaders has been a staple strategy when combating infectious disease. Inevitably, however, the pathogens develop resistance to these treatments and the subsequent rise in drug resistance has sparked numbers calls for new treatment options and strategies. Some infectious agents, however, exploit native host proteins, raising the possibility of host-orientated treatment options. Our project focuses on the inhibition of Cathepsin B, a human protease found in lysosomes that is exploited by both Anthax and Ebola. It is our hope that the development of a potent inhibitor of Cathepsin B will lead to a new host-based treatment option against these deadly infectious agents.

MEDI 115

Novel boron-enhanced compounds with broad spectrum antifungal activity

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With the emergence of severe fungicide resistance in crop protection, and the increasing morbidity and mortality of fungal infections due to drug-resistance in human health, novel antifungal agents with new mode-of-action are urgently needed. After screening the boron-containing chemical library at Boragen, we discovered a novel series of boron-containing compounds showing good antifungal activity. An in-depth structure-antifungal activity relationship was carried out, and we identified compounds with broad spectrum antifungal activities. This study demonstrates that the novel boron-containing compounds disclosed herein have significant potential as antifungals agents.

MEDI 116

Synthesis of prodrugs from a quinazoline derivative

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Cancer is a major public health problem due to its incidence worldwide. Nowadays, chemotherapy is one of the principal treatments for these ailments; 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 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. MLB13, an in-house compound, 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 117

Discovery of allosteric inhibitors of NF-κB inducing kinase (NIK)

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Dysregulated activation of non-canonical NF-κB (ncNF-κB) signaling contributes to the pathogenesis of various autoimmune and inflammatory diseases and human cancers. In the ncNF-κB pathway, NF-κB-inducing kinase (NIK) is a central regulatory component and its activity is essential for ncNF-κB activation. Consequently, selective small molecule inhibitors of NIK are highly desired as mechanistic chemical probes and potential therapeutics. Although active in mouse disease models, current ATP-competitive NIK inhibitors suffer from either off-target effects or poor drug-like properties. Allosteric kinase inhibitors are a validated approach towards achieving high selectivity for a desired kinase target, thereby overcoming limitations of ATP-competitive inhibitors. Therefore, in this project, we are developing allosteric NIK inhibitors. Through molecular dynamics (MD) simulations, we identified two putative allosteric sites on NIK that are amenable to small molecule binding. A virtual screen against these sites was performed that yielded 120 high-scoring small molecules that were subsequently screened for NIK enzymatic inhibition. Biochemical assays revealed 13 compounds that inhibit NIK enzymatic activity at or below 100 µM. Ongoing work is focused on further characterization and optimization of these hit compounds. Our novel NIK inhibitors, once fully optimized, will represent the first-in-class NIK allosteric modulators with
anticipated high selectivity for NIK and the ability to regulate aberrant ncNF-κB signaling in disease models.

MEDI 118

Structure property relationship of fluorinated carboxylic acid bioisosteres

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The strategic deployment of fluorine atoms in biologically active molecules is an increasingly common tactic in drug design and optimization. Among the different applications of fluorine in medicinal chemistry, one that continues to evolve is in the context of bioisosteric replacements. Although fluorine has long been utilized as a possible replacement for hydrogen, the incorporation of one or multiple fluorine atoms in more elaborate structural motifs can be exploited in the design of surrogate structures of several functional groups. One such example is the use of fluorine in the construction of carboxylic acid bioisosteres. To enable a direct comparison of the properties of fluorinated carboxylic acid surrogates with those of other commonly used, non-fluorinated bioisosteres we conducted a structure property relationship (SPR) study based on matched molecular pair (MMP) analyses. Different fluorine containing
carboxylic acid surrogates, including a series of fluorinated alcohols and phenols have been characterized by determining experimentally a series of physicochemical properties, such as acidity (pKa), lipophilicity (logP and logD7.4), permeability (PAMPA), as well as H-bonding.

MEDI 119

Leveraging atropisomerism to obtain a selective inhibitor of RET kinase with secondary activities towards EGFR mutants

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Aberrant kinase activity is involved in many different diseases, leading to the development of over 40 FDA approved kinase inhibitors. Due to a high degree of kinase active site conservation, most kinase inhibitors possess activities towards several kinases causing off-target side effects limiting the safety and efficacy of a potential therapeutic and its usefulness as a chemical probe. 81% of FDA approved kinase inhibitors contain at least one rotational axis between two aromatic rings. This leads to an extended form of chirality called atropisomerism, where the two different rotational conformers can either exist as a rapidly racemizing mixture or isolable enantiomers. Most bioactives, as designed, exist as a rapidly interconverting atropisomeric mixture, however, when they bind to their target active site, they tend to do so in an atropisomeric fashion. The presence of the non-relevant atropisomer via interconversion or stable racemic mixture can result in off-target inhibition.

We have leveraged atropisomerism as a design element to rapidly obtain simple, selective potent inhibitors of RET kinase, whose aberrant activation is found in subsets of breast, lung and thyroid cancers. We hypothesize that the basis of the improved selectivity is the narrowing of the accessible dihedral conformations about the atropisomeric axis. To test this hypothesis, we evaluated the lead inhibitors against EGFR mutants which bind ligands with comparable dihedral angles to RET, discovering a potent inhibitor of the vaunted triple mutant L858R T790M C797S EGFR. Importantly the (Ra)-atropisomer displayed potent cellular activities in RET and mutant EGFR driven cellular models of cancer. As more compounds are tested, we will iteratively optimize towards RET and EGFR T790M, potentially leading to valuable chemical probes and/or novel therapeutics.

MEDI 120

Benzimidazole derivatives as new potential antibacterial and antifungal agents
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The current misuse of antibiotics in the treatment of infectious diseases of different origins, including bacteria and fungi, has triggered the development of resistance by microorganisms to common therapies. As a consequence, the synthesis of new compounds with analogous activities to the commercial antimicrobials has become of great importance. Previous studies have shown that different azoles including pyrazoles and benzimidazoles with different structural characteristics can act as antibacterial or antifungal drugs. In this work, different trifluoromethyl functionalized benzimidazoles and benzimidazole iodine salts were synthesized and tested against clinical strains of Escherichia coli, Staphylococcus aureus, Candida spp and Cryptococcus gatti, in order to explore the effect of these modifications in their biological activity. These strains were shown to be resistant to common antibiotics such as ketoconazole and fluconazole for fungi and gentamicin for bacteria. These results suggest that some of the modified benzimidazoles have great potential as antibacterial and antifungal agents. Specifically, trifluoromethyl functionalized benzimidazole iodine salts inhibit the growth of Candida spp and Cryptococcus gatti and to a lesser extent inhibit the growth of Staphylococcus aureus. Further studies will be performed in order to determine the MIC in reference and clinical strains.

MEDI 121

IODVA1, a di-pyridine derivative with in vivo activity against cancer models

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Here, we report the synthesis and preliminary characterization of IODVA1, a novel and potent small molecule that is active in xenograft mouse models of breast and Ras-driven lung cancers. In an effort to inhibit oncogenic Ras signaling, we conducted an in silico screen against a Ras conformation that mimics the structure of nucleotide-free Ras in complex with Sos (Ford et al., 2005 & 2009; Soisson et al., 2001). Top scoring candidates identified in the in silico search were screened for inhibition of proliferation of A549 and H292 lung cancer cells and inhibition of colony formation of NIH-3T3 cells expressing RasG12V. NSC124205, a NCI/DTP Open Chemicals Repository molecule, was among the top candidates that fulfilled both criteria. Biochemical analysis showed that even though NSC124205 is potent on several cell lines harboring active Ras, its mechanism of action is Ras-independent. Mass spectroscopy analysis revealed that NSC124205 was a mixture of at least three compounds. Attempts to identify and synthesize the active ingredient in NSC-124205 yielded IODVA1. IODVA1 decreased
proliferation and actin polymerization and filopodia formation in MDA-MB-231. Compared to vehicle treated, tumors of breast cancer MDA-MB-231 and lung cancer H2122 cells xenograft mice significantly decreased when treated with IODVA1. Immuno-histochemistry analysis of tumor sections suggests that cell death occurs by increased apoptosis. Therefore, IODVA1 holds promise as a therapeutic agent to inhibit tumor growth.

MEDI 122

Design, synthesis, and biological evaluation of the inhibitors of fatty acid binding protein 5 (FABP5) as next-generation therapeutics for chronic pain and inflammation

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Fatty Acid Binding Protein 5 (FABP5) is a tissue specific transporter protein, expressed in cells of the central and peripheral nervous system, which facilitates the diffusion of endocannabinoids, N-acylethanolamides, and other lipids within the cytosol. The catabolism of endocannabinoid, Anandamide (AEA) is aided by FABP5 activity, and the increased levels of AEA act on cannabinoid 1 (CB1) receptors, eliciting analgesic and anti-inflammatory effects. Thus, FABP5 shows promise as a novel protein target for sustainable therapy for chronic pain and inflammation. Previous work by our group has identified SB-FI-26, a 1-naphthyl α-truxillic acid monoester (TAME), as a biologically active inhibitor of FABP5, exhibiting analgesic and anti-inflammatory effects in mouse models. Extensive SAR studies have been carried out to identify more potent and selective analogs of SB-FI-26, such as SB-FI-102 and SB-FI-103. In silico techniques such as docking and molecular dynamics simulations have been used to predict the affinity and stability of potential drug candidates, as well as elucidate the interactions of well performing modifications. X-ray co-crystal structures of SB-FI-26 with FABP5 and FABP7, recently determined by us, serve as excellent models for these calculations and design. A co-crystal structure of FABP3 is also available with natural ligand oleic acid bound.

Our models have disclosed structural and physicochemical features which improve potency in FABP5 and exhibit selectivity against FABP3 and FABP7, promoting the design and synthesis of novel analogs. Herein, we will report a new series of potent TAME-based FABP5 inhibitors, their predicted efficacy and pharmacological properties, chemical synthesis, biological evaluations and SAR.
Beyond the traditional antibacterial uses, aminoglycosides have been explored for their unforeseen applications, including potential treatment for genetic neural disorders, diseases associated with mutations of gap junction proteins and fungal infection. Among these novel applications of aminoglycosides, chemical modification of naturally occurring aminoglycosides is often necessary. One of such modified aminoglycosides, TC007, has been identified as a potent lead in the treatment of spinal muscular atrophy (SMA). However, the synthesis of 3-aminoglucopyransyl donor, essential for the synthesis of this compound is challenging, it either involves metal-based reagents or requires more than ten synthesis steps with a very poor overall yield. Therefore, there is a need for improving the synthesis of 3-aminoglucopyransyl donor that is crucial for the preparation of TC007. Many naturally occurring or synthetic bioactive compounds contain 3-aminoglucopyranosyl moieties. An alternative approach is to utilize natural products containing 3-aminopyranose. Herein, the acid catalyzed hydrolysis of kanamycin is utilized to obtain 3-aminoglucopyranose. The synthesis of the donor by this alternative method reduce the synthesis steps resulting in an overall improved yield of TC007.
Schistosomiasis, also known as snail fever and bilharzia, is a chronic parasitic disease caused by trematode flatworms of the genus *Schistosoma*. The disease affects hundreds of millions of individuals worldwide and it ranks among the most prominent neglected diseases due to the lack of interest from pharmaceutical companies. In the absence of a vaccine, currently treatments rely on a single agent, praziquantel, which does not prevent reinfection and the emergence of drug resistance is a concern. The potential loss of the only effective available schistosomicidal drug underscores the need of new/alternative treatments. Using *in vitro* whole-organism screens of *S. mansoni*, we evaluated the anti-schistosomal activity of several representatives from a compound collection of tubulin/microtubule-interacting molecules, including the natural products, paclitaxel, vinblastine, colchicine and epothilones, as well as non-naturally occurring small molecules. The screening and selection of compounds, which was based on both qualitative and quantitative assessments of anti-schistosomal activity led to the prioritization of a series of phenylpyrimidines (Figure 1) with promising parasiticidal activity against both schistosomula and adult worms.

The design, synthesis and evaluation of a series of phenylpyrimidines congeners leading to a characterization of the structure anti-schistosomal activity relationship will be presented.

**Figure 1.** Structure-activity relationship studies of phenylpyrimidines.
Design and synthesis of tri-aryl methyl amine compounds for biological evaluation as anti-infective agents

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Clotrimazole is an antifungal medication commonly prescribed for the treatment of yeast infections and oral thrush. Its resonating aromatic rings and electron withdrawing group, a halogen, significantly contributes to its unique chemical structure and overall medicinal success. To expand on this pharmaceutical lead molecule, our lab is synthesizing a focused library of tri-aryl methyl amine compounds in order to foster possible anti-infective drug candidates that will inhibit the growth of various pathogenic organisms. Our lab has previously used similar tri-aryl methyl amine compounds to test protein inhibition and aggregation which has led to the creation of several successful lead molecules. This library of molecules will be synthesized utilizing similar organic chemistry practices that were conducted in our lab for the first tri-aryl methyl series of compounds. These methods rely on synthetic knowledge of various reaction mechanisms and purification techniques. Upon the initial development of the first generation of tri-aryl methyl amine molecules, they will be sent to our Biological collaborator, Dr. Tricia Van Laar, who will conduct biological assay studies within her Microbial Lab at CSU Fresno. The biological assays will involve screening these molecules against several strains of bacteria in order to assess their potential activity as anti-infective agents. Data will be then revisited in our lab to refine and expand on possible lead molecules via Structure-Activity Relationship (SAR) studies in order to develop an efficient anti-infective drug that can inhibit one or several strains of bacteria. The mechanism of pathogenic inhibition will also be determined once a possible drug candidate is found. This poster presentation will describe the SAR study of this collaborative biomedical project that’s being conducted at CSU Fresno.

MEDI 126

Design, synthesis, and evaluation of GUNW-3 as a brain-targeting agent

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Brain disease treatment has been hampered by a highly selective semipermeable barrier called the blood-brain barrier (BBB). The BBB protects the brain by restricting the entry of endogenous and exogenous toxins. Most therapeutics are prevented from passing through the BBB resulting in a treatment failure of brain diseases.

Various transporters and receptors are located in the BBB helping transport needed substances to the brain such as nutrients, amino acids, and peptides or interacting with
a ligand to play a cellular function. Ligands for some of these transporters or receptors have been used as brain-targeting agents to improve drug delivery to the brain. Glutathione (GSH) is an endogenous tripeptide. It enters the brain by a sodium-dependent GSH transporter that is highly distributed over the BBB. GSH has been found to be a good brain-targeting ligand.

In this poster, we would like to present the design, synthesis, and characterization of GUNW-3 as a brain targeting agent. GUNW-3 was synthesized in 4 steps in an overall 60% yield. The brain-targeting ability of GUNW-3 was demonstrated by its ability to deliver effectively liposomes and micelles to the brain. The preparation and characterization of GUNW-3 liposomes and GUNW-3 micelles will be presented. Our preliminary studies with mice through in vivo bioimaging technique using near-infrared dye DiR revealed that the GUNW-3 liposomes improved the brain delivery of liposomes by 21 folds. More impressively, GUNW-3 micelles demonstrated an even better and lasting brain-targeting effect than GUNW-3 liposomes with a minimal distribution in the liver. GUNW-3 is a promising brain-targeting agent.

MEDI 127

Diversity oriented synthesis encoded by deoxyoligonucleotides

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DNA-Encoded Libraries (DELs) have proven to be powerful hit-generation tools; however, traditional DEL libraries are dominated by planar C(sp\textsuperscript{2})-rich compounds that lack the stereochemical and structural diversity found in diversity-oriented synthesis (DOS) libraries. We seek to combine the unmatched efficiency of the DEL screening platform with the chemical richness of a DOS screening collection, in an approach we name DOSEDO: diversity-oriented synthesis encoded by deoxyoligonucleotides. We are pursuing three complementary approaches for DOSEDO library production: 1) adapting existing DOS scaffolds from the Schreiber lab for incorporation in our libraries; 2) developing new synthetic pathways for generating diverse DEL-compatible scaffolds off-DNA; and 3) developing new DNA-compatible reactions for generating scaffold diversity on-DNA. In this poster, the first two approaches we have taken towards the
production of our DOSEDO library will be presented. Upon completion, we will be making our DOSEDO library an open-source screening tool that the academic community will be able to freely access. Our goal is to enable the cost-effective discovery of high-quality chemical matter and hope to introduce the ACS community to this upcoming resource.

**MEDI 128**

**Synthesis and evaluation of small molecule scaffolds as potential protein-protein interaction inhibitors to prevent gankyrin-MDM2 binding**

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Tumor suppressor proteins, such as p53 and RB play an important role in suppressing abnormal cell proliferation. Regulation of the levels of these proteins is linked to the activity of gankyrin, an ankyrin-repeat protein that is overexpressed in various tumor types. It has been shown that gankyrin binds to MDM2, an E3 ligase, and enhances the proteasomal degradation of p53 through gankyrin-MDM2 interaction. The overexpression of gankyrin results in decreased cellular levels of tumor suppressors, including p53, and promotion of tumorigenesis. Based on this observation, development of small molecules to target gankyrin-MDM2 interaction has been identified as an attractive strategy. A recent study has disclosed the discovery of a small molecule (cjoc42) that binds to gankyrin at the proposed MDM2 binding region. Our research lab is developing structurally novel small molecule scaffolds that are likely to interact with the concave face of gankyrin in a similar manner to cjoc42. Our synthetic compounds contain an ‘aryl-heteroaryl’ fragment that can be elaborated into complex structures to optimize the binding interactions. As an initial phase of our project, we have synthesized a library of ten novel small molecules to study their affinity towards gankyrin. We are utilizing a computational approach to better understand the binding interactions, and a thermal shift assay to determine the binding affinity of these small molecules towards gankyrin. In additional to binding affinity determination, we are testing these compounds against two different cancer cell lines (breast cancer and lung cancer cell lines) to test their ability to suppress growth. We also plan to profile the expression of p53 and RB, the two key tumor suppressors in those cells treated with proposed compounds that exhibit strong binding affinity to gankyrin. Based on our preliminary results, a second library of analogs will be designed and synthesized for further investigations. Since, a very few chemical scaffolds have been studied as potential protein-protein interaction inhibitors to rescue the tumor suppressors from gankyrin, our research outcomes will provide valuable data to develop novel classes of protein-protein interaction inhibitors.

**MEDI 129**

**Use of neomycin as a side chain for phenanthroline based G-quadruplex binding ligands and telomerase inhibitors**
G-Quadruplexes are unique non-canonical nucleic acid secondary structures formed by stacking of G-tetrads in the presence of monovalent cations, abundant in replication origins, gene promoters, and ends of the chromosomes. There are more than 370,000 putative G-quadruplex forming sequences in the human genome. High conformational variability is present in the G-quadruplexes depending on the sequence, loop length and bulges. The facilitation in the formation and stabilization of G-quadruplexes by small molecules in the gene promoter regions of oncogenes and ends of the chromosomes can be a promising therapy for cancer remediation. Most of the G-quadruplex (G4) binding ligands contain an extended planar aromatic surface that maximizes the stacking with the end G-tetrad in a G-quadruplex. However, this common feature also reduces the G4 ligands’ ability to bind to different G-quadruplex conformations selectively. Introducing side chains to G4 ligands could be a suitable approach to enhance their binding specificity. In the present work, we synthesized two conjugates by coupling an aminosugar (neomycin) side chain to a known G4 ligand (phenanthroline) with different linker lengths. Results from thermal denaturation monitored by CD suggest that one of the conjugates exhibits a large synergistic effect on the binding affinity to the hybrid-type G-quadruplex conformation. Interestingly, the binding of the conjugates to G4 does not require metal ions such as Ni(II) and Pt(II) for complexation of phenanthroline. The data is consistent with the binding affinity measurements using isothermal titration calorimetry and ESI mass spectrometry. The conjugates inhibited the activity of human telomerase at the submicromolar concentrations. Length of the linker found to have a profound effect on the binding affinity and conformation selectivity of the conjugates toward G4.

MEDI 130

**In silico** screening and synthesis of 2,5,6-trisubstituted benzimidazoles as a new class of antitubercular agents targeting FtsZ

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Multi-drug resistance in *Mycobacterium tuberculosis* (*Mtb*) remains a prevalent threat to public health. Hence, it is imperative to discover novel drug targets. FtsZ, an essential protein of bacterial cytokinesis, has emerged as a validated target for antibacterial therapy and the inhibition of FtsZ assembly has shown to affect the cell division process. In our laboratory, we have successfully designed and synthesized a novel series of trisubstituted benzimidazoles that displayed excellent antitubercular activity by inhibiting FtsZ. Based on the SAR studies, a new series of 2,5,6-trisubstituted benzimidazole library containing a dimethylamino group at the 6-position and various
modifications at the 2- and 5-positions was designed and synthesized. Further studies to design new and more efficacious trisubstituted benzimidazole inhibitors of \textit{Mtb}-FtsZ with promising pharmacological properties, \textit{in silico} methodologies such as 3D-QSAR, molecular docking, and prediction of ADMET properties were performed. Several compounds that displayed better docking scores than the previous lead compound SB-P17G-A38 were identified. The results of the \textit{in silico} screening and predictions along with the synthesis of the new compounds will be presented.
**MEDI 131**

**eIF4E mRNA-cap-competitive covalent inhibitors: Design, synthesis and effectiveness**

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Disclosed here are a series of novel cap-competitive covalent inhibitors of eukaryotic initiation factor 4E (eIF4E) that display potent mass modification, efficacy and target occupancy of eIF4E compared to their non-covalent counterparts 7-methylguanosine monophosphate (m7-GMP) and compound 1. eIF4E plays a central role in gene translation and protein synthesis in eukaryotic cells and is associated with the proliferation and growth of tumors, due to the observed over-expression of eIF4E in multiple tumor types. Through the use of modeling, x-ray crystallography and exploratory covalent lysine warhead chemistry, we were able to structurally modify compound 1 to optimize the interaction between lysine 162 and various warheads, while also attempting to improve potency.

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**MEDI 132**

**Light-activated, targeted treatment of traumatic brain injury**

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Every year large numbers of people are affected by traumatic brain injury (TBI), caused by physical activities or accidents. Although the majority of TBI patients have the mild form of this condition, over time numerous TBI victims develop secondary TBI damage that can last for years and lead to further neuronal damage. Despite the large impact of TBI, there is a lack of available treatments specifically for TBI. Given the difficulty to determine the specific location in the brain where the major damage occurs, TBI remains difficult to fully diagnose or treat, and currently there are no FDA-approved therapeutics for TBI.

Although a variety of medical interventions are used to treat TBI, there is a major unmet need for a safe and effective treatment of TBI soon after the primary injury, in order to prevent the neuroinflammatory cascade responsible for secondary injury to the affected sites in the brain. Thus, there is a major unmet need for a safe and effective treatment of TBI shortly after the primary injury to prevent the neuroinflammatory cascade responsible for secondary injury. Although a variety of medical interventions are used to treat TBI, there are currently no FDA-approved therapeutics for targeting these mechanisms.

In order to address the challenge for the timely treatment of TBI, we have developed a novel strategy for directing therapeutic agents to TBI sites, without the need to first determine the precise site of TBI activity in the brain. Our approach is based on the use of a near infrared light-activated system, that delivers known TBI therapeutics selectively at the TBI-affected sites. Through the timely treatment of TBI, it is likely that the secondary mechanisms that lead to further neuronal damage would be diminished or avoided.

MEDI 133

Atropisomerism and PROTACs as strategies towards increased potency and selectivity of analogs of common kinase inhibitors

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Kinases are enzymes that catalyze the addition of phosphate groups from high-energy ATP molecules to other molecules, causing proteins in the cell to become either active or inactive. Kinases are important because they control most biochemical pathways and if mutated they can lead to serious diseases such as cancer. Therefore, many medicinal chemists focus on designing kinase inhibitors that mimic ATP to inhibit mutated kinases.
and hopefully treat diseases caused by malfunctioning kinases. However, due to many kinases having very similar active sites, many inhibitors have off-target inhibition which can lead to numerous side effects.

Due to modern drug design, small molecule inhibitors contain many sp2-sp2 bonds, leading to instances of atropisomerism. Atropisomerism is a form of chirality that arises from hindered rotation about a bi-aryl bond. Kinase inhibitors bind to kinases in an atroposelective fashion with one enantiomer being the active conformer and the other enantiomer possibly binding off-target and leading to poor selectivity and potentially undesirable side effects.

In the Gustafson Lab we focus on using atropisomerism as a tool to design selective kinase inhibitors. The Gustafson Lab has successfully designed a kinase inhibitor that is selective to the RET kinase but in order to see the scope of this strategy, we will apply it to other kinase inhibitors and work to improve their potency and selectivity against other kinases such as BTK, mTOR, and Src. We are currently in the process of synthesizing the scaffolds for these other kinase inhibitors. These kinase inhibitors can also be used to create bifunctional molecules called PROTACs which involve the recruitment of an E3 ligase, a protein that marks other proteins for degradation by the proteasome. These specialized molecules can be used not only to inhibit the function of problematic proteins, but fully degrade said proteins.

MEDI 134

Design, synthesis and biological evaluation of new anti-Candida agents

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The opportunistic pathogen Candida albicans is the second etiological agent of vaginitis. Candidiasis causes inflammation of the genital tract, which has been associated with complications of pregnancy and increased risks of stillbirth or neonatal death. Also, it is known that 75% of women have at least one vaginal infection caused by this yeast at some point in their lives. Treatment with azoles results in relief of symptoms, but it is only effective in 80%–90% of cases. A clear reflection of many shortcomings of current antifungal therapy includes the limited approved antifungal agents, toxicity and resistance.

As part of our efforts to find new anti-Candida agents, we design by bioisosteric replacement and molecular simplification a series of sixteen 2,3-diphenyl-2H-indazole, 3-phenyl-1H-indazole and 1H-pirazole derivatives. The synthesized compounds were tested against two strains of Candida (C. albicans and C. glabrata) using the cylinder-plate method. Compounds showed promising activity in preliminary assays.
MEDI 135

Co-crystal structure-based drug design and synthesis of plinabulin derivatives

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Plinabulin is a synthetic analog of marine natural product. The combination of plinabulin and docetaxol has been pushed into Phase III clinical trials to treat non-small cell lung cancer (NSCLC). MBRI-001, a deuterium-substituted plinabulin derivative, is under preclinical phase on account of its better pharmacokinetic and similar antitumor effects in comparison with plinabulin. Based on SAR study, plinabulin derivative Compound 8 (Fig. 1) showed better inhibitory activity on tubulin polymerization than
plinabulin. To get insight into the binding mode, the co-crystal structure of Compound 8 in complex with tubulin (PDB: 5YL4) was made and analyzed. The analysis results indicated that the hydrogen bonds with Glu198, Asn165 and Val236, the π-π interaction with Phe167 and the H-π interaction with Phe20 probably contribute to the binding affinity (Fig. 2). Based on the Compound 8-tubulin co-crystal structure, we further designed and synthesized a series of plinabulin A/B/C tricyclic modified derivatives. One novel phenoxy substituted plinabulin derivative Compound 3-6o (4.0 ± 0.43 nM) had been observed having similar cytotoxicity activity against NCI-H460 cancer cell in comparison with Compound 8 (4.1 ± 0.60 nM). In addition, Compound 3-6o had better cytotoxicity activity against HepG2/HCT116/MCF-7/Hela cancer cell lines than plinabulin (Fig. 3).

MEDI 136

Selective bromodomain inhibition of BRD4-D1 using trisubstituted-imidazoles and triazoles

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As regulators of transcription, proteins that interpret post-translational modifications to N-terminal histone tails through molecular recognition are known to be essential for maintaining cellular homeostasis. When dysregulated, these ‘reader’ proteins become drivers of disease. In the case of bromodomains, which recognize N-e-acetylated-lysine, developing domain selective inhibitors has been a significant challenge to the field. Using a Protein-observed 19F NMR screen, we previously identified N-terminal Bromodomain and Extra Terminal (BET) bromodomain selectivity (BRD4(D1), Kd = 1.2 µM, BRD4(D2) > 100 µM) of a tri-substituted imidazole MAP kinase inhibitor series
(p38α, Kd = 470 pM). Affinity for the BET family of bromodomains was characterized using a fluorescence anisotropy method to displace fluorescently labeled pan-BET inhibitor, BI-6727. In further support of bromodomain inhibition, this series of molecules suppressed production of the c-Myc oncoprotein in multiple myeloma cells. Our ongoing medicinal chemistry efforts are evaluated in a cellular thermal shift assay, where in cell target engagement of our lead molecule with BRD4 and p38α is tested. From these studies, we have identified scaffolds without kinase activity as selective inhibitors of BRD4(D1), the aberrant functions of which play a key role in cancer and inflammatory signaling.

MEDI 137

Identification of protein-RNA interaction inhibitors using a simple fluorescence intensity-based binding assay

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Protein–RNA interactions play critical roles in diverse cellular pathways including RNA splicing. Dysregulation of the interaction can lead to develop and progress various diseases such as cancer and neurodegeneration. Despite the importance of understanding protein–RNA interactions, their functions and dynamics have still largely remained to be elucidated. The identification of new chemical modulators of protein–RNA interactions will be worthwhile, and developing new methods for detecting protein–RNA interactions is the key step. Therefore, we developed a simple fluorescence intensity-based binding assay using environmentally sensitive organic dyes. For oncogenic Lin28–let-7 microRNA interaction as a model system, we validated that the assay specifically show fluorescence intensity changes upon binding between Lin28 and let-7. By performing the assay in high-throughput manner, we newly identified a flavone-based Lin28 inhibitor. Biophysical analysis revealed that the inhibitory effect was mediated by specific binding to Lin28. The inhibitor successfully increased the mature let-7 miRNA levels and decreased the expression of their target genes. We expect that our assay development approach can be applied to other protein–RNA interactions for identifying small-molecule modulators.
MEDI 138

Preparation of intermediate of asenapine

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On August 14, 2009, the FDA approved the Asenapine maleate for emergency treatment of adult schizophrenia, mania or mixed attacks with type I bipolar disorder. In addition an alter native process for the conversion of the mixture of cis- and trans-lactam into the desired trans-isomer has been developed with good yield.

MEDI 139

Label-free target identification reveals mode-of-action of small molecule adiposity modulator

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Adipocyte functions as energy storage and a regulator of metabolic homeostasis by secreting several adipokines. However, the adipokines are abnormally secreted under
excess lipid accumulation, called obesity, leading to metabolic dysfunction and insulin resistance. Hence, there have been urgent needs for medication for treating obesity and obesity-related diseases.

To discover small molecule adiposity modulator, we performed image-based high throughput screening using fluorescent molecule, SF44, which can selectively stain cellular lipid droplet. Among library of ~5000 small molecules, we discovered SB1501, which has the most effective lipid-decreasing effect without cellular toxicity in HeLa cervical cancer cell, and 3T3-L1 adipocyte.

Obese db/db mice model was used to consolidate the lipid-decreasing effect of SB1501. Compared to control mice, SB1501-treated mice showed significant reduction in body weight, and adipose tissue (IWAT, BAT). SB1501 also affected glucose homeostasis, substantiated by improved glucose tolerance in db/db mice.

To elucidate how the SB1501 can reduce cellular lipid, we aimed to investigate molecular target of SB1501. In conventional target identification method, molecular modification of small molecule is inevitable to introduce diverse functional group, such as bioorthogonal group, photoreactive group, and so on. However, even a little modification on SB1501 abolished the original activity, so SB1501 itself should be used for target identification. We already developed thermal stability shift-based label-free target identification method, TS-FITGE, and utilized this to investigate mode-of-action of SB1501.

Several target protein candidates known to be related to metabolism were obtained from TS-FITGE experiment, and diverse assay and experiments like CETSA, ITDRF, SPR, knock-down, overexpression were performed to biophysically and functionally validate real target protein of SB1501.

MEDI 140

Development of a chemoproteomic platform for identifying cell membrane proteins as drug targets from live cells and tissues using chemical probe

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Chemoproteomic approaches are undoubtedly powerful tools to identify drug target proteins. To investigate ligand-protein interaction, chemically reactive probes such as photoaffinity labels have been widely used in live cells and tissues. However, detection of cell membrane proteins including G protein-coupled receptor using these techniques remains a challenge due to low abundance of these proteins and low photo-cross-linking yields. Herein, we have developed a novel chemoproteomic platform that enables identification of cell surface proteins as drug targets from live cells and tissues using 2-aryl-5-carboxytetrazole (ACT)-based chemical probe. This probe consists of three functional groups: (1) a ligand moiety, (2) an ACT as a photoaffinity label and (3) a biotin group for affinity enrichment. After treatment of live cells or tissues with ACT
probe and photo-irradiation, biotin labeled proteins were enriched by streptavidin beads and then identified by LCMS-MS analysis. In our model studies using Chinese hamster ovary (CHO) cells stably expressing dopamine D2 receptor (DRD2), we demonstrated that ACT was the most suitable reactive group for capturing DRD2 in live cells compared with diazirine, benzophenone, aryl azide and acyl imidazole, widely used for protein labeling. Furthermore, we synthesized a new tetrafunctional ACT probe with N-1-(4,4-dimethyl-2,6-dioxocyclohexylidene) ethyl (Dde) as a cleavable linker, which allowed to reduce contamination of nonspecific proteins from streptavidin beads. Application of the tetrafunctional probes to mouse brain slices successfully detected drug target receptors. To the best of our knowledge, this is the first report that allows isolation and identification of target membrane proteins from living tissues utilizing chemoproteomic profiling. This technology would be useful for elucidating the mode of action of new drug candidates.

MEDI 141

Significance of chirality in drug design and synthesis of bitopic ligands as D₃R selective agonists

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The development of selective dopamine receptor agonists is a subject of increasing interest due to the potential therapeutic applications in neurological disorders. Due to the large degree of homogeneity among the D₂-like family of dopamine receptors, achieving ligands capable of discrimination among them remains a significant challenge. Previous work from our lab has shown the use of bitopic ligands to be a powerful strategy in achieving increased D₃R selectivity for antagonists. Inspired by the potential for chemical modification of the D₃ preferential agonists (+)-PD128907 and PF592379, we sought to synthesize and test a variety of bitopic structures to further improve their D₃R selectivity. When in a bitopic configuration, the (S,S) conformation of the PF592379 primary pharmacophore resulted in a privileged architecture with increased affinity and selectivity for the D₃R orthosteric binding site. Driven by an earlier finding revealing the inclusion of a cyclopropyl moiety in the linker of the bitopic molecule may induce a structural orientation favorable for D₃R selectivity and allosteric modulations, we proceeded to synthesize the bitopic compounds of the privileged (S,S)-PF592379 primary pharmacophore with a cyclopropyl ring in the linker. Incorporation of the ring in the linker and full resolution of the chiral centers present allowed us to analyze the effect of the stereochemistry of the linker on the final affinity and selectivity of the bitopic molecules synthesized. Binding studies were performed in presence of agonist radioligand, to specifically assess affinities for the receptors’ active states. Lead compound FOB02-04 (D₂R Kᵢ: 106 nM, D₃R Kᵢ: 2.84 nM, D₄R Kᵢ: 315 nM, D₂R/D₃R: 37.3, D₄R/D₃R: 111) and its most active enantiomer FOB02-04A (D₂R Kᵢ: 87.8 nM, D₃R Kᵢ: 1.85 nM, D₄R Kᵢ: 286 nM, D₂R/D₃R: 47.5, D₄R/D₃R: 155), may have the highest D₃R to D₂R selectivity reported for agonists, to date. The high structural complexity of these
compounds may inspire future computational studies to better understand ligand-receptor interactions, as well as underscore potential biased agonism as a consequence of specific receptor conformations. Moreover, due to their high D₃R selectivity and metabolic stability in mice liver microsomes, **FOB02-04** and the eutomer **FOB02-04A**, may have the potential to become the main pharmacological reference tools for future D₃R *in vitro* and/or *in vivo* studies.

**MEDI 142**

**D₄R-Selective compounds reveal structure-activity relationships that engender agonist efficacy**

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The dopamine D₄ receptor (D₄R) plays important roles in cognition, attention, and decision making. Novel D₄R-selective ligands have promise in medication development for neuropsychiatric conditions, including Alzheimer’s disease and substance use disorders (SUD). To identify new D₄R-selective ligands, and to understand the molecular determinants of agonist efficacy at D₄R, we report a series of eighteen ligands based on the classical D₄R agonist A-412997 (2-(4-(pyridin-2-yl)piperidin-1-yl)-N-(m-tolyl)acetamide). Compounds were profiled using radioligand binding displacement assays, β-arrestin recruitment assays, cAMP inhibition assays, and molecular dynamic computational modeling. We identified several novel D₄R-selective (Kᵢ ≤ 4.3 nM and >100-fold vs. other D₂-like receptors) compounds with diverse partial agonist and antagonist profiles, falling into three structural groups. These compounds highlight receptor-ligand interactions that control efficacy at D₂-like receptors and may provide insights to targeted drug discovery leading to a better understanding of the role of D₄Rs in neuropsychiatric disorders.

**MEDI 143**

**Discovery of pyrrolo[3,2-d]pyrimidine-containing compounds as inhibitors of NIK kinase**

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Aberrant stabilization and activation of NIK correlates with an augmented activity of NF-κB2, which is often associated with autoimmune diseases, inflammatory diseases, and cancer. Therefore, the inhibition of NIK has been pursued as an attractive strategy for treatment of certain diseases such as systemic lupus erythematosus, inflammatory
disease, multiple myeloma, and pancreatic cancer. Herein, we report our efforts to design and synthesis of novel and potent small molecules inhibitors of NIK. Our lead compounds is characterized by a novel pyrrolo[3,2-d]pyrimidin core structure, which shows potent inhibition of NF-κB2 signal pathway in intact cells. Our data show that the lead compound 1 has an IC₅₀ value in nM range in inhibition of NIK kinase activity. It has also been found that 1 was active in MM.1S cancer cells and caused changes of gene expression level of c-Myc, p21, and p100.

MEDI 144

Discovery of ‘all-in-one’ nitric oxide-donor cephalosporin-3′-diazeniumdiolates with dual-antibacterial and antibiofilm properties

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Bacteria encased in biofilms are up to 1000x more resistant to antibiotics than their planktonic counterparts. It is thought that all chronic bacterial infections are biofilm-mediated and there are currently no effective drugs for treating such infections. Biofilm dispersing cephalosporin-3′-diazeniumdiolate (C3D) nitric oxide (NO)-donor prodrugs show great promise as potential new therapeutics for addressing chronic infections. Our original 1st-generation C3D's were specifically designed to be locally activated to release biofilm-dispersing NO following reactions with bacterial β-lactamases. However, a shortcoming of this approach is that the compounds could only be used against β-lactamase expressing biofilms, and the requirement for co-treatment with a standard of care antibiotic would complicate clinical development. A more appealing strategy would be to create C3Ds with increased β-lactamase stability and enhanced reactivity towards penicillin binding proteins (PBPs), the bactericidal target of all broad spectrum β-lactam antibiotics, because reaction with PBPs also releases NO from C3Ds. This presentation will describe the development of prototypical ‘all-in-one’ C3Ds that show dual antibacterial and biofilm dispersing properties. Our lead C3D, AMINOPIP2-ceftazidime, shows higher antibacterial activity than its parent (non-NO donor) cephalosporin antibiotic (ceftazidime) against Pseudomonas aeruginosa clinical isolates from cystic fibrosis sputum, greater clearance of biofilms formed from these isolates and in vivo efficacy in a mouse model of respiratory P. aeruginosa infection.
Fructose metabolism may play an important role in the initiation and development of cancer. Certain types of cancer overexpress Glut 5, the highly selective fructose transporter, to increase fructose uptake. The de novo synthesis of fructose from glucose via polyol pathway is also upregulated. Recently, Christofk’s group and others discovered that Ketohexokinase (KHK), an enzyme that catalyzes the conversion of fructose to fructose-1-phosphate, is upregulated in several cancers and is critical for cancer cell proliferation both in vitro and in vivo. Additionally, KHK is a safe target for pharmacological inhibition for cancer treatment, because humans born with KHK deficiency are asymptomatic. Since KHK is important for cancer growth but not for normal tissues, it is considered a highly desirable target for cancer treatment.

Efforts in medicinal chemistry and biology are being taken to develop novel KHK inhibitors. Through collaboration with Prof. Daniel Nomura at UC Berkeley, four small
molecules that bind with KHK via covalent bond formation have been developed via chemoproteomics-enabled covalent ligand discovery. Additionally, a high throughput screen of 200,000 small molecule covalent library will be conducted soon to discover novel molecules to inhibit KHK activity. Finally, starting with one existing KHK inhibitor, more than twenty analogues have been synthesized in order to improve the original compound’s potency and pharmacokinetic property. Two KHK activity assays, the CellTiter-Glo and pyruvate kinase/lactate dehydrogenase-coupled assay, have been developed to test KHK activity with small molecule inhibition.

In conclusion, KHK is a promising target for cancer treatment and more effort is required to develop novel inhibitors. The novel KHK inhibitors we develop will be useful to further study the role of KHK in cancer development and may result in an anticancer drug targeting cancer metabolism.

MEDI 146

Ester bioisostere analogues of Astemizole as potential antiplasmodium agents

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Malaria is one of the most important parasitic infectious diseases as far as human suffering is concerned, with its burden being felt worldwide as seen by the huge numbers of deaths recorded each year. This is in part due to the unfortunate spread of resistance to most of the drugs that were once effective and safe. It is therefore crucial to invest research efforts into novel and structurally diverse antimalarials with different modes of action, that are not only able to circumvent resistance but are also efficacious at the different life cycle stages of the parasite in order to contribute to the disease eradication.

A high-throughput screening of marketed drugs led to the identification of Astemizole as an antimalarial agent with activity in vitro and in vivo against both chloroquine-sensitive (CQ-S) and multi-drug resistant (MDR) strains of the human malaria parasite Plasmodium falciparum. Unfortunately, astemizole also possesses a serious cardiotoxicity risk due to its ability to potently block the hERG (human ether-a-go-go-related gene) potassium channel. Structure-activity relationship (SAR) studies have been conducted to employ different strategies aimed at countering hERG and improve intrinsic solubility while maintaining antimalarial activity. We have identified a series of ester bioisostere analogues of astemizole with in vitro asexual blood stage antiplasmodium potency in the nanomolar range, with some analogues also showing moderate in vitro gametocytocidal activity at both early and late gametocyte stages. Although hERG activity and solubility remain a concern within the series, the study has revealed critical molecular features that create a basis for further optimization.

MEDI 147
Modification of lactoferrin by peroxynitrite reduces its antibacterial activity and changes protein structure

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Lactoferrin (LF) is an important ocular protein with polyfunctional properties, such as anti-inflammatory. Inflammation can enhance production of nitrated proteins, leading to changes in protein structure and functions. Lacoteferrin can be nitrated by common processes within the body, yet few studies have investigated the properties of chemically modified LF. Our goal of study was to investigate the effect of nitration on the antibacterial function of LF by testing the function of nitrated lactoferrin (NLF) by an antibiotic susceptibility test to measure the loss of antibacterial activity upon nitration, circular dichroism (CD) to measure changes in secondary protein structure, and iron binding assay to measure the effect on this critical LF function.

Human lactoferrin was nitrated using peroxynitrite (ONOO-) and produced nitrated lactoferrin. The structure of NLF vs. LF was investigated using CD to determine the secondary structure. The iron binding capacity of NLF was tested using a ferric nitrilotriacetic acid solution, with detection by absorbance. The antimicrobial activity of LF vs. NLF was evaluated against Escherichia coli (E. coli) using a broth susceptibility test.

The nitration reaction by ONOO- changed the chemical structure of LF, with increasing effect at higher nitration ratios. The antibacterial activity of LF was reduced after nitration. The measured absorbance after assay testing was 0.38 ± 0.04 for untreated E. coli, 0.31 ± 0.02 for LF, and 0.37 ± 0.04 for NLF, suggesting that upon nitration LF loses nearly 100% of its antibacterial activity. The t-test showed the difference in the activity of NLF compared to LF to be significant p-value < 0.001. The iron binding assay showed a minor reduction in binding after nitration. The CD spectra of NLF show a major change in secondary structure compared to LF. Further test will be needed to understand the structural changes account for decreased antibacterial activity of LF by nitration.

Our results suggest that NLF provides reduced antimicrobial activity compared to LF, due to changes in the molecular structure rather than due to changes at the iron-binding site. These results are the first to show the effect that nitration can play in reducing antimicrobial activity in human fluids. The combination of CD and iron-binding results also provide the first evidence for a mechanism of reduction of antimicrobial activity due to changes in protein structure.

MEDI 148

Synthesis of [18F]FPEB through radiofluorination of a diarylselenoxide and diarylselenone precursor
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New methods for incorporating no-carrier-added (NCA) fluorine-18 into aryl C-F bonds are of great interest due to the enhanced metabolic stability of $[^{18}F]$fluoroaryl species in candidate PET radiotracers. Our previous work has demonstrated that diarylselenones and diarylselenoxides can react efficiently with NCA $[^{18}F]$fluoride ion to give $[^{18}F]$fluoroarenes. Here we report the use of such hypervalent selenium precursors for the synthesis of $[^{18}F]$FPEB ($[^{18}F]$3-fluoro-5-[(pyridin-2-yl)ethynyl]benzonitrile), a selective mGluR5 ligand and useful PET radioligand. A Sonogashira coupling between 3,5-diiodobenzonitrile and 2-ethynylpyridine afforded the iodo analogue of FPEB. Subsequent reaction with diphenyl diselenide provided the phenylselenenyl analogue, and oxidation with meta-chloroperbenzoic acid resulted in selenoxide precursor 1. This compound was further oxidized with Oxone to give selenone precursor 2. Both precursors were treated with $[^{18}F]$F$^{-}$-K$^{+}$.K2.2.2 in DMF and microwaved (90 s, 90 W, 150 °C) twice in a 1-mL V-vial, and production of $[^{18}F]$FPEB was identified by observation of coelution with commercial reference compound in HPLC. Selenoxide 1 produced the desired radioligand in moderate yield (27%), which is comparable to that reported from other precursors, including arylidonium salts. Additionally, selenone 2 produced $[^{18}F]$FPEB in much higher yield (88%). The facile production of this radioligand from selenium-based precursors under mild microwave conditions warrants investigation of selenium-based precursors for producing other useful PET radioligands.

Figure. Synthesis of selenoxide precursor 1, selenone precursor 2, and radioligand $[^{18}F]$FPEB.
Phosphoramidate derivates as controlled-release prodrugs of L-Dopa

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Parkinson’s disease (PD) is an incurable neurodegenerative disease that currently affects about 10 million people worldwide. PD mainly affects dopamine-producing neurons in the substantia nigra leading to decreased levels of dopamine which causes symptoms like tremors, bradykinesia, limb rigidity, and balance problems. Dopamine itself cannot cross the blood-brain barrier so starting in 1968, Levodopa (L-Dopa) was used to treat PD symptoms since it has the ability to cross the blood-brain barrier. Once L-Dopa crosses the blood-brain barrier its carboxylic functional group is cleaved thus releasing dopamine in the brain. Unfortunately, L-Dopa has a short biological half-life (around 1-1.5 hours) and in more advanced cases of PD where dopaminergic neuronal cells are depleted, long-term motor complications develop which is termed “dyskinesia”. In the Berkman lab, we are developing a once-a-day L-Dopa double prodrug that will have a long circulation half-life to achieve slow release of L-Dopa in systemic circulation.

Herein, we have reported a series of L-Dopa Phosphoramidates and their subsequent L-Dopa release half-lives at pH 7.4 and 3. The kinetics data supports our hypothesis that a proximal carboxylic acid can promote hydrolytic release of L-Dopa under mildly acidic conditions; particularly, compounds 1b and 2b showing interesting promise. 1b has a hydrolytic half-life of 9.6 h in plasma pH while 2b has tremendous stability in plasma pH prior to enzymatic activation into 1b. We envision that the tunability of this L-Dopa-Phosphoramidate scaffold can be optimized for slow controlled-release application of L-Dopa in treating Parkinson’s disease.
MEDI 150

Discovery of tetrahydroisoquinoline-containing CXCR4 antagonists with enhanced ADMET properties and evaluation as anti-cancer agents

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Under normal physiological conditions, chemokine receptor CXCR4 is mainly expressed on the surface of hematopoietic stem cell lineages, while its cognate chemokine ligand CXCL12 is predominantly secreted by stromal cells in the bone marrow, lymph nodes, liver, and lungs. Under the pathophysiological conditions driven by > 48 different cancers however, CXCR4 and CXCL12 are substantially upregulated in tumor tissue relative to healthy tissue. Overactivation of CXCR4/CXCL12-mediated cell signaling and chemotactic migration has 3 chief consequences: 1) tumor-localized stimulation of autocrine and paracrine proliferation cascades, 2) CXCR4⁺ immunosuppressive regulatory T cell and myeloid-derived suppressor cell infiltration of tumor microenvironments, and 3) CXCR4⁺ cancer cell metastasis to distant CXCL12-rich niches. Although this implicates inhibition of the CXCR4/CXCL12 axis as an attractive therapeutic strategy in oncology, the utility of current clinical antagonists is limited due to poor pharmacokinetics and off-target activities. Accordingly, a series of tetrahydroisoquinoline-containing CXCR4 antagonists were designed to address these shortcomings. Out of > 250 compounds synthesized by our team, the in vitro activity profiles of the top 8 inhibitors are competitive with or superior to current clinical candidate AMD11070. These activity profiles, as well as the results of in vivo pharmacokinetic and pharmacodynamic experiments will be disclosed.

MEDI 151

Synthesis of PPAR ligands for the control of mesenchymal stem cell differentiation: Novel treatment avenue for osteoporosis

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Peroxisome proliferator-activated receptors (PPARs) are a family of ligand-activated transcription factors that play a role in regulating cell differentiation, development, and lipid metabolism. The PPARs are categorized into three subtypes, PPARα, PPARγ, and
PPARδ (or –β) and numerous selective synthetic ligands, including marketed drugs, are available for the PPARα and PPARγ isoforms. PPARδ remains the only PPAR subunit where there is no available marketed drug. Also, there are only a few known investigational selective and potent PPARδ agonists, with GW0742 and GW501516 being the most studied. Previously, we have shown that a PPARδ agonist can control mesenchymal stem cell (MSC) differentiation by promoting osteogenesis. Others have confirmed this observation and reported that this differentiation occurs by PPARδ direction of the Wnt pathway. In lipid metabolism, PPARγ and PPARδ function in similar but opposite ways, and we have shown that this opposing action can be extended to contrasting control of MSC differentiation. Treatment of bone marrow-derived MSCs with the PPARγ agonist, rosiglitazone, results in adipogenesis whereas treatment with the PPARδ agonist, GW0742, results in osteogenesis. We have synthesized a library of novel, small molecule PPAR ligands for further exploring the structure-activity relationship (SAR) of the PPARδ subunit and the role it plays in MSC osteogenesis. Our results show that our library contains compounds with various MSC differentiation phenotypes, with several giving an osteogenic response comparable to that of GW0742. These select compounds have been further tested in an ovariectomy (OVX) induced mouse model of postmenopausal osteoporosis. Our compounds showed the ability to increase tibial bone density and trabecular thickness with the overall results suggesting PPARδ agonists as a possible novel treatment option for osteoporosis and other bone-related diseases.

MEDI 152

Microwave-assisted expeditious and efficient synthesis of novel quinolin-4-ylmethoxychromen-2- and -4-ones catalyzed by YbCl₃ under a solvent free one-pot three component domino reaction and their antimicrobial activity

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An efficient and highly eco-friendly synthesis of diverse and functionalized quinolin-4-ylmethoxychromen-2- and -4-ones via a one-pot three-component domino reaction of propargylated-flavone or -coumarin with aldehydes and anilines under solvent-free and microwave conditions is described using YbCl₃ as catalyst. The reaction took 4 min to give the desired products in excellent yields (80–95%) at 100 °C. This approach has advantages such as high yields, solvent-free mild reaction conditions, functional group tolerance, 95% atom-economy and recyclability of catalyst. The synthesized compounds were examined for their antimicrobial activity. Among the tested compounds, some compounds showed excellent antimicrobial activity.

MEDI 153
Structure-activity relationship and evaluation of non-electrophilic NRF2 activators in a diabetic mouse model

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Chronic, non-healing wounds of the skin are serious medical complications that affect over 6.5 million Americans, especially diabetic patients and older adults. Strikingly, there are almost no pharmaceutical therapies to accelerate healing of chronic wounds. A major contributor to chronic wounds is a prolonged inflammatory state, and reducing inflammation may be a way to accelerate healing of chronic wounds. Unfortunately, many commonly used anti-inflammatory drugs hinder chronic wound healing; thus, new ways of reducing inflammation are needed. An essential factor in wound healing and an important regulator of inflammation, NRF2 is a transcription factor that induces many cytoprotective and antioxidant genes. As seen in other inflammatory disorders, activating NRF2 could be a useful therapeutic strategy to treat chronic skin wounds. Non-covalent NRF2 activators can be developed by inhibiting the interaction of NRF2 with its negative regulator, KEAP1. We have developed a structure-activity relationship around a known, naphthalene-based non-covalent NRF2 activator, to create a NRF2 activator based on an isoquinoline scaffold. This work highlights some of the SAR work of the peripheral aryl rings, in the hopes of increasing metabolic stability, as well as positive charge to balance the overall charge of our lead compounds. The compounds’ affinities are tested in a fluorescence anisotropy assay. Western blot data shows compounds increase protein levels associated with NRF2. Using a mouse model, we show that one of these isoquinolines can decrease the time to wound healing in a mouse model.

MEDI 154

Modeling drug metabolism identifies intermediate metabolites which precede reactive metabolite formation

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Adverse drug reactions are a substantial cause of early termination of clinical trials and drug withdrawal from the market. Adverse drug reactions are a product of unintended consequences during drug metabolism: drug molecules can be metabolized into reactive metabolites, which can conjugate to biomolecules, like protein and DNA, in a process termed bioactivation. Experimental assays for assessing the formation of reactive metabolites are low-throughput and require investment of substantial resources. In contrast, computational methods are appealing for rapid, high-throughput screening of potentially toxic compounds during the early stages of the drug development pipeline. Commonly used methods focus on detecting and structurally
characterizing reactive metabolite-biomolecule adducts or predicting sites on a drug compound that are liable to form reactive metabolites. However, such methods are often only concerned with the structure of the initial drug compound or of the adduct formed when a biomolecule conjugates to a reactive metabolite. Thus, these methods are likely to miss intermediate metabolites that may be required for subsequent reactive metabolite formation. In fact, approximately 57% of drugs that form reactive metabolites require the formation of at least one intermediate metabolite. Therefore, modeling the sequential metabolism of drugs to determine the intermediate metabolite structures that precede reactive metabolite formation would provide a better mechanistic understanding of how reactive metabolites form. We set out to create a tool that can take a compound and a corresponding reactive metabolite and (1) enumerate pathways, or sequences of intermediate metabolite structures, between the pair, and (2) compute the likelihood of those pathways and each individual step preceding reactive metabolite formation. This tool will be applied to withdrawn drugs with known reactive metabolites to identify previously unknown intermediates. Identification of the presence and likelihood of intermediate metabolites in pathways which lead to reactive metabolites could guide rational drug modification in order to lower the likelihood of the intermediate metabolite's formation, which would diminish the chance of reactive metabolite formation.

MEDI 155

Design of GSK9742, a chemical probe for the TAF1/TAF1L bromodomains

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A chemical probe is a tool molecule that selectively binds to a target and is used to elucidate its biological function, helping bridge together chemical biology and drug discovery. TATA binding protein (TBP) associated factor 1 (TAF1) and TAF-1-like (TAF1L) are multidomain proteins that have been implicated with oncology and neurodegenerative diseases. The biological role of these proteins and their bromodomain regions within disease is still unknown with further target validation required. Herein we report the discovery of GSK9742, a potent, selective and cell penetrant TAF1/TAF1L bromodomain chemical probe and accompanying negative control GSK5121 for pre-clinical target validation.
Assessing the liability of isoxazole containing compounds to form reactive metabolites

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Isoxazole, a five-membered heterocyclic ring with an oxygen atom adjacent to a nitrogen atom, is often used in medicinal chemistry since it can be used for a wide variety of protein targets and provides advantageous physical and chemical properties when integrated into a potential drug compound. Specifically, 3,5-dimethylisoxazole containing compounds have garnered interest since they inhibit bromodomain, and the extra-terminal domain family of bromodomains, which are target for cancer treatments. Efficacy studies have been performed on these ligands, but the field's knowledge of the metabolism and subsesequent toxicity risk of these ligands is lacking. Here, we report that in many cases, bromodomain inhibitor ligands with 3,5-dimethylisoxazole that are under development have a relatively high likelihood of forming highly reactive quinone-species in reactions. We also present strategic modifications that lower the likelihood of quinone formation, without modifying key interactions between the ligand and the
bromodomain binding pocket. Our study uses three different computational models of metabolism to infer if a quinone is likely to form, what the quinone metabolite structure is, and how likely it is to be reactive towards protein across a set of 3,5-dimethylisoxazole bromodomain inhibitor ligands obtained from the literature. Therefore, our modelling efforts provide directly testable hypotheses that can guide experimentalists to better understand the metabolism and toxicity risks of 3,5-dimethylisoxazole bromodomain inhibitor ligands. We validate that each of these models are highly accurate by evaluating them with isoxazole-specific test sets we derived from the accelrys metabolite database.

MEDI 157

Combatting the opioid and benzodiazepine epidemic by the synthesis of novel safer drugs designed to be functionally selective for α5- or α6-containing GABA_\text{A} receptors
The opioid and benzodiazepine epidemic is on the rise resulting in an average of 115 deaths daily and over 11,000 deaths in 2017 due to prescription drug overdoses in the United States, according to the CDC. Clearly, alternative treatments are needed and the search for new ligands (potential new drugs) that selectively interact with specific subtypes of GABA<sub>A</sub> receptors (GABA<sub>A</sub>Rs) is required. The problem with current neurological drugs on the market is that they lack functional selectivity, meaning that in addition to the desired receptor or receptor subtype of interest, these drugs also target undesired receptors causing serious side effects. For example, the commonly prescribed benzodiazepine, Xanax is used to treat anxiety and panic disorders but also causes side effects such as sedation, ataxia, and amnesia, as well as euphoria, which can lead to addiction. Xanax interacts with four of the major GABA<sub>A</sub>R subtypes (α1, α2, α3 and α5) and therefore is not considered functionally selective. Since α5- or α6-containing GABA<sub>A</sub>Rs are not associated with the typical benzodiazepine-type side effects, utilization of novel ligands that are functionally selective for α5- or α6-containing GABA<sub>A</sub>Rs could provide a key to combat this epidemic.

In a different area, the lead imidazodiazepine, GL-II-73 was designed as an α5-GABA<sub>A</sub>R subtype selective ligand and exhibits promise in the area of treating memory loss and depression.

By design, these α5-targeting imidazodiazepines and α6-targeting pyrazoloquinolinones are functionally selective positive allosteric modulators (PAMS) for the GABA<sub>A</sub>R subtype of interest. Thus, these ligands are devoid of the sedative, amnesic, euphoric, and
ataxic side effects associated with current GABAergic drugs on the market today. Therefore, these novel and safer drugs provide a potential alternative treatment for GABA$_A$R-related neurological diseases and solution for ending the opioid and benzodiazepine epidemic.

**MEDI 158**

**Computationally bridging the gap: From fragment hit to lead**

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BioBlocks’ proprietary Leap-to-Lead™ platform was built to generate lead compounds from fragment screening hits. Fragment-based lead discovery (FBLD) methods have entered the mainstream of drug discovery and are routinely applied to complement high-throughput screening campaigns. While FBLD screening routinely generates hit compounds, particularly for difficult-to-drug targets, general fragment hit-to-lead approaches are lacking. BioBlocks has developed the Leap-to-Lead™ platform as part of our effort to better address target-ligand interaction space with fragments. The Leap-to-Lead™ platform includes the Comprehensive Fragment Library (CFL), a set of small, rigid, medicinally interesting fragments selected to provide multiple independent starting points from each hit. Using advanced clustering methods, the design of the CFL connects each fragment hit to thousands of potential analogs. This enables maximal representation of fragment structure space by a small physical library, providing multiple paths forward to efficiently generate lead-like compounds from fragment hits.

We have screened the CFL against multiple target classes to produce fragment hit sets. In all cases, our built-in cluster analysis paths led to rapid identification of novel fragment analogs with improved activity and high ligand efficiency. Further analysis groups these analogs into families to guide medicinal chemistry priorities. We will present details of the screening methods, results and analog family analysis across multiple target classes, including a case where Leap-to-Lead™ methodology enabled advancement of a series to lead optimization for a challenging kinase target.
The mechanical microenvironment of the body strongly impacts a multitude of cellular processes, including proliferation, transcription and organogenesis. For example, the mechanical properties of the extracellular matrix (ECM) play integral roles in the processes of stem cell differentiation, the development of cancer cell chemoresistance, and the regulation of cellular locomotion in wound healing and inflammatory responses. In particular, the stiffness of the ECM has emerged as a key regulator of cellular spreading, migration, and differentiation. The magnitude of these effects is enhanced by the broad variation of the specific mechanical properties from one tissue to the next – Young’s modulus ($E_0$), for example, varies from ~0.1 kPa in super-soft brain tissue to ~30 kPa in rigid, precalcified bone. Assorted polymeric systems, mainly hydrogels, have been developed in an attempt to mimic ECM mechanical properties and thereby study cell-substrate interactions. However, their application is limited because adjusting a given mechanical property requires simultaneous variation of multiple compositional parameters such as water content, crosslinking scheme, and chemical composition, which generates cross-correlated cellular responses. Herein, we outline the
development of model substrates for mechanobiology that will independently encode tissue-like softness and strain-stiffening via architectural engineering of brush-like polymer networks. Specifically, we synthesized a series of super-soft dry PDMS elastomers with $E_0$ ranges of 0.1-1, 4-5, 10-12, and 30-35 kPa to mimic the stiffness of neural, adipose, muscle, and pre-calcified bone tissues, respectively. Cell culture studies using mesenchymal stem cells revealed the application of designed solvent-free biogel to study cellular behaviors.

MEDI 160

Metabolism enhanced multiplexed FDA-approved drug screening for novel antibacterial activities

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The emergence and spread of resistance to current antibacterial agents is a major public health threat, and there is an urgent need to develop new strategies to address this issue. This study demonstrates a "dimensionally enhanced" (multiplexed) antibacterial activity library screening approach against MRSA. As the first dimension of this approach, we evaluate the use of an in vitro microsomally metabolized FDA approved drug library screen for the discovery of novel anti-MRSA agents. This comparative un-met (UM) vs pre-met (PM) screening strategy allows agents with antibacterial metabolites to be identified. To further enhance the ability of this approach to identify interesting antibacterial activities (second dimension), it was combined with a +/- resistant-to-antibiotic (cefoxitin) screen that allows synergistic (or antagonistic) agents to also be identified. This approach provides an information rich and interesting set of active agents with high translational and clinical potential. Capecitabine was identified as an exemplary drug only active after metabolism, with three identified active anti-MRSA metabolites. This screen also identified several agents with strongly synergistic interactions with cefoxitin. This study illustrates the potential of such a multidimensional screening approach to identify interesting lead agents.

MEDI 161

Novel computational strategy for neuroprotection prediction: Identification of novel nicotine-analogs as potential Parkinson therapeutic agents

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Neuroprotection is a fundamental preventive alternative for Parkinson’s disease (PD) therapeutics. Dopaminergic replacement has been used for PD treatment with positive effects over motor symptomatology but without effect over disease progression and early-treatment perspective. Epidemiological studies have shown that nicotine consumption decreases PD prevalence through the activation of neuroprotective mechanisms over dopaminergic neurons. Nicotine neuroprotection has been associated with the overstimulation of PI3K/Akt signaling pathway (SP), induced by nicotinic acetylcholine receptors (e.g. a7 nAChR), leading to Bcl-2 over-expression. Due to nicotine toxicity and dependency, analogs with less secondary effects and similar neuroprotective activity are relevant for PD pharmacology. In this work a computational strategy integrating structural bioinformatics, SP manual reconstruction, and machine learning was performed to predict the neuroprotective activity of a series of 8 novel nicotine analogs over PI3K/Akt behavior. We made a molecular docking between analogs and a7 nAChR receptor using a conformational analysis and performed a physicochemical characterization of the analogs. In order to elucidate the relationship between a7 nAChR receptor and Bcl-2 activation a Markov Chain Monte-Carlo transition matrix approach was constructed across PI3K/Akt SP. To develop a machine learning model, random training datasets were generated from a manually curated neuroprotective database of physicochemical properties using dimensional reduction. Contrasting 4 methods of prediction with each dimensional reduction, we developed an artificial neural network model using the synthetic datasets as training. Our model predicted the neuroprotective capacity of seven nicotine analogs suggesting them as putative PD neuroprotective molecules. Hereby we present a new computational strategy in which a predictive machine learning model is used to assess the neuroprotective activity of ligands based on SP. Our new method is applicable to a variety of diseases based in SP and can be coupled with drug discovery methodologies to improve pharmacological research in neurodegenerative diseases.

MEDI 162

New rhodium(I) NHC complex targeting TrxR inhibits hepatocellular carcinoma in vivo

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Hepatocellular carcinoma (HCC) is one of the most serious cancer worldwide especially in China. To develop a kind of small molecule drug that can effectively inhibit the overexpression of TrxR in liver cancer cells is one of the effective strategies for the treatment of liver cancer. Here we designed and synthesized a series of Rh(I)-NHC derivatives with 1,5-cyclooctadiene. These complexes were evaluated their antiproliferative properties in three cancer cell lines including HepG2 (liver hepatocellular cells). All of them displayed high antitumor potencies against cancer cells especially 1e in HepG2 cells. The in vivo testing showed that 1e repressed the tumor
growth in a liver cancer nude mice model and restored the liver lesions in a chronic liver cancer model caused by tetrachloromethane. Noteworthy, mechanism study showed that this complex can significantly inhibit the TrxR on the enzyme level and cellular level.

MEDI 163

Discovery of potent hits and solving ADME challenges with free energy perturbation and deep learning

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We will present case studies from hit identification to lead optimization, to illustrate how new physics-based and machine learning computer-aided drug design technologies can help advance and accelerate drug discovery projects. These case studies include uses of core-hopping free energy perturbation (FEP), to rapidly discover multiple novel picoMolar hit series; convolutional deep neural network based approaches to solve a series-specific efflux problem; FEP solubility calculations to ameliorate solubility liabilities; and FEP to achieve selectivity against highly similar off-target proteins.

MEDI 164

Structure and ligand-based design of promising small molecule EZH2 inhibitors

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Epigenetic pathways are being recognized as determinants to cancer development and progression. Polycomb repressive complex 2 (PRC2) is an epigenetic regulator that catalyzes the trimethylation of lysine 27 in Histone 3 (H3K27me3), a process that facilitates chromatin compaction and gene silencing. The overexpression of EZH2, the catalytic subunit of PRC2, is implicated in the development and progression of a variety of cancers with the worst prognosis. Thus, the therapeutic targeting of EZH2 emerged as a hot topic and the development of selective small-molecule EZH2 inhibitors is currently a promising research challenge for drug discovery.

Using computer-aided drug design (CADD) methods we identify new starting points for designing EZH2 inhibitors. We created 3D-pharmacophore models, using LigandScout Advanced 4.2.1 software to support hit finding. In a first stage, a panel of unique
pharmacophoric models were generated, validated and optimized. The prioritized models were used for two hit finding campaigns: virtual screening and de novo design. First, using the unique 3D-pharmacophore-based virtual screening method (iscreen) from LigandScout, several databases (e.g., DrugBank, NCI, MuTaLig Chemotheca, and our in-house libraries) were computed and screened. Interesting virtual hit molecules with high inhibition potential were found. Selected hits were tested in biological assays to determine their ability to inhibit EZH2. We found several hits with inhibition rates comparable to the reference compounds (in clinical trials). Toxicity profiles are being tested. In parallel, we started a de novo design campaign based on selected pharmacophore models. We found new scaffold cores for EZH2 inhibitors. Those from de novo design are being synthesized to further determine their EZH2 inhibition and ADMET profiles.

MEDI 165

Milestone based computational approach to estimate energy barriers in the drug designing, and application to P38-MAP kinase-SB2 system

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Drug binding kinetics and drug residence time is identified as an essential parameter for drug discovery. Here we present a computational technique, and a computational package to estimate the protein-ligand binding kinetics describing the factors assisting the drug-design. The method uses molecular dynamics simulations and partitions the dissociation pathway in the number of milestones. The computational package uses a novel strategy to define the milestones by analyzing dissociation pathways obtained by a sampling method. We applied the package to estimate the free energy barriers and residence time of a model system consisting of P38 MAP kinase and SB2 (SmithKline Beecham) ligand. The calculated binding free energy well agree with the measured values, and critical intermediate barriers along the dissociation path of the system as mentioned earlier were identified using the package.
Energy barriers of the P38-SB2 binding computed using the milestoning theory. The dissociation pathway of the system was modeled from the accelerated molecular dynamics method.

**MEDI 166**

**Development of bioactive γ-AA peptides based peptidomimetics to control angiogenesis**

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Angiogenesis, formation of new blood vessels from existing vascular network, is an important process in early developmental, healing and female reproductive cycling processes. Notably, this process is quiescent in adults, however, during tumor progression this process is activated and leads to tumor vascular proliferation and
consequent tumor metastasis. It is for this reason that the prospect of affecting this process has gained considerable interest in the fight against cancer. Sustained angiogenesis constitutes one of the hallmarks of cancer cells and is modulated through vascular endothelial growth factor (VEGF). Protein-protein interactions (PPIs) mediate almost all biological processes and represent unparalleled potential targets for novel therapeutics, hence tremendous efforts have been undertaken in recent years towards effective PPI modulations. γ-AA peptides are a unique class of peptidomimetics with exceptional stability, bioavailability and protein domain mimetics. Here we report two approaches of developing γ-AA peptides-based PPI inhibitors. The first approach is a One-Bead–Two-Compound macrocyclic γ-AApeptide library synthesis and the second approach is the sulfonyl-γ-AA peptides based helical mimetics of VEGF helix α1 (16–24). We report cell-based assays of the effective downregulation of angiogenesis and inhibition of VEGF pathway.

**MEDI 167**

**Preformulation analysis and stability of hydrophobic small molecular echinomycin for injection formulation**

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Echinomycin is quinoxaline-containing depsipeptide antibiotic and proposed to treat acute myeloid leukemia (AML) as molecular targeting HIF-1a in cancer stem cells (CSCs). Through targeting HIF-1a, echinomycin selectively eliminates CSCs in hematological tumors. Formulation of echinomycin for injection was challenging due to its hydrophobic nature. Cyclodextrins (CDs) are a group of cyclic oligosaccharides, consisting of 6 or more 1-4 linked aanhydroglucose moieties. CDs have hydrophobic cavity and hydrophilic exterior. Here we report preformulation study in development of echinomycin for injection formulation using various CDs. Also stability studies of the drug in the formulation over years using HPLC assay method will be reported. Cavasol and Captisol (CDs) were tested and Cavasol was chosen for further study. Study variations to modify the proper formulation method were including stirring time with magnetic stirrer, type of syringe filter, concentration of solution, and type of diluent. Stress condition analysis performed with echinomycin-cavasol formulation stored in 0.1N HCl, 0.1N NaOH, and 3% H2O2 at RT and 60°C for 24 hours. HPLC assay procedure is a gradient assay using water and acetonitrile as mobile phase. A Waters XBridge BEH C18 Column was used for elution in 40°C and detection was set at 254 nm. The analyses of echinomycin-cavasol formulation under stress conditions indicated that the assay procedure is stability indicating and linearity of the procedure was established with six points over the concentration range of 0.004 to 0.227 mg/mL (R2=0.9998). Echinomycin injection (2mL of 20 mcg/mL in pre-siliconized 2mL clear type I vial) was made and on going stability study performs using products stored in two different temperature conditions. Echinomycin injections are stable for at least eighteen months when stored in freezer while for only one month in refrigerated condition. Continuous stability monitoring over the course of the clinical trial will be conducted.
Biological and computational assessment of (-)-Incarvillateine mechanism of action

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Incarvillea sinensis is a natural herb attributed with pain relieving effects. Despite many years of use, its mechanism of action remains debated. One of the key biologically active substituents of incarvillea sinensis is (-)-Incarvillateine (INCA), which shares multiple key structural features with another anti-nociceptive compound, SB-FI 26. One major difference is that INCA is a diester of truxillic acid, whereas SB-FI 26 is a monoester. Since esters are readily hydrolyzed in vivo, a metabolite of INCA would chemically resemble SB-FI 26 even more.

Due to similar chemical and biological properties, it was hypothesized that INCA and SB-FI 26 yield anti-nociception via the same mechanism. SB-FI 26 was proven to yield anti-nociception through FABP inhibition, which lead to the postulate that INCA has a similar mechanism of action, especially if one of the ester moieties of INCA is hydrolyzed in vivo. However, in vitro experiments demonstrate neither INCA nor its putative metabolite have appreciable affinity for FABPs. INCA still produced robust anti-nociceptive effects in mouse models, although there was a motor suppression associated with INCA administration. This motor suppression was reversed with administration of an adenosine 2A receptor antagonist, suggesting INCA affinity towards adenosine receptors. The INCA monoester did not produce the same anti-nociception as INCA itself.

In order to further investigate the mechanism of INCA anti-nociception, machine learning algorithms and docking programs were applied to INCA and INCA monoester. In silico docking results of INCA and INCA mono ester suggest a poor affinity of both compounds towards FABPs, which was indeed observed in vitro. Docking towards classical anti-nociception targets suggest both INCA and INCA mono ester have affinity for PPAR-γ, Adenosine 2A, Serotonin 1B, and TNF-α proteins. These results, as well as the behavioral effects of INCA in vivo, suggest INCA binds to multiple proteins related to nociception.

Approaches to demonstrate pharmaceutical equivalence of Ibrutinib cocrystal complex for the follow-on generic drugs

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Imbruvica® is an important oncology drug. Literature reported several polymorphs and solvates for drug substance Ibrutinib, including co-crystals with benzoic acid, fumaric
acid, and succinic acid. This poster examines viability of Ibrutinib co-crystal as an active ingredient for the follow-on generic drugs. We will discuss recent FDA (February 2018) Guidance for Industry: Regulatory Classification of Pharmaceutical Co-Crystals and will provide approaches to demonstrate compliance to 505(j). According to 505(j), an ANDA must contain the information to show that the proposed generic product (1) is the same as the RLD with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences) and (2) is bioequivalent to the RLD.

MEDI 170

Introduction of BBXC (building block exchange): New business model to efficiently access novel monomers

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Pfizer and pharmaceutical companies have partnered on a novel approach to access novel chemical building blocks — we will exchange the building blocks with each other. To accomplish this, we have formed the Building Block Exchange (BBXC) in which each member contributes a set amount of chemical building blocks to be shared by participants in the BBXC. We will be discussing how the BBXC works, the value it brings and how new partners can join the BBXC.

MEDI 171

Strategies for targeting aberrant microRNA activity in cancer

Amanda L. Garner, algarner@umich.edu. Medicinal Chemistry, University of Michigan, Ann Arbor, Michigan, United States

MicroRNAs (miRNA) are an emerging class of small RNAs that play critical roles in human development and disease. These micromangers function at the level of post-transcriptional gene regulation, and alteration of miRNA expression levels have been implicated in many human diseases. In cancer, miRNAs can have both oncogenic and tumor suppressive functions, indicating that multiple strategies will be necessary in order to target miRNAs in cancer for therapeutic development. Using our laboratory’s innovative high-throughput screening approach, catalytic Enzyme-Linked Click Chemistry Assay or cat-ELCCA, we have developed platforms for assaying RNA-small molecule and RNA-protein interactions toward our goal of developing small molecule-based modulators of miRNA biology. Our progress toward the goals of
selectively targeting Dicer-mediated pre-miRNA processing and miRNA-miRNA-binding protein interactions with small molecules and natural products will be discussed.

**MEDI 172**

**Fragment to lead: Discovery and optimization of a novel bromodomain inhibitor**

**Ashley Adams**, ashley.margaret.adams@gmail.com. **AbbVie, Inc, Glenview, Illinois, United States**

This presentation will cover a recent application of AbbVie’s Fragment-Based Drug Discovery platform and highlights the optimization of a fragment with high fsp3 character. This fragment hit was rapidly advanced to a lead compound with high BEI, LE, and LipE. The unique properties and challenges associated with fragments containing high sp3 character will also be discussed.

**MEDI 173**

**Chemical targeting of deubiquitinating enzymes**

**Sara Buhrlage**, saraj_buhrlage@dfci.harvard.edu. **Dana-Farber Cancer Institute, Boston, Massachusetts, United States**

Protein degradation is controlled by the ubiquitin-proteasome and autophagy-lysosome systems. Both of these systems use ubiquitin as a signal for degradation – any cellular protein labeled with a specific ubiquitin mark is directed towards an appropriate degradation pathway. Deubiquitinating enzymes, or DUBs, survey the ubiquitinated proteome and remove ubiquitin marks, thus stabilizing the protein in question and prolonging its cellular life. Therefore, inactivation of DUBs causes specific proteins to undergo accelerated degradation and could offer a new avenue for the development of drugs leading to targeted degradation. DUBs are relative newcomers as potential drug targets and thus there are few selective small molecule inhibitors for DUBs, no approved drugs, and many open questions regarding their function and therapeutic potential. My research group is focused on developing small molecule inhibitors targeting DUBs that act with precision towards a specific DUB. The inhibitors are then deployed by us and others to decipher how DUBs function and determine the most promising contexts, within the fields of cancer and neurodegeneration primarily, for DUB-targeted drugs. Since starting the lab in late 2015, we have established a platform for developing rigorously characterized DUB inhibitors and using them to study DUB biology in both biased and unbiased fashions. Our platform integrates DUB library synthesis, medicinal chemistry, biochemistry, high-throughput screening, chemoproteomics, chemical genomics, structural biology, target validation and cancer biology. In the first part of the presentation, I will describe our platform for DUB inhibitor development. I will then present examples, including structure-guided development of USP7 inhibitors and chemical genetic screens to identify DUBs that stabilize leukemia.
oncogenes, that demonstrate the power of our platform in producing best-in-class DUB probes and unraveling DUB biology.

**Figure 1.** Ubiquitin marks client proteins for degradation. DUBs cleave ubiquitin to prevent substrate degradation.

**MEDI 174**

**PROTAC™ targeted protein degraders: Exciting modality for drug discovery**

*Erika Araujo, erika.araujo@arvinas.com. Arvinas, Woodbridge, Connecticut, United States*

Proteolysis targeting chimera (PROTAC™) molecules can reduce intracellular levels of a targeted pathogenic protein by making use of a cell’s own protein disposal machinery. These heterobifunctional molecules, composed of two ligands linked through a chemical bridge, are designed to recruit an E3 ubiquitin ligase complex to a targeted protein to induce its degradation through exploitation of the ubiquitin-proteasome pathway. As a platform for drug discovery, the PROTAC™ modality is a small-molecule protein knockdown approach that results in drastically different pharmacodynamics in comparison to traditional occupancy-driven small-molecule inhibition of protein activity or gene-based medicines. This presentation will focus on the inroads that Arvinas has made to develop, understand, and advance this technology into the clinic.

**MEDI 175**

Generating new synthetic transformations and unique heterocycles to drive anti-infective agent discovery and development
**Jennifer E. Golden**, jennifer.golden@wisc.edu. **Pharmaceutical Sciences, University of Wisconsin-Madison, Waunakee, Wisconsin, United States**

Through the development of efficient synthetic methodologies, we have constructed multiple classes of nitrogen-containing heterocycles to study biology, elucidate new therapeutic opportunities, and advance medicinal chemistry campaigns. These strategies were pioneered to deliver new structural frameworks containing pharmacologically-enriched, privileged motifs with drug-like characteristics. Further, these compounds have been assessed for activity against various pathogens in partnership with our expert collaborators from the world of virology, parasitology and genetics. Early results emerging from the screening of some of these new scaffolds will be discussed, and a mature antiviral project will be highlighted that demonstrates the pivotal role that new synthetic chemistry methods have played in mapping a pharmacophoric model and engineering a modified scaffold worthy of preclinical evaluation and development.

**MEDI 176**

**Enabling medicinal chemistry as a process chemist**

**Jamie McCabe Dunn**, jamie.mccabe.dunn@merck.com. **Process Research and Development, Merck, Rahway, New Jersey, United States**

Process Research & Development at Merck & Co., Inc. encompasses a number of diverse research groups that seek to enable discovery chemistry (Discovery Process Chemistry), discover new & innovative technologies (Enabling Technologies), and/or develop the ideal process for a manufacturing route (Process Chemistry). This presentation will exemplify my work while in the Discovery Process Chemistry group on the Soluble Guanylate Cyclase (sGC) program. Amino-pyrimidine lactams, accessed through coupling of malononitriles and amidines, represent a class of highly functionalized heterocycles of interest as sGC stimulators. One of the key bottlenecks in compound preparation was accessing highly functionalized malononitriles which had been historically prepared via a linear synthetic approach. In order to streamline compound synthesis, a more convergent, general and scalable approach to these intermediates was required. I will describe novel methods to obtain highly functionalized malononitriles, including a diastereoselective approach and subsequent manipulations as a convergent and adaptive approach to sGC stimulators.

**MEDI 177**

**Overview of current drug discovery approaches for childhood epilepsies**

**Ana Mingorance**¹⁴³, ana@draccon.com. (1) Loulou Foundation, London, United Kingdom (2) Dravet Syndrome Foundation Spain, Madrid, Spain (3) Dracaena Consulting, Madrid, Spain
Epilepsy is one of the most common neurological conditions. It is also a field where medicinal chemistry has experienced a great success, and more than 25 anti-convulsant drugs have been approved. However, about a third of these patients fail to respond to any of the approved medications, and pharmacoresistance has become a big hurdle and unmet medical need.

The recent years have seen a revival of the epilepsy field, and a great increase in the number of drug programs in development. This revival is driven by a focus of drug developers in rare (orphan) childhood epilepsies, many of which are caused by gene mutations. The orphan drug incentives, the ability to complete clinical development programs with less than 100 patients, and the knowledge of the gene defects causing the epilepsy, have made childhood epilepsies an attractive target for drug discovery. As a result, there are multiple approaches currently in development for a variety of childhood epilepsy syndromes.

Some of these approaches represent improved therapeutics acting on validated receptors, for example positive allosteric modulation of GABA receptors using synthetic neuroactive steroids. By acting on the general pathology underlying epilepsy, and not on syndrome-specific mechanisms, these drugs have the potential to treat multiple rare epilepsy syndromes. Other approaches specifically target the pathological change. Examples include inhibitors of the sodium channel Nav1.6 for SCN8A encephalopathy, caused by gain-of-function mutations, or activators of the sodium channel Nav1.1 for Dravet syndrome, caused by loss-of-function mutations in the SCN1A gene. Similarly, there are ongoing clinical development programs to specifically target childhood epilepsies caused by mutations in potassium channels.

This presentation reviews the current drug discovery approaches for childhood epilepsies and discusses the challenges and opportunities.

MEDI 178

Phytocannabinoids in the modern treatment of catastrophic epilepsies

Geoffrey Guy, gwg@gwpharm.com. GW Pharmaceuticals plc, Cambridge, United Kingdom

Historical references to the use of various forms of cannabis to treat the seizures in Epilepsy abound. From Sumerian runes, Arabic texts to modern day peer reviewed publications there have been clear and credible signals of therapeutic benefit. Translating this knowledge and understanding into a modern day pharmaceutical medicine that can be approved by the regulators represented a series of interesting challenges especially in terms of pharmaceutics, appropriate standards, analytical methodology and manufacturing processes. Developing a medicine from a highly purified preparation of a whole plant extract and then subjecting this to pre-clinical and clinical research created one of the most complex programmes in recent times. The approach to clinical evaluation and evidence generation in paediatric populations with
rare and catastrophic epilepsies and associated behavioural phenotypes has yielded a novel methodology which may be appropriate for future medicines discovery and development.

**MEDI 179**

**Nav1.6 inhibitors: Approach to treat severe childhood epilepsies**

*Thilo Focken, thilo.focken@gmail.com, Mike E. Grimwood, Verner A. Lofstrand, Kristen Burford, Wei Gong, Qi Jia, Abid Hasan, Matt Taron, Wei Zhang, Michael Wilson, Parisa K. Tari, Girish Bankar, Sarbjot Singh, Karen Nelkenrecher, Kuldir Khakh, Elaine Chang, Jenny B. Li, Janette Mezeyova, Samuel Goodchild, Noah G. Shuart, Sophia Lin, Rainbow Kwan, Luis Sojo, Charles J. Cohen, Nina Weishaupt, Steven S. Wesolowski, J P. Johnson, Christoph M. Dehnhardt, James R. Empfield. Xenon Pharmaceuticals Inc, Burnaby, British Columbia, Canada*

Despite an abundance of available antiepileptic drugs (AEDs), there is a significant unmet medical need as many patients are refractory to current available therapeutics or often suffer from undesired side effects. Inhibitors of voltage gated sodium channels (Nav) have long been a mainstay of the anti-seizure pharmacopeia. Classic Nav inhibitors, including phenytoin and carbamazepine, are not selective and block all Nav subtypes indiscriminately, and their utility is often reduced by relatively narrow therapeutic indices. Adult central nervous system (CNS) neurons primarily express three Navs: Nav1.1 (SCN1A), Nav1.2 (SCN2A), and Nav1.6 (SCN8A). While Nav1.6 and Nav1.2 are highly expressed in excitatory neurons, Nav1.1 is primarily expressed in GABAergic inhibitory interneurons. It is believed that inhibition of Nav1.1 is pro-convulsant, as indicated by the seizure phenotype of SCN1A heterozygous null patients who suffer from Dravet Syndrome. Inhibition of Nav1.5, the cardiac sodium channel, introduces additional risk for non-selective compounds. On the other hand, block of Navs expressed in excitatory neurons, in particular Nav1.6, can be linked to anticonvulsant activity.

We discovered a series of zwitterionic aryl sulfonamides as Nav1.6 blockers with excellent isoform selectivity, in particular over Nav1.1 and Nav1.5, and that we hypothesize will provide greater potential for efficacy and an improved therapeutic index. We report on our multi-parameter optimization strategy to augment potency, metabolic stability and CNS penetration of this series. Structural modifications allowed for tuning of the Nav1.6/Nav1.2 selectivity profile. We report on the anticonvulsant activity of our Nav1.6 inhibitors in a seizure model employing a heterozygous mouse with the incorporation of a gain-of-function mutation in the Nav1.6 channel (N1768D). This mutation in humans is one of the hyper-exitable etiologies of the childhood epilepsy, Early Infantile Epileptic Encephalopathy type 13 (EIEE13).

**MEDI 180**
Novel synthetic neurosteroids to reduce seizure burden and improve survival in preclinical models of catastrophic epilepsies

Maria-Jesus Blanco, mjblanco@comcast.net. Dept. Medicinal Chemistry, Sage Therapeutics, Inc., Cambridge, Massachusetts, United States

The tragedy of epilepsy emerges from the combination of its high prevalence and impact upon patients and their families. Childhood epilepsies are typically severe, often presenting in infancy with pharmaco-resistant seizures. These are thought to contribute to developmental disabilities and debilitating comorbidities commonly present in these patients. In addition, there is an increased risk of sudden unexpected death in epilepsy or SUDEP in these populations. Despite the availability of multiple antiepileptic drugs (AED), approximately one third of epilepsy patients still experience pharmaco-resistant seizures, representing a significant unmet medical need. New therapies with a differentiated mechanism of action are desperately needed.

Neuroactive steroids (NAS) are a family of steroid based compounds of both natural and synthetic origin, which display an array of central nervous system (CNS) activities, including the modulation of the GABA<sub>A</sub> and NMDA receptor systems. As the primary inhibitory neurotransmitter in the nervous system, GABA influences the activity of neural circuits governing brain states and behaviors, including mood, anxiety, seizures and sleep.

The neuroactive steroid, SGE-516, is a positive allosteric modulator of both gamma- and delta subunit containing GABA<sub>A</sub> receptors. This broad GABA<sub>A</sub> receptor activity differentiates neuroactive steroids like SGE-516 from benzodiazepines, a class of anticonvulsants which have been shown in vitro to selectively target gamma-subunit containing GABA<sub>A</sub> receptors. This presentation will highlight the medicinal chemistry efforts towards the discovery of SGE-516 and other neurosteroids for the treatment of epilepsy.

MEDI 181

Probabilistic MPO (pMPO) and its application in CNS drug discovery

Hakan Gunaydin, gunaydin.hakan@gmail.com. Relay Tx, Cambridge, Massachusetts, United States

Multiparameter optimization (MPO) scoring functions are popular tools for providing guidance on how to design desired molecules in medicinal chemistry. The utility of a probabilistic MPO (pMPO) scoring function and its application as a scoring function for CNS projects will be discussed. This new scoring metric attempts to minimize the number of parameters that define MPO scores while maintaining a high level of predictive power. Results obtained from a test-set of orally approved drugs show that the pMPO approach can be used to separate blood–brain barrier penetrant drugs from the peripherally restricted ones. The application of this scoring function in medicinal chemistry projects that require CNS penetration will be discussed in this presentation.
MEDI 182

Harnessing preclinical data as a predictive tool for human brain tissue targeting

Nandini Patel, nandini.c.patel@pfizer.com. Pfizer Inc., Cambridge, Massachusetts, United States

Among the most devastating disorders of our time, neurologic and psychiatric diseases combine to cause more disability than any other disease area. Access to the central nervous system (CNS) is essential for most neuro-therapeutics to elicit their effects. One of the key objectives within the medicinal chemistry discipline is to design molecules that penetrate into the target tissue. The objective of tissue specificity can be to gain or restrict drug access to the compartment of interest. In brain tissue targeting, the active transport proteins such as P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP) are key components of the blood brain barrier (BBB) and it has been well established that drug candidates with high efflux ratios (ER) of these proteins have poor penetration into brain tissue. In the current work, we describe our efforts of leveraging design strategies by harnessing structural and physicochemical properties assessment coupled with the P-gp and BCRP transporters’ impact in determining brain penetration and its translation from rodent to human brain tissue targeting. This work will include our investigations of alternate MDR-MDCK cell lines as better predictions of brain penetration and establishment efforts of a correlation between in vitro, rodent data, non-human primate (nhp), and human in vivo data.

MEDI 183

BBB organoid platform for modeling therapeutic delivery to the brain

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Culture-based blood-brain-barrier (BBB) models are crucial tools to enable rapid screening of brain-penetrating drugs. However, reproducibility of in vitro barrier properties remains as a major challenge. Here, we report that self-assembling multicellular BBB organoids display reproducible BBB features and functions, and can be utilized as a screening tool for brain-penetrating molecules. The organoid core is comprised mainly of astrocytes, while brain endothelial cells and pericytes encase the outer surface of the organoid, acting as a ‘barrier’ that regulates transport of molecules, and which can be permeabilized in the presence of VEGF. The barrier is characterized by the presence of intact tight junctions and efflux-pump (i.e. P-glycoprotein) activity.
Furthermore, we have used this model to successfully demonstrate the transport of angiopep-2 (a well-known brain delivery vector) and its conjugates (containing cargoes of various sizes such as peptide, protein and affibody), thereby displaying the versatility of this model to screen and study a wide range of therapeutic agents. We demonstrate that this model is superior to the conventional transwell model in maintaining essential BBB characteristics (i.e., tight/adherens junctions and P-glycoprotein expression) and as a drug-screening tool. We have utilized the organoid model to screen and identify several molecules with high brain-penetration potential, which are then verified in mice. The BBB organoid platform represents an accurate, versatile and cost-effective in vitro tool that can be easily scaled to a high-throughput format, offering a next-generation tool for BBB modeling that could accelerate therapeutic discovery for the treatment of various neuro-pathologies.

**MEDI 184**

**Use of a CSF cannulated dog model in development of BACE1 inhibitors**

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In discovery programs for CNS targets, prediction of human brain penetration is critical for predicting efficacious exposure and dose. To predict brain penetration, compounds with favorable in vitro permeability and Pgp efflux parameters are typically evaluated in animal models (usually mouse) to determine the penetrance of unbound drug from the plasma into the CNS ($K_{pu,u}$). Variations between preclinical species, including mice, and humans in Pgp expression and measured $K_{pu,u}$ have been observed, suggesting mouse may not always be a good surrogate for human when evaluating brain penetration. In a BACE inhibitor (Alzheimer’s disease treatment) development program, a CSF cannulated dog model was utilized to evaluate PD following administration of BACE1 inhibitors. Beagle dog was chosen because the sequences of BACE1 and its substrate, APP, are very similar in humans and dogs. The cannulation and subsequent weekly CSF collection was well tolerated, with cannula patency generally maintained for a minimum of 6 months. Full PK time courses of both plasma and CSF in individual animals were collected, allowing determination of CSF:plasma AUC ratios. These ratios, along with CSF biomarker data, were used for PKPD modeling and dose projections in humans. Four BACE1 inhibitors developed through this paradigm have been administered to humans. In addition, 2 externally developed BACE1 inhibitors with reported human CSF:plasma ratios were evaluated with the dog model. These six compounds span a range of CNS penetration, physical-chemical properties, and protein binding. CSF $K_{pu,u}$ in humans was very well predicted from dog data, including compounds for which mouse underpredicted human $K_{pu,u}$. These data indicate dog is an excellent predictor of CNS penetration for the BACE1 inhibitor program. This model allowed non-terminal, serial CSF collections and required a relatively small number of animals to prosecute entire discovery programs. Assessment of applicability for other scaffolds is warranted.
MEDI 185

Considerations for optimizing CNS penetration and successful programs

Craig W. Lindsley, craig.lindsley@vanderbilt.edu. Dept of Pharmacology, Vanderbilt University, Nashville, Tennessee, United States

This talk will focus on strategies and tactics to assess and optimize small molecules for CNS penetration. Key considerations for species differences and human projections for CNS exposure will be discussed. Finally, examples of both successes and failures will be disclosed, along with lessons learned.

MEDI 186

Optimization and identification of brain penetrant, M4 subtype-selective muscarinic receptor positive allosteric modulator (M4 PAM) clinical candidate

Christopher Butler, christopher.r.butler@pfizer.com. Medicine Design, Pfizer, Cambridge, Massachusetts, United States

M4 muscarinic acetylcholine receptor (mAChR4) activators offer a novel strategy for the treatment of psychosis in a number of neurological disorders. Advancement of non-selective orthosteric muscarinic agonists has traditionally been challenging due to poor toleration and side effects traditionally linked to concomitant activation of other mAChR subtypes (M1- M3). To overcome the issue of subtype selectivity, we focused on developing brain penetrant M4 selective positive allosteric modulators (PAMs). This presentation will focus on the design efforts employed to overcome a number of specific challenges in the discovery of novel M4 PAM series, ultimately resulting in the identification of high quality compounds that were suitable for development. Strategies to overcome brain penetration challenges will be also be presented.

MEDI 187

Cyclic peptide ternatin-4 promotes degradation of the translation elongation factor, EF1A

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We recently discovered that ternatin-4, a cyclic peptide related to the natural product ternatin, blocks cancer cell proliferation by targeting elongation factor 1A (EF1A). Similar to the unrelated cyclic depsipeptide, didemnin B, ternatin-4 traps EF1A at the ribosome A site, inhibiting translation elongation. Cryo-electron microscopy studies revealed that, while ternatin-4 and didemnin both bind to an interdomain allosteric site on EF1A, the conformation of the EF1A GTPase domain is distinct in the two complexes. In cells, ternatin-4 potently and directly induces proteasome-dependent degradation of EF1A.
degradation of EF1A, whereas didemnin does not. We speculate that ternatin-4 induces the accumulation of stalled elongating EF1A/ribosome complexes, which are subsequently recognized and ubiquitinated by an as yet unknown quality control system.

**MEDI 188**

**Small-molecule estrogen receptor degraders (SERDs): Chemical exploration and optimisation at AstraZeneca**

*Jamie S. Scott, jamie.scott@astrazeneca.com. Oncology Chemistry, AstraZeneca, Cambridge, United Kingdom*

The estrogen receptor alpha (ERα) is expressed in >70% of breast cancers and is a clinically validated target in oncology. Anti-hormonal therapies that directly block ER function (e.g., tamoxifen) or therapies that block the production of estrogen itself (e.g., aromatase inhibitors) have proven to be effective treatments of the disease. Further advances have been made with the development of SERDs (Selective Estrogen Receptor Degraders) such as fulvestrant which both antagonise ERα-driven tumor cell growth and cause degradation of the ERα receptor.

This presentation will describe work carried out at AstraZeneca to discover novel, orally bioavailable SERDs across a range of chemotypes. The challenges of working on phenol containing chemotypes will be discussed, together with the identification of a tricyclic indole scaffold that led to the clinical candidate AZD9496. Additional work to identify novel chemotypes including phenol 1 and indazole 2 will be described together with some of the medicinal chemistry challenges that were faced along the way. The use of NMR derived solution phase conformations as part of an optimisation strategy will also be discussed.
Small molecules that catalyze the degradation of splicing factors

**Deepak Nijhawan**, deepak.nijhawan@utsouthwestern.edu. *Biochemistry and Internal Medicine, UT Southwestern Medical Center, Dallas, Texas, United States*

Indisulam is a small molecule that is selectively toxic to a subset of human cancer cell lines, including hematopoietic and lymphoid derived cancers. Previously, our lab discovered that both indisulam and related sulfonamides recruit the splicing factor RBM39 to DCAF15, a substrate receptor that forms part of a CUL4 E3 ubiquitin ligase complex. This recruitment results in RBM39 ubiquitination and degradation, leading to splicing defects and cell death. RBM39 has a serine-arginine (SR) domain and three cognate RNA recognition motifs (RRMs). The second RRM (RRM2) is critical for recruitment of RBM39 to DCAF15 by indisulam. Mutations in the second RRM (RRM2) block recruitment of RBM39 to DCAF15 raising the hypothesis that proteins with related RRMs might also be degraded by indisulam. RBM23 is a closely related paralog to RBM39, with more than 95% sequence identity in the RRM2 domain. We found that RBM23, like RBM39, is recruited to DCAF15 by indisulam, ubiquitinated, and degraded. Using purified components, we have reconstituted the in vitro ubiquitination of both RBM39 and RBM23. Indisulam and related sulfonamides catalyze the degradation of two predicted splicing factors, RBM39 and RBM23. These findings provide a novel strategy to target RNA binding proteins in disease. Future studies will help determine whether specific derivatives can selectively degrade RBM39, RBM23, or other RRM containing proteins.

**MEDI 190**

**Discovery of CC-92480: CRBN E3 ligase modulating drug (CELMoD) for the treatment of relapsed and refractory multiple myeloma**

**Joshua D. Hansen**, doctorhansenchemist@gmail.com, **Mark Nagy**, **Matthew Correa**, **timothy kercher**, **roy harris**, **Matthew D. Alexander**, **Dehua Huang**, **veronique plantevin**, **Virginia H. Grant**, **brandon whitefield**, **Antonia Lopez-Girona**, **Courtney Havens**, **Derek Mendy**, **Rama Krishna Narla**, **Yang Tang**, **Joseph R. Piccotti**, **Brian E. Cathers**, **gody khambatta**, **laurie LeBrun**. (1) Celgene, La Jolla, California, United States (2) Medicinal Chemistry, Celgene, San Diego, California, United States (3) Chemistry Department, Celgene Corporation, San Diego, California, United States (4) Nonclinical Development, Celgene Corporation, San Diego, California, United States (5) Celgene Corporation, San Diego, California, United States

Induction of protein degradation as a therapeutic strategy has been clinically validated by the class of immunomodulatory drugs lenalidomide and pomalidomide which are known to target Ikaros/Aiolos for degradation. In this session, we will disclose the structure of CC-92480, a CELMoD that was specifically designed to address relapsed and refractory multiple myeloma (RRMM). CC-92480 drives the formation of a protein–protein interaction between zinc finger proteins such as Ikaros and Aiolos with cereblon (CRBN), which induces targeted docking to the CRL4\textsuperscript{CRBN} E3 ubiquitin ligase complex.
The CC-92480-dependent binding of Ikaros/Aiolos to CRBN leads to polyubiquitination and ultimately proteasome-mediated degradation of Ikaros/Aiolos. Our strategy to discover cereblon modulators with activity against RRMM employed an approach guided by both phenotypic and protein degradation data. In this presentation, a description of the SAR, preclinical DMPK, and efficacy data leading up to the discovery and selection of the novel protein degrader, CC-92480 will be shared.

MEDI 191

ASTX660, a small molecule antagonist and degrader of cellular inhibitor of apoptosis proteins in phase I/II clinical trials

Rhian Holvey, rhian.holvey@astx.com. Astex Pharmaceuticals, Cambridge, United Kingdom

The inhibitor of apoptosis proteins (IAPs) are key regulators of apoptosis and pro-survival pathways. Overexpression of IAPs has been associated with tumour progression and resistance to treatment. As a result, IAPs have been proposed as anticancer therapeutic targets and several IAP antagonists have entered clinical trials. Binding of antagonists to cellular inhibitor of apoptosis proteins (cIAPs) causes auto-ubiquitination and degradation of the protein.

We have successfully applied our fragment-based screening approach, Pyramid™ discovery platform, to identify non-peptidic fragments binding with millimolar affinities to both cellular inhibitor of apoptosis protein 1 (cIAP1) and X-linked inhibitor of apoptosis protein (XIAP). Structure-based hit optimisation guided by computational studies and NMR solution conformational analysis allowed us to significantly increase the binding affinity of the starting hits. The subsequent lead optimisation campaign resulted in ASTX660, a potent non-peptidic antagonist of cIAPs and XIAP, structurally distinct from all previously reported antagonists. Potent cIAP degradation has been demonstrated with ASTX660 in multiple in vitro and in vivo models and the compound is currently being tested in a Phase I/II clinical trial (NCT02503423) in cancer patients, where we have seen deep and sustained cIAP1 suppression in peripheral blood mononuclear cells (PBMCs) sampled from ASTX660-treated patients.

MEDI 192

Discovery and characterization of a novel small molecule BRD4 protein degrader

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BRD4 is a member of the bromodomain and extra-terminal (BET) family of proteins (BRD2, 3, 4 and T) and functions as an epigenetic “reader” of acetylated histone lysine residues via its two bromodomain motifs (BRD1 and BRD2). Disruption of BRD4-histone interactions is currently viewed as an attractive strategy for the development of novel anti-cancer agents, and many BRD4 inhibitors are currently undergoing clinical trials for various oncology indications. Recently, chimeric Chemical Inducers of Degradation (CIDEs) which form ternary complexes between BRD4 and various E3 ligases (e.g., VHL, CRBN, XIAP, MDM2) were shown to potently degrade the BRD4 protein, and these entities may offer additional therapeutic opportunities relative to simple inhibitors. As part of our exploration of BRD4-targeting CIDE molecules, we unexpectedly discovered a monomeric (i.e., non-chimeric) small molecule which potently degraded the BRD4 protein in a manner that was similar to that observed for larger CIDE compounds. This presentation describes the identification of this novel, small-molecule BRD4 degrader (GNE-0011) along with its chemical, structural, and biological characterization.

GNE-0011 was highly active in cell-based assessments of MYC transcription inhibition activity and antiproliferation properties. It also exhibited stronger potency in these in vitro assays as compared to structurally-related BRD4 inhibitors which did not degrade the protein. In addition, western blot and global proteomics analyses indicated relatively selective GNE-0011-mediated degradation of BRD4 over the closely related BRD3 and BRD2 BET family members. GNE-0011 was active in a mouse xenograft tumor model in vivo where it also exhibited significant intratumor degradation of the BRD4 protein. Several GNE-0011 analogs were subsequently synthesized (both active and inactive molecules), and the resulting structure-activity relationships will be disclosed. A crystal structure of GNE-0011 in complex with BRD4 will also be presented and discussed.

MEDI 193

Translational chemistry

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There can be no more noble undertaking than the invention of medicines. Chemists that make up the engine of drug discovery are facing incredible pressure to do more with less in a highly restrictive and regulated process that is destined for failure more than 95% of the time. How can academic chemists working on natural products help these heroes of drug discovery – those in the pharmaceutical industry? With selected examples from our lab and others, this talk will focus on that question highlighting interesting findings in fundamental chemistry and new approaches to scalable chemical synthesis.
Progress in the discovery of kinase inhibitors for treatment of parasitic diseases

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Parasitic diseases such as malaria, filariasis and leishmaniasis remain challenging to treat in part because of the unique features of the life cycle and/or responses of organisms to the host immune system. Like other infectious diseases, resistance to existing therapies is an important and ongoing concern, as are the adverse events associated with currently available agents. In an effort to address these issues, our group is investigating the discovery and optimization of kinase inhibitors that target multiple steps in the life cycle of a kinase in Plasmodium falciparum that plays a role in at least two distinct points in the life cycle and a kinase in Brugia malayi that is believed to play an important role in the organism's response to the human immune system. This presentation will describe progress in these efforts.

Joining forces: Discovery of novel biological tools and utilising new therapeutic modalities

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The pharmaceutical industry has suffered many challenges in its endeavours to improve human health. However, as our understanding and replication of complex biological systems is increasing and exciting novel biological targets are being discovered it is creating new opportunities for scientists to innovate and discover new medicines. These targets include growth factor receptors, protein-protein and protein nucleic acid interactions, which are often refractory to classical small molecule approaches. Other types of molecules, or modalities, can therefore be used to address these targets. Applying new therapeutic modalities suggest a more impactful and successful future to discover new innovations to save patient’s lives.

This talk will outline these opportunities and some recent advances across modalities. I will showcase different possibilities including peptides. Peptides are often highly selective and potent signalling molecules and this class of molecules have contributed towards many drugs which are used to treat disease. However, the inherent instability of peptides in plasma leading to a short half life after dosing has limited the broader application of peptide-based drugs. A range of approaches are now being explored and applied to extend the half life of bioactive peptides including the use of more stable, natural and unnatural peptidic frameworks and utilising other modalities, such as small molecules, conjugated to peptides to enhance their properties. In addition to acting as therapeutic agents themselves, the exquisite selectivity of peptides is also now being
used to target other agents to specific tissues. Once a bioactive peptide with the desired biological properties has been discovered, many challenges remain including optimising the physicochemical and biophysical properties of the peptide-based molecules to allow effective development, ultimately allowing future treatment options for patients. All of these perspectives will be discussed with examples during this presentation.

MEDI 196

How I spent my summer vacation: Insights from a 30-year career in drug discovery (and molecules that have broken my heart)

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"How I spent my summer vacation: insights from a 30-year career in drug discovery (and molecules that have broken my heart)" will cover numerous truisms and stories of molecules that almost became marketed drugs (some still have a chance). Insights from philosophers such as Confucius, Mike Tyson, Clint Eastwood, and others will be interspersed with vignettes of the successes and heart-breaking failures of drug discovery.

MEDI 197

Property-based drug design: bRo5

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Abstract
Lipinski’s Rule of Five (Ro5), introduced in the late 90’s, ushered in the dogma of property-based drug design. Its premise is based upon the observation that compounds occupying the physicochemical property space mapped by Lipinski, have a higher probability of achieving good oral absorption and solubility compared with compounds beyond this frontier of property space. In recent years, however, due to the emergence of new less druggable targets, pharmacological property space (the property space of ligands likely to bind to a given targeted protein) has diverged beyond Ro5, making the path to developing an oral drug agent rather more challenging. This presentation will examine small molecule drug discovery beyond Ro5 and map areas of property space beyond Ro5 where it is possible to design orally bioavailable agents with the potential to drug high value, less druggable, protein targets.

Disclosure: All authors are employees of AbbVie. The design, study conduct, and financial support for this research were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication.

MEDI 198
Onward, beyond the rule of 5! Understanding and controlling cell permeability in macrocyclic peptides

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Cyclic peptides have undergone a renaissance in medicinal chemistry, as studies into structure-property relationships have revealed that passive cell permeability can be designed into synthetic cyclic peptide scaffolds when conformational factors are considered. My group has been studying the physico-chemical properties that underlie passive membrane permeability in cyclic peptides, and we have determined a set of rules that may help to bias large, encoded libraries toward cell permeability. I will discuss new directions for our group using high-content, image-based screening to evaluate the phenotypic diversity of libraries inspired by highly bioactive and cell permeable cyclic peptide natural products.

MEDI 199

Approaches to targeting protein-protein interactions

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Protein-protein interactions (PPI) are ubiquitous in biology and comprise a large set of potential drug targets. Whereas PPI were once considered ‘undruggable,’ the past several years have seen a number of successful efforts to develop small-molecule inhibitors of PPI. This presentation will summarize the state of the field of PPI inhibition, including progress on selection of ‘druggable’ targets and small-molecule discovery methodologies. Additionally, it is also important to acknowledge that PPI occur in complex networks; hence drug discovery should account for selective inhibition of PPI within a network. Furthermore, it is increasingly clear that these networks can be altered in disease states, and drug discovery efforts have been directed towards disease-specific PPI. Examples from our own lab, including PPI stabilization, inhibition of PPI within networks, and allosteric regulation of PPI, will also be described.

MEDI 200

Breaking the rules to interdiction at a protein-protein interface: Structure-based design of the Mcl-1 inhibitor AMG 176

Sean P. Brown, seanpomeroy@yahoo.com. Chemistry, Proneurotech, South San Francisco, California, United States

The prosurvival BCL-2 family member MCL1 is frequently dysregulated in cancer. To overcome the significant challenges associated with inhibition of MCL1 protein-protein
interactions, we rigorously applied small-molecule conformational restriction, which culminated in the discovery of a Rule of Five noncompliant clinical candidate, AMG 176.

MEDI 201

Design of orally bioavailable proteolysis targeting chimera (PROTAC) small-molecule degraders

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In the last few years, design of proteolysis targeting chimera (PROTAC) small-molecule degraders has gained a tremendous momentum for its promise for the discovery and development of a completely new type of medicines for the treatment of human cancer and other diseases. A typical PROTAC small-molecule degrader consists of a small-molecule ligand, which binds to the target protein of interest, a ligand to binds to and recruits a E3 ligase complex, and a linker, which tethers the two ligands together. A typical PROTAC small-molecule degrader hence has a molecular weight of >800. Therefore, design of orally bioavailable small-molecule degraders suitable for clinical development has presented a considerable challenge to the medicinal chemistry community. In this talk, I will present our efforts in the design of orally bioavailable PROTAC small-molecule degraders and the lessons we have learned from our research efforts.

MEDI 202

Chemical induced dimerization for targeted protein degradation
James Bradner, james.bradner@novartis.com. Novartis Institutes for BioMedical Research, Cambridge, Massachusetts, United States

The increasingly atomic resolution of human biology presents an unprecedented opportunity for the innovation of definitive medicines for life-threatening diseases. Still, many well-defined, high-value protein targets remain beyond the limits of historical efforts in ligand discovery. Often challenging the discovery of therapeutics that disable intracellular proteins is the real or perceived limitation of small molecules to engage non-canonical protein folds and disrupt a biophysical or biochemical function. We have therefore undertaken to invest in the discipline of chemical biology as an organizing principle in drug discovery, so as to create vast numbers and new types of small molecules to advance the science of therapeutics. In this seminar, I will discuss progress in the field of targeted protein degradation, inspired by natural products and advances in chemical-induced dimerization. I will highlight both foundational research as well as our recent, first all-chemical approach that establishes design principles for new ligands, demonstrates extensibility to numerous cellular targets and informs mechanistic cellular biology. Importantly, lead optimization of chemical probes brings extraordinary (sub-nanomolar) potency, reveals catalyst-like activity, and now emanates first-in-class therapeutics. Finally, I will discuss learnings from our Targeted Protein Degradation Initiative, including curious challenges around which our ongoing research organizes.

MEDI 203

Targeted small molecule degradation of a hypoxia-associated non-coding RNA enhances the selectivity of an RNA targeted small molecule

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Small molecule targeted recruitment of nucleases to RNA is a powerful method to affect RNA biology. Informa, a sequence-based design approach to target RNA, enables the design of small molecules that bind and cleave RNA in a selective and substoichiometric manner. Herein, we investigate the ability of RNA targeted degradation to improve the selectivity of small molecules targeting RNA. The microRNA-210 hairpin precursor (pre-miR-210) is overexpressed in hypoxic cancers. Previously, a small molecule (Targapremir-210, TGP-210) targeted this RNA in cells, but with only a 5-fold window for DNA binding. Appendage of a nuclease recruitment module onto TGP-210 locally recruited ribonuclease L onto pre-miR-210, triggering its degradation. The chimera has enhanced selectivity compared to TGP-210 with nanomolar binding to the pre-miR-210, but no DNA binding, and is broadly selective for affecting RNA function in cells. Importantly, it cleaved pre-miR-210 substoichiometrically and induced apoptosis in breast cancer cells.

MEDI 204
Novel phyllanthusmin derivatives as anticancer agents: Pharmaceutical optimization and mechanistic insight

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Diphyllin glycosides have recently garnered significant interest for their antiproliferative properties. A particularly potent member of this class, phyllanthusmin D, served as inspiration for lead optimization. After the synthesis of over 60 analogues, PHY-34 stood out as a novel lead compound displaying a 500-fold improvement in in vitro activity over phyllanthusmin D. PHY-34 also showed promising in vivo efficacy and late stage autophagy inhibition and hinted at potential oral bioavailability (2.5%). To further improve pharmacological properties, efficient routes to several late stage intermediates have been developed to investigate both the glycone and aglycone portions of the molecule as well as to develop a series of carbasugar analogues. The current hypotheses regarding mechanistic target(s) for this class of molecules, acquired through the synthesis of a variety of mechanistic probes, will also be discussed.

MEDI 205

Altering the tumor microenvironment to improve immunotherapy: Molecular imaging of PD-L1 in pancreatic cancer
Immunotherapy targeting the PD-1/PD-L1 axis has shown promise in some cancer subtypes but has failed in many solid tumors, including pancreatic ductal adenocarcinoma (PDAC). This is largely attributed to the migration of immune cells into the characteristically desmoplastic stroma in PDAC, creating an immune-quiescent tumor microenvironment (TME). MYC is an oncogenic protein that orchestrates an immune-suppressive TME and has been linked to PD-L1. We hypothesize that MYC-targeted therapy will make tumors “hot” by activating the TME, increasing PD-L1 antigen presentation for therapeutic targeting. In order to test this hypothesis, we created a molecular imaging agent from an anti-PD-L1 antibody (clone 6E11, Genentech) to noninvasively assess effects of targeted therapy on PD-L1 antigen presentation in vivo. Anti-PD-L1 was conjugated to desferrioxamine to enable labeling with zirconium-89 ($^{89}$Zr) for positron emission tomography (PET) imaging. KPC PDAC cells were inoculated orthotopically into the pancreas of C57BL/6J mice. KPC tumor-bearing mice were then treated with ERK inhibitor SCH772984 (90 mg/kg daily for 6 days) and injected with $[^{89}$Zr]$^{89}$Zr-anti-PD-L1 to undergo serial PET imaging and biodistribution. Tumors were resected and stained for MYC and PD-L1 via immunofluorescence. The specific activity and molar activity for $[^{89}$Zr]$^{89}$Zr-PD-L1 were 4 mCi/mg and 600 mCi/mmol, respectively, and radiochemical yield and purity was >98%. We observed statistically significant increase in uptake of $[^{89}$Zr]$^{89}$Zr-PD-L1 (P < 0.05) upon treatment with ERK inhibitor, with a correlation to increased expression of PD-L1 via ex vivo immunofluorescence. In conclusion, we have shown a significant increase in the uptake of $[^{89}$Zr]$^{89}$Zr-PD-L1 from indirect MYC-targeted therapy, correlated to an increased expression of PD-L1 ex vivo. Further studies to fully characterize the immune microenvironment via ex vivo flow cytometry and immunohistochemistry are underway to dissect the mechanism of this phenomenon. We anticipate our noninvasive $[^{89}$Zr]$^{89}$Zr-PD-L1 tool will drive synergistic combinatorial therapeutic approaches in PDAC.

MEDI 206

Encoding all stereoisomers of homologous cyclic β-aryl amino acids

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DNA-encoded libraries of small molecules have emerged as efficient tools for the identification of hit-matter in the early phases of drug discovery. However most published libraries, owing to the synthetic restrictions of DNA being present, have low scaffold diversity – both within a given DEL and when compared to existing screening collections.
To address low scaffold diversity a synthetic route leveraging stereospecific CH arylation of cyclic amino acids was used to access all stereoisomers of the resulting trifunctional compounds. The Fmoc amino acids resulting from this synthesis have been linked to DNA and elaborated into a DEL of 520,800 compounds.

This talk will cover aspects of synthetic optimization on and off DNA, as well as library validation and early screening results against targets of interest.

MEDI 207

Adventures in allosteric drug discovery

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The Scarborough lecture will feature caveats in key lessons learned over 20 years of drug discovery efforts focused on allosteric modulation of kinases, GPCRs and other targets. I will cover critical considerations regarding pharmacology, Medicinal chemistry and lead optimization flow charts unique to allosteric targets. Specifically, I will cover the journey from HTS to Phase I of an M1 PAM, devoid of cholinergic toxicity in preclinical safety species and man.

MEDI 208

Immunopharmacotheraphy for the treatment of substance use disorders

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Substance use disorders are a global public health concern with less than optimal treatment outcomes. This is most evident with the national emergency declared against the opioid crisis. Our ability to prevent the spread of drug abuse and aid individuals with a substance use disorder is handicapped by the lack of sufficient treatment modalities. For example, many patients receiving treatment relapse; therefore, there is an urgent need to discover effective medications to treat opioid abuse. Traditional, small-molecule approaches have only been marginally successful in treating substance use disorders; as such we have sought alternative treatments to conventional drug pharmacotherapies. “Biologics” based therapeutics offer an alternative to customary pharmacodynamic approaches for treating both substance use disorders as well as lethality threats from many of these drugs. Specifically, I will discuss the history and some basic tenets on vaccination as well as how vaccination can alter the pharmacokinetic properties of drugs without burdening the recipient with untoward CNS side effects. Moreover, the lecture will detail the chemistry, immunology and behavioral findings from some of our vaccines against opioids including heroin, the fentanyl’s and
oxy/hydrocodone. Finally, I will detail how we can utilize a biologic from a bacterial source as a means of treating nicotine substance disorders.

**MEDI 209**

**Natural product derived privileged scaffolds in drug discovery**

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Natural products (NPs) are an invaluable source of inspiration in drug design and development and have long been regarded as “Nature’s medicine chest” providing invaluable platforms for developing front-line drugs. 65% of the 1211 small-molecule new drugs approved between 1981-2014 were “inspired by” natural products. Having evolved over several millennia to acquire specific ligand-protein binding motifs, NP structures cover a wide range of biologically relevant chemical space that cannot be efficiently explored by synthetic compounds in commercially available screening libraries. These privileged scaffolds serve as important, biologically pre-validated platforms for the design of compound libraries in the search for new drug candidates. NPs favour inclusion of aliphatic over aromatic rings, as well as more sp$^3$-hybridised bridgehead atoms and chiral centres than synthetic small molecules. As the clinical success of drug candidates is directly correlated to three-dimensionality of the molecules, NPs clearly possess an advantageous structural foundation over synthetic small molecules in the development of drug candidates. The neglect of chirality has been recognized as a key deficiency of contemporary drug discovery methodology. However, the structural complexity, toxicity, and unfavourable pharmacokinetics (PKs) often associated with NPs can limit their clinical potential, and as such, structural modification is often required. To this end, many leading chemists are not only targeting bioactive NPs, but also libraries of structurally related compounds for biological evaluation. The core scaffold of NPs and their analogue libraries may therefore be considered “privileged” since contemporary use of the term typically refers to multiple compounds with the same core scaffold possessing bioactivity. Herein advances in the use of NP-derived privileged scaffolds in drug discovery are described. This lecture will also showcase the synthesis of bioactive NPs and peptides from our own research as examples of unexplored novel structural chemotypes.
There is an ongoing need in biomedical research to rapidly identify high-quality chemical probes and drug candidates. The exchange of a CH group with a N atom in aromatic and heteroaromatic ring-containing lead compounds can have many important effects on molecular and physicochemical properties and intra- and intermolecular interactions that can meaningfully impact pharmacological profiles. This presentation will provide a perspective on leveraging the "necessary nitrogen atom" in probe and drug design, including case studies of its successful application to achieve program goals.

Exchange of a CH group with a N atom: A small structure modification with potentially large impact
Geminal diheteroatomic motifs in drug design: Applications of acetals, ketals, and their sulfur and nitrogen homologues in medicinal chemistry

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There is a widespread perception within the medicinal chemistry community that acetals and ketals and their nitrogen and sulfur homologues are unsuitable scaffolds for the design of orally delivered drugs due to an anticipation of instability under the acidic conditions of the stomach and upper gastrointestinal tract. However, the chemical stability of acetals, ketals and their nitrogen and sulfur homologues can readily be modulated by the judicious use of substituents that allows their application in circumstance that require either enhanced or diminished stability toward low pH. Moreover, acetals, ketals and aminals can combine conformational restriction with unique electronic-withdrawing properties that can lead to improved biological activity and pharmaceutical properties for a chemotype. This presentation will survey some of the applications of acetals, ketals and their sulfur and nitrogen homologues in the discovery of both orally bioavailable drugs or drug candidates and applications in drug delivery.

MEDI 212

Design of ligands targeting carbohydrate binding sites: Galectin 3

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Designing small high affinity lectin inhibitors starting from natural saccharides is a major challenge due to their polarity and that the matching lectin binding sites not only are polar but also shallow. The lectin/ligand interactions are often made up by complex hydrogen networks which in some cases are strengthened by other interactions such as CH-π stacking between the ligand carbohydrate skeleton and aromatic aminoacids. Therefore, natural mono- and disaccharides in general have low binding affinities in the µM-mM range. Polar ligands like saccharides in general also have low passive uptake over the intestine and often rapid renal or biliary excretion. Despite these challenges several ligands targeting carbohydrate binding sites of different target classes have been discovered and developed into medicines. Examples are the heparin mimetic fondaparinux, the glifozins which are glucose transporter inhibitors (SGLT2), inhibitors of the uropathic E. coli adhesin FimH, influenza neuraminidase inhibitors zanamivir and oseltamivir, selectin inhibitors, siglec inhibitors and the iminosugar miglastat, which last year was approved by FDA for treatment of Fabry disease.

We have developed small high affinity carbohydrate-based ligands targeting galectin 3, a target involved in the pathology of inflammation and fibrosis. Our first inhibitor TD139 is currently in phase llb trials, being developed as an inhaled treatment of idiopathic...
pulmonary fibrosis (IPF). Recently we discovered an orally available galectin 3 inhibitor GB1211 which has been taken into phase 1 clinical trials in healthy volunteers targeting non-alcoholic steatohepatitis (NASH). This presentation will discuss learnings from the design of ligands targeting carbohydrate binding sites with examples from both our own galectin research and literature.

**MEDI 213**

**Sulfoximines in drug discovery revisited: What has happened since 2013?**

*Ulrich T. Luecking, ulrich.luecking@bayer.com. Pharmaceuticals Division, Bayer AG, Berlin, Germany*

In 2013, the first review article recommending the introduction of the sulfoximine group as a versatile pharmacophore to the medicinal chemist’s toolbox was published.[1] Sulfoximines, the mono-aza analoges of sulfones, by then had received little interest in drug discovery, despite their very interesting properties.[1,2]

However, interest in this unusual functional group has increased substantially in recent years, which is exemplified by the selection of several novel sulfoximine compounds for clinical evaluation (e.g. atuveciclib, BAY 1251152, AZD6738). Moreover, a significant and ever-increasing number of sulfoximines featured in scientific articles and life science patent applications, as well as commercially available sulfoximine building blocks, serve to highlight the increased acceptance of this functional group by the drug discovery community.

This presentation provides an overview on the use of the formerly neglected sulfoximine group in drug discovery since 2013, focusing on selected use cases from the literature.
Endogenous and synthetic neuroactive steroids (NASs) or neurosteroids have been shown to be effective modulators of neuronal signaling pathways, most notably, the γ-aminobutyric acid A (GABA_A) and the N-methyl-D-aspartate (NMDA) receptor systems. These receptors play a major role in inhibitory and excitatory signaling pathways within the central nervous systems and have been the target for many drug discovery efforts over the past decades, although mostly focusing on multiple receptors sites not associated with allosteric modulation. Proposed endogenous ligands have been reported for the allosteric modulatory sites in both receptors and there is growing evidence suggesting that synthetic modulators may have an impact on disease states rooted in the dysregulation of these receptors. The significant unmet medical need for treatment of CNS disorders has increased the interest for these types of novel drugs. This presentation will highlight recent progress in the drug discovery and early clinical development of NAS drug candidates at Sage Therapeutics, which has focused on treating various GABA_A and NMDA based disorders.

**MEDI 215**

**Discovery of MK-8719: Potent O-GlcNAcase inhibitor as a potential treatment for tauopathies**

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This presentation will describe the medicinal chemistry and pharmacological studies leading to identification of the first-in-class clinical O-GlcNAcase (OGA) inhibitor, MK-8719. The development of preclinical pharmacodynamic biomarkers and translation to clinical (Ph I) results will also be presented.

One of the pathological hallmarks of Alzheimer's disease (AD) and other neurodegenerative tauopathies is the accumulation of neurofibrillary tangles (NFTs) in the brain. NFTs are composed primarily of aggregates of the microtubule-associated protein tau. Aggregation of tau appears to be driven by its abnormal hyperphosphorylation leading to self-assembly into the paired helical filaments that make up NFTs. Pathological species of tau are thought to play a central role in driving...
neuronal cell death in these diseases and the extent of NFT pathology correlates with clinical progression in AD. Emerging evidence also supports the idea that soluble hyperphosphorylated tau species are involved in prion-like propagation of tau pathology throughout the brain in AD. Consequently, major efforts are focused on targeting pathogenic tau species to develop disease-modifying therapies for AD and related tauopathies.

O-GlcNAcylation is a reversible post-translational modification that involves addition of O-linked N-acetylglucosamine (O-GlcNAc) to serine and threonine residues, and is regulated by two enzymes: O-GlcNAc transferase, which catalyzes addition of O-GlcNAc to proteins, and OGA, which catalyzes cleavage of O-GlcNAc from proteins. O-GlcNAcylation of tau has been proposed to regulate its phosphorylation state, with increased O-GlcNAc modification being correlated with lower tau phosphorylation. In addition, in vitro studies indicate that increased O-GlcNAcylation of tau hinders its propensity for aggregation. These data suggest that OGA inhibition could increase O-GlcNAc modification of tau and reduce the formation of pathogenic tau species. Consistent with this idea, multiple independent studies using transgenic murine models of tauopathy have shown that administration of the small-molecule OGA inhibitor Thiamet-G confers beneficial effects, including: reduced phosphorylated tau species and tau aggregates, reduced tau levels in cerebrospinal fluid, decreased neuronal cell loss, and reduced disease-associated behavioral phenotypes. On the basis of these findings, OGA inhibition has emerged as a therapeutic strategy to treat tau pathology in AD and other tauopathies.

MEDI 216

Discovery of SAR439859, an orally bioavailable Selective Estrogen Receptor Degrader (SERD) to treat ER+ breast cancers

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More than 75% of breast cancers are estrogen receptor alpha (ERα) positive and resistance to current hormone therapies occurs in one third of ERα patients. Clinically resistant tumors are still ERα dependent, but mutations usually confer constitutive activation to the hormone-receptor, rendering ERα modulator drugs such as tamoxifen and aromatase inhibitors ineffective. Fulvestrant is a potent Selective Estrogen Receptor Degrader (SERD), which degrades the ERα receptor in tamoxifen-resistant tumors which has been approved in 2002 for the treatment of hormone receptor positive metastatic breast cancer following antiestrogen therapy. However, fulvestrant shows poor pharmacokinetic properties, linked to its low solubility, weak permeation and high metabolism which limit its efficacy in cancer patients.

This lecture will describe the discovery of SAR439859, a novel, orally bioavailable SERD, which is a potent degrader of ERα both in vitro and in vivo. Elements of Structure-activity relationships of SAR439859 will be reported as well as preclinical and preliminary clinical data obtained in patient.
SAR439859, is currently in phase I/IIa clinical development for the treatment of ERα positive breast cancer.

**MEDI 217**

**Movement to the clinic of soluble epoxide hydrolase inhibitor EC5026 as an analgesic for neuropathic pain and for use as an non-addictive opioid alternative**

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The soluble epoxide hydrolase (sEH) is an alpha/beta hydrolase fold enzyme that rapidly converts epoxyfatty acids (EpFAs) to the corresponding diols. EpFAs are lipid mediators which resolve inflammation including neuroinflammation, block pathological fibrosis, reduce hypertension and ameliorate both inflammatory and neuropathic pain. sEH inhibitors (sEHI) stabilize EpFAs thus increasing their biological lives and potency. sEH act in a variety of disease states to increase mitochondrial stability and reduce endoplasmic reticulum stress. Target occupancy was found to be the best in vitro predictor of in vivo efficacy for the sEHI, and the clinical candidate is a transition state mimic with slow off rate. The analgesic potency of the class has been shown in a number of rodent models as well as in equine and other veterinary patients. Operant tests fail to indicate addiction potential and in fact suggest a reduction in opioid withdraw hyperalgesia (pain). sEHI synergize with NSAIDs and COXIBs. sEHI do not show the gastrointestinal side effects of COXIBs and NSAIDs and reverse GI erosion in animal models. The previously described sEH inhibitor TPPU is a commonly used tool compound with a low Ki and good in vivo target occupancy, excellent oral bioavailability and good pharmacokinetics. TPPU shows strong activity in a number of human pluripotent stem cell and murine models of CNS disorders including Alzheimer’s, autism, depression, Lewy body dementia, schizophrenia and others. The sEH protein and message are increased in key regions of the brain and EpFAs are altered as expected in both murine models and human cadaveric samples with CNS inflammation suggesting broad application to CNS disorders. The novel clinical candidate sEHI, EicOsis 5026, has low picomolar potency on the human recombinant sEH, good oral availability and excellent PK-ADME. It has completed initial CMC and IND enabling work showing a good safety profile and an excellent therapeutic index. This peripherally restricted compound is expected to enter human Phase 1 trials in June under the NIH-NINDS Blueprint Development Program. Diabetic neuropathic pain is our principle clinical target, but EC5026 also shows promise as a non-addictive opioid replacement in many pain indications.

**MEDI 218**
Discovery of AB928, a potent first-in-class dual $A_{2a}$ and $A_{2b}$ receptor antagonist for cancer immunotherapy

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In the tumor micro-environment (TME), extracellular ATP is sequentially hydrolyzed to adenosine by the ecto-nucleotidases CD39 (ATP→AMP) and CD73 (AMP→adenosine), driving the suppression of immune cell function. $A_{2a}$R is expressed by a variety of lymphocyte populations, mainly T and NK cells, while myeloid cells express both $A_{2a}$R & $A_{2b}$R. $A_{2a}$R activation results in decreased T cell activation, while binding of adenosine to $A_{2b}$R on myeloid cells promotes a tolerogenic phenotype. To alleviate immune suppression within the TME, we designed AB928, a potent, first-in-class, dual antagonist of $A_{2a}$R and $A_{2b}$R. We will describe our SAR efforts leading to the discovery AB928, which was designed specifically for the oncology setting, with minimal CNS penetration. AB928 inhibits both $A_{2a}$R and $A_{2b}$R with similar potencies ($K_i$: 1.4 nM and 2 nM, respectively). Adenosine-mediated suppression of CD8$^+$ T cell activation was reversed by AB928, which restored IFN-gamma and granzyme B production from these cells. AB928 exhibited good selectivity against $A_1$R and $A_3$R, the other two adenosine receptors. AB928 potently inhibited NECA-induced CREB phosphorylation in CD8$^+$ T cells in whole human blood in a dose-dependent manner. AB928 has demonstrated a significant reduction in tumor growth and enhancement of tumor inflammation when tested as monotherapy and in combination with chemotherapy and anti-PD-1 antibody in mice. AB928 has exhibited excellent safety, PK, and PD profiles in a Phase 1 clinical trial in healthy volunteers and is currently being evaluated in cancer patients.

MEDI 219

Discovery of JNJ-61393215: Selective orexin-1 receptor antagonist


The neuropeptides orexin-A and orexin-B are derived from a common precursor peptide exclusively produced by perifornical and lateral hypothalamic neurons. These neurons project widely to key areas of the brain involved in the control of sleep-wake states, regulation of food intake, reward, addictive behaviours, panic, and anxiety.

The orexin neuropeptides mediate their effect by stimulating two distinct G-protein coupled receptors, termed orexin-1 (OX1R) and orexin-2 (OX2R), that are co-located or
selectively located in specific brain regions which suggest differentiated roles. For example, the OX2Rs are exclusively expressed in the tuberomammillary nuclei which are known to play a critical role in wake promotion. In agreement with this, the ability of OX2R antagonists to promote sleep is now well established and has led to a marketed dual OX1/OX2 receptor antagonist (DORA) Belsomera® (Suvorexant). Alternatively, Janssen and others have shown that the selective OX2R antagonist (SORA2) Seltorexant, is also effective at promoting sleep. These findings, are consistent with pre-clinical studies indicating that antagonism of the OX2 receptor is required to induce sleep, however, administration of a selective OX1 receptor antagonist has no effect. In addition to the ventral tegmental area, which is thought to mediate addictive behaviours, the OX1Rs are selectively expressed in the bed nucleus of the stria terminalis, amygdala, cingulate cortex, and locus coeruleus which play a role in panic and anxiety.

Presented here will be the structure, discovery, and first in human data of the selective OX1R antagonist JNJ-61393215, which was predicted and shown to provide targeted C_{trough} levels for 24hr coverage after a QD dose. Furthermore, the presentation will highlight strategies to optimize OX1R selectivity and pharmacokinetics by taking advantage of the kinetic isotope effect. These efforts culminated in the discovery of JNJ-61393215, which has improved brain penetration and safety margins relative to our first SORA1 candidate, JNJ-54717793.

MEDI 220

Discovery of clinical candidate, BMS-986235/LAR-1219: Selective FPR2 agonist for prevention of heart failure

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Myocardial infarction (MI) is the most common cause of heart failure (HF) worldwide. Therapeutics, such as glucocorticoids and COX-2 inhibitors, that suppress inflammation have been unsuccessful at preventing progression to heart failure following an MI. In contrast, our laboratories have shown that resolving inflammation by stimulation of the formyl peptide receptor 2 (FPR2) has the potential to promote myocardial healing, thereby preserving cardiac tissue and improving heart function. This disclosure will highlight the discovery, optimization and mechanistic studies of selective 4-phenylpyrrolidinone FPR2 agonists. BMS-986235/LAR-1219 was nominated as a clinical candidate based on a compelling in vitro and in vivo profile, including efficacy in a mouse heart failure model. The molecule is currently in Phase 1 clinical development.

MEDI 221
Discovery of potent reversible inhibitors of LSD1

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Histone demethylase LSD1 (KDM1A) belongs to the FAD dependent family of monoamine oxidases and is vital in regulation of mammalian biology. However, overexpression of LSD1 is a hallmark of a number of human diseases, including cancer. To date, the most advanced inhibitors of LSD1 are covalent inhibitors derived from tranylcypromine (TCP). Herein, we report the discovery of novel series of reversible and selective LSD1 inhibitors. SAR exploration and optimization of challenging ADME properties resulted in the discovery of clinical candidate CC90011. The clinical candidate exhibits potent on-target cellular activities and robust tumor growth inhibition in AML and SCLC xenograft models.

MEDI 222

Issues in the evaluation and validation of targets for substance use disorder medication development

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The opioid crisis is producing 130 deaths per day from overdose, including from prescription pain relievers, heroin, and synthetic opioids like fentanyl. In addition, an estimated two million Americans have opioid use disorders (OUDs). The major HHS/NIH initiatives to address the crisis are broad-based and comprehensive, focusing on enhanced access to treatment, better practices regarding pain treatment, and the support research. In addition, the HEAL initiative was created to speed scientific advances in better management of chronic pain, new innovative medications for OUDs, and improved medications for overdose reversal. Existing treatments for OUD are effective in reducing drug use and maintaining abstinence when they are taken; but often people stop taking their treatments and subsequently relapse. One of the reasons that people may stop taking their OUD treatment medications is described in an FDA report entitled, “The Voice of the Patient,” describing a meeting convened on April 18, 2018 in which OUD patients described the unmet clinical needs that were not addressed by their treatments with methadone, buprenorphine, or naltrexone. It is these unmet needs that may suggest new targets and the possibility of “add-on” medications to address specific issues. These include non-benzodiazepine anxiolytics and sleep aids, as well as compounds to block “protracted” withdrawal including persistent negative affect, and cue induced craving. The identification of these clinical endpoints
as well as their translation to molecular targets and how they might be evaluated will be discussed.

**MEDI 223**

**Serotonin 5-HT$_{2C}$ receptor-based molecular therapeutics for substance use disorders**

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The anti-obesity medication and 5-HT$_{2C}$ agonist lorcaserin (APD-356, Belviq) suppresses intake of cocaine, nicotine and opioids (e.g., oxycodone) in preclinical self-administration studies, and has demonstrated efficacy to improve smoking cessation rates in a phase II study. The orthosteric site of the 5-HT$_{2C}$R binds 5-HT and has been the traditional target for ligand discovery, and recent studies have identified positive allosteric modulators (PAMs) that increase the efficacy of 5-HT. Several analogues of our new molecule series potentiated 5-HT$_{2C}$R, but not 5-HT$_{2A}$R, mediated signaling in cultured cells and did not appreciably displace binding to 5-HT$_{2C}$R, 5-HT$_{2A}$R or 5-HT$_{2B}$R. A selected PAM (CYD-1-79) exhibited a favorable overall pharmacokinetic and behavioral profile in rats, and inhibited cocaine-seeking behaviors in rats. In addition, protein:protein interactions at the 5-HT$_{2C}$R cytosolic face provide an alternative approach to explore development of novel allosteric modulators. Phosphatase and tensin homolog deleted on chromosome 10 (PTEN), interacts within several amino acids of the third intracellular loop of the 5-HT$_{2C}$R (termed 3L4F). The peptide fragment 3L4F, labelled with the cell-penetrating peptide TAT, exhibited the profile of a 5-HT$_{2C}$R PAM *in vivo*, solidifying the potential therapeutic use for ligands that disrupt the 5-HT$_{2C}$R:PTEN complex. We then crafted peptidomimetic molecules with increased drug-like properties and retained activity to potentiate 5-HT$_{2C}$R signaling *in vitro* while not disrupting the lipid phosphatase activity of PTEN. Together, these data suggest that the sequence of 5-HT binding to the 5-HT$_{2C}$R, and subsequent activation of downstream signaling, can be positively modulated by binding of ligands at topographically-distinct allosteric sites as well as at the interface of a protein interactor (PTEN) with the 5-HT$_{2C}$R.

**MEDI 224**

**Discovery of VMAT2 modulators as potential treatments for methamphetamine use disorders**

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Methamphetamine addiction remains a serious public health problem, yet no approved pharmacotherapies for methamphetamine use disorders (MUD) are available. Considering the important role vesicular monoamine transporter 2 (VMAT2) plays in the mechanism of methamphetamine addiction, our collaborative research focus has been on the discovery of small-molecules that target VMAT2. Extensive structure-activity relationship studies have been carried out. In this presentation, I will talk about the progress on identifying VMAT2 modulators that specifically decrease methamphetamine’s behavioral effects as potential therapies for MUD.

**MEDI 225**

**Design, synthesis, and preclinical characterization of small molecule group II metabotropic glutamate receptor positive allosteric modulators**

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Recent findings suggest that neuroadaptations in glutamatergic transmission produced by repeated exposure to drugs of abuse such as cocaine or nicotine are likely to contribute to the maintenance of addictive behaviors including drug use, craving and relapse to drug taking in humans. Specifically, it has been shown that repeated cocaine exposure alters the function of the Group II metabotropic glutamate mGlut2 and mGlut3 receptors. Furthermore, nicotine increases glutamatergic neurotransmission by activating excitatory nicotinic acetylcholine (nACh) receptors located on presynaptic glutamatergic terminals. The Group II mGlut receptors, which couple to G<sub>i/o</sub> proteins to negatively regulate the activity of adenylyl cyclase, are primarily localized presynaptically and modulate glutamate release. Brain regions implicated in different aspects of drug abuse and drug dependence, including the cerebral cortex, hippocampus, striatum, amygdala, frontal cortex and nucleus accumbens display high levels of mGlut2 and mGlut3 receptor binding, suggesting a role for the mGlut2/3 receptor subtypes in the development of nicotine dependence and as potential targets for therapeutic agents. We previously reported our preliminary results on a novel series of mGlut2 receptor positive allosteric modulators (PAMs). Using the mGlut2 receptor PAM 3'-(2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yloxy)methyl)biphenyl-4-carboxylic acid (biphenyl indanone-A, BINA) as a starting scaffold we designed and synthesized new mGlut2 receptor PAMs that are significantly more potent than BINA in vitro and possess superior drug-like properties. We also recently reported the design, synthesis and characterization of mGlut2/3 receptor PAMs with in vivo activity. From these two series we have identified compounds which are active in behavioral models of self-administration in rats, providing proof-of-concept for the use of Group II mGlut receptor PAMs for the treatment of substance abuse.

**MEDI 226**

**Discovery of selective OX<sub>1</sub> antagonist HTL0027772 by structure-based drug design**
The orexin G protein-coupled receptors, OX₁ and OX₂, are neuropeptide receptors activated by the ligands orexin-A and orexin-B. The orexin system is highly conserved across mammalian species and is implicated in a range of functions with a common theme of arousal, including energy homeostasis, feeding, control of reward and sleep-wake regulation. Antagonists with diverse selectivity profiles have been identified over the past two decades, with the dual orexin antagonist suvorexant approved in 2014 for the treatment of insomnia. More recently there has been a focus on selective OX₁ antagonists for the treatment of addictive disorders. Despite the amount of effort invested in this target family over the years, many chemical series have ultimately not been progressed into the clinic, with common issues being high clearance / poor PK properties and unacceptable physicochemical / developability properties.

Sosei Heptares has a core platform called the StaR® technology that facilitates generation of optimised membrane protein samples for use in biophysical and structure-determination techniques. We have been pursuing structure-based drug discovery (SBDD) approaches for the discovery of orexin receptor modulators for a number of years. Within this body of work we have identified a fascinating diversity of ligand binding modes within the orthosteric sites of the OX₁ and OX₂ receptors, by ligand-receptor X-ray co-crystallisation of numerous in-house and literature chemotypes. Aspects of the structural insights and how we have leveraged these in pursuit of our dual and OX₁ selective antagonists will be presented.

In our OX₁ selective program we have identified and progressed a number of chemical series, targeting an agent for cocaine addiction. The development of one such series, culminating in discovery of the lead compound HTL0027772 will be described. The chemical structure and properties of this optimised agent will be disclosed for the first time.

MEDI 227

Discovery of CAD-1883: Clinical-stage positive allosteric modulator of the SK channel for the treatment of essential tremor and spinocerebellar ataxia

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Herein we describe the drug discovery efforts of Cadent Therapeutics and its collaborators to identify development candidate CAD-1883, an allosteric modulator of the small conductance calcium-activated potassium (SK) channel, for the treatment of essential tremor (ET) and spinocerebellar ataxia (SCA).

Positive allosteric modulation (PAM) of SK channels represents a potential therapeutic approach for the treatment of ET, SCA, and other movement disorders which are characterized by dysregulated firing of the cerebellum. SK modulation will affect the afterhyperpolarization event of an action potential in Purkinje cells of the cerebellum and is expected to restore a normalized firing pattern.

In order to identify novel chemical matter for modulating SK channels, a FLIPR screen was performed and identified the commercially-available compound CyPPA as a screening hit. Subsequent electrophysiological assays confirmed CyPPA’s PAM activity on the SK2 and SK3 subtypes.

While CyPPA was a promising starting point, significant optimization was required in order to address several issues such as its lack of oral bioavailability, limited brain penetration, low metabolic stability, and inhibition of various Cyp isoforms. Structure-activity relationships were developed to understand how to increase solubility, enhance brain/plasma ratio, maintain sufficient free fraction, and reduce some off-target liabilities. Further improvements in chemical stability, PK properties, off-target profile, and CMC developability were achieved as well.

After the design and synthesis of more than 1400 analogs, CAD-1883 was identified as having the most exceptional properties in the chemical series. CAD-1883 demonstrated efficacy in a harmaline-induced rodent model of essential tremor and a mouse efficacy model of hereditary ataxia.

After successful synthetic scale-up and completion of GLP toxicology studies, CAD-1883 has recently been evaluated in a Phase 1 clinical study in human healthy volunteers. Based on the promising safety, tolerability, and pharmacokinetics, Cadent Therapeutics has initiated a Phase 2 study in ET with CAD-1883.

MEDI 228

DNA-encoded libraries at GSK

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This session will review the development and application of DNA-encoded library technology at GSK, including a perspective on portfolio impact. Recent advances in methodology development and application to library synthesis will be discussed, with a particular focus on opportunities where academic collaborations and cross-pharma approaches have the potential to advance the field.
DOSEDO: Diversity-oriented synthesis encoded by deoxyoligonucleotides

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Diversity-oriented synthesis has been used to enrich small molecule screening collections with unusual scaffold architectures, well defined stereochemistry and high sp3 content. As a result, novel mechanisms of action have been elucidated, often opening exciting avenues in drug discovery. Some barriers to the more widespread adoption of such screening collections by the community are cost and time — with many synthetic routes being long and complex.

DNA-encoded libraries (DELs) have emerged as an effective and highly efficient screening tool. However, the majority of published syntheses are limited to the constraints of working at low concentration, in an aqueous environment, with sensitive DNA present. As such, most DELs are composed primarily of peptides and sp2-rich molecules.

As part of a deep collaboration between Novartis and the Schreiber lab we endeavor to combine modern synthetic chemistry with the DEL format. The resulting collection of structurally diverse compounds will serve as a high quality tool for early phase drug discovery. Moreover, library production will be performed on sufficient scale to share with the scientific community. We foresee this resource enabling many future projects.

This presentation will cover the design of the library, the synthetic strategy employed to produce it, and a roadmap for how we envisage this ambitious open-source tool being implemented for your projects.
DNA-encoded libraries (DEL) have emerged as rich sources of small molecules interacting with targets of interest. However, the limited arsenal of DNA-compatible reactions required for library generation naturally translates into an overrepresentation of sp2-rich architectures and peptidomimetics. For the synthesis of complementary libraries, chemical transformations that enable access to more complex, sp3-rich entities are therefore highly desirable. Despite the successful history of strain-promoted cycloaddition reactions in the field of chemical biology (i.e. in the presence of water and biopolymers), there has been no report on the use of this concept in DEL synthesis. Strained allenes for example, usually generated under anhydrous conditions, are known to exhibit various reactivity modes when allowed to react with activated olefins ([2+2]), 1,3-dipoles ([3+2]) or dienes ([4+2]), and the resulting sp3-rich products exhibit high structural diversity. We document the successful in-situ generation and trapping of DNA-conjugated strained allenes in the presence of various coupling partners. The significance of our findings for future libraries is demonstrated by two-step diversification of DNA-linked substrates involving strain-promoted cycloadditions and N-capping reactions. Due to the mild conditions and general applicability, the process is thought to be an attractive addition to existing on-DNA bond forming reactions.
DNA-encoded libraries have emerged as a powerful hit generation technology. Combining the power of combinatorial chemistry to enumerate large compound collections and the efficiency of affinity selection screening methods, the technology makes it possible to interrogate vast chemical space against biological targets of pharmaceutical relevance. Thus, the organic chemistry transformations that can be deployed to the synthesis of encoded libraries play a crucial role in the identification of attractive medicinal chemistry starting points: a novel synthetic method that significantly changes the scope of DNA-compatible reactions will be discussed.

MEDI 232

Structure-based design of an N-terminal bromodomain selective bromodomain and extraterminal (BET) inhibitor retaining an antiproliferative phenotype

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The bromodomain and extra terminal domain (BET) family of epigenetic regulators comprises four proteins (BRD2, BRD3, BRD4, BRDT) each containing tandem bromodomains. To date, small molecule inhibitors of these proteins typically bind all eight bromodomains of the family with similar affinity resulting in a diverse range of biological effects. To enable further understanding of the broad phenotype characteristic of pan-BET inhibition, development of inhibitors selective for individual, or sets of, bromodomains within the family is required. In this regard, this presentation describes the discovery of imidazoquinoline 1, a potent probe molecule possessing up to 200-fold selectivity for the N-terminal bromodomains (BD1s) over the C-terminal bromodomains (BD2s) of BET. Guided by structural information, a specific residue difference between BD1 and BD2 domains was targeted for selective interaction with chemical functionality appended to the previously developed I-BET151 scaffold. Subsequent modification of the imidazoquinolinone scaffold resulted in imidazoquinoline 1 which demonstrated sufficient exposure in vivo to be capable of engaging BD1 domains while minimizing interaction at BD2 domains. Data presented here demonstrates that selective inhibition of BD1 domains is sufficient to drive antiproliferative effects.
New piperazine-based siderophore-antibiotic conjugates to fight antimicrobial resistance

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Among Gram-negative bacteria, Pseudomonas aeruginosa and Burkholderia pseudomallei are particularly worrying. P. aeruginosa is often involved in nosocomial infections (6.2% of infected hospitalized patients) and B. pseudomallei, formerly classified as P. pseudomallei, causes melioidosis which prevails in tropical climates. The most common form of the Whitmore disease, pulmonary melioidosis, resembling tuberculosis, is particularly recalcitrant to therapy and has a high relapse rate. We are interested in the development of new ways to combat the Pseudomonas group, targeted due to its high level of resistance to antibiotics via a lack of membrane permeability or efflux. Using iron transport systems is a promising strategy to overcome this phenomenon by restoring the activity of conventional antibiotics. Indeed, iron is a micronutrient necessary for the survival of bacteria. It is essential to many biological processes such as respiration, DNA synthesis... However, the ferric iron has a low bioavailability due to its low solubility in water. Under iron limited conditions, many bacteria synthesize molecules of low molecular weight, called siderophores, able to chelate the surrounding iron. According to their kind, bacteria express different types of outer membrane receptors (OMR) that recognize their endogenous siderophores but also xenosiderophores or synthetic siderophores. In particular, P. aeruginosa and B. pseudomallei possess catecholate receptors. Thus, we exploited a piperazine platform to graft iron chelator group, such as catecholate and its bioisostere,
hydroxypyridinone group, to form siderophore analogs which can be recognized by the *Pseudomonas* sp. After synthesis, physicochemical properties of the siderophore (pFe and coordination mode of the metal) as well as the effective transport of the corresponding Sid-Fe(III) complexes through iron uptake pathways will be evaluated. Finally, the siderophores with the best *Pseudomonas* OMR recognition and iron chelation capacities will be chosen to form siderophore-antibiotic conjugates or toxic siderophore-gallium complexes.

**MEDI 234**

**Experimental identification of protein-ligand interactions in fragment-based drug discovery with high-throughput protein crystallography screening of fragment libraries**

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Fragment-based drug discovery (FBDD) is widely used in the pharmaceutical industry to provide novel leads for developing new therapeutics. FBDD allows a more efficient scanning of chemical space with a higher hit rate compared to high-throughput screening, and this has important outcomes in early drug discovery and can be especially relevant for challenging non-druggable targets. FBDD has resulted in 30 new drugs entering clinical trials with 2 that have entered the market.

X-ray crystallography is the gold standard for determining the exact binding orientation of a fragment as an essential step in this process. Absence of crystal structures of the target with bound fragments is a significant impediment in FBDD. Conventional crystallography is inefficient for screening a large fragment library due to expense and effort. Complementary techniques, such as Surface Plasmon Resonance, Thermal Shift Assay or Nuclear Magnetic Resonance are often used to prescreen for fragments that bind, while protein crystallography is used in a second step to determine the exact binding of each fragment. Absence of crystals structures of drug targets bound to fragments is a significant impediment to medicinal chemistry optimization of the fragment hits.

With foundational expertise in structural genomics and high-throughput protein X-ray crystallography, Accelero Biostructures has developed a novel high-throughput FBDD and SBDD platforms (ABS-OneStep™ and ABS) focused on unique technology and applications to counter the above bottleneck in early drug discovery. Our ABS-OneStep™ platform for crystallography-based fragment screening accelerates the development of lead compounds by directly providing 3D structures of fragments bound to a target of interest, potentially leading to ~5-7x reduction in early drug discovery times. This provides unprecedented experimental route to high quality, high reliability and high value results simultaneously: identification and assessment of fragment binding sites and poses; target ligandability; and differentiation of orthosteric and allosteric sites and binders. We will present results from applying our platform to
different classes of drug targets including a lysine demethylase, a phosphatase and an endonuclease.

MEDI 235

Structure-based design of potent and selective CGRP receptor antagonists for the treatment of migraine

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Calcitonin gene-related peptide (CGRP) plays an important role in migraine headache and inhibition of the function of CGRP has been demonstrated to be an effective approach to migraine treatment with both small molecule and monoclonal antibody modalities. We previously described the identification of novel aminopyridine-based CGRP receptor antagonists as part of a program to identify orally active CGRP receptor antagonists. While these compounds exhibited good potency and oral bioavailability, they possessed only modest selectivity for the CGRP receptor over the closely related amylin (AMY₁) receptor. We now describe a structure-based approach to improving the CGRP to AMY₁ receptor selectivity of this class of aminopyridines. While the binding site of these compounds is largely conserved between the CGRP and AMY₁ receptors, analysis of the X-ray crystal structure of a lead aminopyridine revealed key interactions that could potentially be exploited to confer enhanced selectivity. Inspired by this analysis, rational modification of the lead structure led to compounds with improved affinity for the CGRP receptor and > 100-fold selectivity versus the AMY₁ receptor. Gratifyingly, BioNMR studies confirmed that the selective compounds interacted with targeted residues in the CGRP receptor as planned. This strategy led to the identification of novel CGRP receptor antagonists with subnanomolar potency and excellent selectivity vs. the AMY₁ receptor.

MEDI 236

BBB-penetrating delivery to glioma using engineered, size-controlled nano phage

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Therapy of glioblastoma, a particularly difficult-to-reach cancer type, is highly limited by the blood brain barrier (BBB) and will benefit greatly from effective drug and contrast agent delivery. Here, we are expanding on the functionality of M13 bacteriophage as an engineerable nanoprobe for targeting glioma cancer sites. M13 bacteriophage, a naturally monodisperse multifunctional nanostructure, consists of thousands of distinct
protein subunits organized in a high aspect ratio, filamentous viral capsid; 900nm in length and 6nm in diameter. All M13 coat proteins are amenable to mutation, and can be tuned for the binding and nucleation of inorganics and nanoparticles, chelation of metal ions, and expression of targeting ligands or even enzymes. To harness these capabilities for medical imaging and therapy applications, we (a) develop a chlorotoxin (CTX) motif on the M13 capsid to cross the BBB, and (b) tailor the assembly of M13 into smaller “inho” phages. CTX display allows phage crossing of the BBB as well as uptake by glioma cells. Second window near infrared (NIR-II) through-skull mouse imaging of CTX-phage, complexed with single walled carbon nanotubes (SWNT) or small molecule NIR-II dyes, reveals localization of the phage to patient derived, orthotopic glioma xenografts, and makes possible phage based shuttling of drug loads to the tumor cells and simultaneous, non-invasive NIR-II tracking of the therapy progression. Such NIR-II optical imaging in the 900nm to 1700nm range allows high depth of tissue penetration and low tissue autofluorescence using quick, inexpensive machinery. To further build on the delivery potential of the M13 phage based nanoprobes, we have constructed a phagemid assembly system to alter the length of M13. Filamentous phages of short lengths, sizes ranging from 20nm to 900nm, are made possible by constructing our own set of small viral ssDNA that are packaged by M13 capsid proteins. With the ability to control the aspect ratio of these rigid, rod-like “inho”-phages we can improve on M13 based disease detection by optimizing for in vivo phage trafficking and tumor extravasation, focusing on inho-phage sizes 20nm to 200nm. Overall, targeted and miniaturized M13 phage is considered here as a complete nano-theranostic that could augment the therapeutic efficacy of drugs shuttled to the site of glioma while also providing clinicians with the information needed to easily track and debulk early-stage, deeply embedded tumor masses.

MEDI 237

Discovery of potent, selective, and brain-penetrant apoptosis signal-regulating kinase 1 (ASK1) inhibitors

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Apoptosis Signal-regulating Kinase 1 (ASK1) is one of the key mediators of the cellular stress response and modulation of this pathway with the small molecule, ATP-competitive inhibitor Selonsertib is being tested in the clinic for the treatment of liver fibrosis. Inhibition of ASK1 may also be beneficial in the treatment of neurological diseases and to investigate the potential therapeutic value of modulating this pathway in the CNS we have identified novel brain-penetrant inhibitors following a structure based drug design approach. The results from this systematic optimization effort will be presented.

MEDI 238
Discovery of novel FoxO1 inhibitors for the treatment of diabetes

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Diabetes type 1 is characterized by destruction of β-cells leading to loss of endogenous insulin production and daily insulin injections are required to control blood glucose levels. An alternative treatment would be to restore insulin secretion by regeneration of β-cells. The forkhead box class O subfamily of forkhead transcription factors are involved in gene expression related to cellular processes such as proliferation and differentiation. The FoxO1 transcription factor regulates many aspects of pancreatic β-cell function and it has been shown that ablation of FoxO1 gene in Neurog3+ enteroendocrine progenitor cells restores insulin production by development of insulin positive intestinal cells. We were interested in identifying novel selective small molecule inhibitors of FoxO1 to investigate pharmacological FoxO1 inhibition as a method to re-establish insulin production. Several chemical series were identified through high throughput screening (HTS). Additional optimization of FoxO1 selectivity and DMPK properties led to the discovery of novel FoxO1 inhibitors suitable for in vivo concept testing.

MEDI 239

Fisetin sensitizes the hypoxia induced chemotherapy resistance in head and neck cancer

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Chemotherapy is often restricted by dose-related toxicity and development of therapeutic resistance. Fisetin, a natural flavonoid found in various fruits and vegetables has shown anticancer and radiosensitizing effect in lung and prostate cancer. We investigated the mechanisms of Fisetin-induced inhibition of growth and survival of human HNC cells in combination with chemotherapy. We found that a pretreatment of Fisetin (1-10 μM) enhanced the effect of cisplatin, 5-fluorouracil (FU) and docetaxel, in colony formation of HNC cells under hypoxic condition (1% oxygen). The pretreatment enhanced the chemotherapy-induced apoptosis by cisplatin, 5-FU and docetaxel. Consistent with this, Fisetin pretreated cells showed elevated level of cellular and mitochondrial ROS followed by the expression of cleaved caspases-3 and -7 and poly(ADP-ribose)polymerase compared with that in control cells after cisplatin, 5-FU, or docetaxel treatment. This drug also induces the mitochondrial membrane depolarization
in pretreated cells. Tagging HNC cells with mito-GFP and mito-RFP showed an elevation in the frequency mitochondrial exchange in chemo treated HNC cells under hypoxic condition. Pre-treatment with Fisetin followed by chemo treatment reduces the rate of mitochondrial exchange in HNC cells. Under hypoxic condition, HNC cells show up to 36% resistance as compared to normoxic condition. But, Fisetin enhances the efficacy of chemo drugs and synergize their effect up to 43%. Overall, our data suggest that Fisetin treatment inhibits the HNC cells and sensitize them for chemotherapy under hypoxic condition.

MEDI 240

Identification of a small-molecule agonist for the APJ receptor as a clinical candidate

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Heart Failure (HF) is a condition where the heart cannot pump sufficient blood to maintain normal organ function and remains a critical, unmet medical need. Studies in pre-clinical animal models and in humans have shown that infusion of the peptide [Pyr1]apelin-13 improves cardiac function. [Pyr1]Apelin-13 is an endogenous ligand for the APJ receptor but has a short plasma half-life which has limited the exploration of its therapeutic potential to intravenous and short duration of dosing. Thus, one critical goal in the field has been to discover modalities that are suitable for oral dosing. Several approaches have centered on PK enhanced peptides and peptidomimetics. Our approach was to identify small molecules with potency consistent to that of [Pyr1]apelin-13 with acceptable exposure for oral and chronic dosing. We disclose SAR studies leading to the identification of a lead molecule in the aryldihydroxypyridine series. The lead molecule shares the in vitro activity profile of apelin with oral bioavailability suitable for chronic dosing and was ultimately selected as a clinical candidate.

MEDI 241

Design of a multi-component reaction scaffold with inhibitory activity on aspartic proteases

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Aspartic proteases represent a protein family with significant drug targets, including renin, HIV-protease, β-secretase (BACE-1) and plasmepsins. Various warheads have been studied for interacting either directly with the catalytic dyad of aspartic acids or indirectly mimicking the tetrahedral intermediate. Here we focus on endothiapepsin, a pepsin-like aspartic protease that has been studied excessively as a model enzyme both for elucidating the catalytic mechanism and also in the clinical development of renin and β-secretase inhibitors.

In this work, we designed a novel multi-component reaction (MCR) scaffold with the potential to interact with both acidic residues. The scaffold can be accessed via a two-step synthesis. Preliminary screening results and crystallization studies supported the choice of the scaffold. Optimized derivatives were designed by docking virtual libraries and the selected hits were synthesized. Finally, novel crystal structures were obtained.

MEDI 242

Discovery and optimization of a novel series of highly selective JAK1 kinase inhibitors

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Janus kinases (JAKs) have been demonstrated to be critical in cytokine signaling, and have thus been implicated in both cancer and inflammatory diseases. The JAK family consists of 4 highly homologous members: JAK1,2,3 and TYK2. The development of small molecule inhibitors that are selective for a specific family member would represent highly desirable tools for deconvoluting the intricacies of JAK family biology. Herein, we report the discovery of a potent JAK1 inhibitor, which displays ~1000 fold selectivity over the other highly homologous JAK family members (determined by biochemical assays), while also possessing good selectivity over other kinases (determined by panel screening). Moreover, this compound was demonstrated to be orally bioavailable, and possesses acceptable pharmacokinetic parameters. In an in vivo study, the compound was observed to dose dependently modulate the phosphorylation of STAT3 (a downstream marker of JAK1 inhibition).

**MEDI 243**

**Discovery of a potent and selective fragment-like inhibitor of SPIN1**

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SPIN1 (Spindlin 1) is a methyllysine reader protein, which interacts with trimethylated histone H3 lysine 4 (H3K4me3). It was found to be overexpressed in several types of malignant tumors, including ovarian cancer, certain types of liver carcinomas, non-small-cell lung cancers and liposarcoma. Upregulation of SPIN1 has been shown to increase cellular proliferation, abnormal mitosis and chromosomal instability. Therefore, small molecules that selectively disrupt the protein–protein interactions between SPIN1 and its respective binding partners (such as H3K4me3) are valuable chemical tools for investigating biological functions of SPIN1 and assessing the potential of SPIN1 as a therapeutic target.

By screening our quinazoline compound library, UNC0638, a highly potent inhibitor of the histone methyltransferases G9a and GLP, was identified as a weak inhibitor of SPIN1. Further optimization of this weak hit resulted in the discovery of a potent, selective and cell-active SPIN1 inhibitor, MS31, which is the first potent, selective and cell-active fragment-like inhibitor of any methyllysine reader proteins. MS31 displayed high potency in orthogonal SPIN1 biochemical assays (IC50 = 77 nM (AlphaLISA) and 243 nM (FP)). And this activity was further confirmed by ITC assay with high binding affinity to SPIN1 (KD = 91 nM). MS31 was highly selective for SPIN1 over a panel of epigenetic targets including G9a and GLP. A crystal structure of the SPIN1–MS31 complex was also obtained, which indicated that MS31 selectively binds Tudor domain II of SPIN1. A structurally similar but inactive compound (MS31N) as a negative control based on the cocrystal structure was designed and synthesized. Furthermore, MS31 directly engaged SPIN1 in cells and was not toxic to non-tumorigenic cells. These results have demonstrated that it is feasible to generate potent, selective and cell-active inhibitors by targeting a single Tudor domain and paved the way for discovering improved inhibitors of methyllysine reader proteins.
MEDI 244

Discovery and development of a novel, class I Core protein Assembly Modulator (CpAM) for the treatment of chronic HBV infection

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The HBV core protein plays important roles in HBV lifecycle, with the most prominent one as the essential component of the nucleocapsid. Interrupting the assembly of core protein into nucleocapsid will block the HBV replication. The core protein is conserved across all HBV genotypes and is thus considered as an attractive target for small molecule intervention. This talk will focus on the discovery and development of a novel, Class I Core protein Assembly Modulator (CpAM).

Compared to previous CpAMs, this new series of Class I CpAM showed greatly increased anti-HBV activity due to an unexpected cooperative H-bonding effect with HBV core protein. The photoaffinity study and the co-crystal structure nicely elucidated how the compound binds to the core proteins and exert strong binding affinity. Further optimization addressed CYP3A4 induction issue of the front-runner and eventually led to the discovery of current clinical candidate with desired liver enrichment, optimal
mouse PK/PD, and preclinical safety profiles. The phase I clinical safety and efficacy data will be disclosed also.

HBV life cycle and capsid inhibitor

**MEDI 245**

**Discovery of RG7834 and target identification: First-in-class selective and orally bioavailable small molecule HBV expression inhibitor with a novel mechanism of action**

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Hepatitis B virus (HBV) infection is a serious public health concern with high unmet medical needs. The current therapies, including both nuleos(t)ides and interferon, cannot effectively achieve HBV functional cure with HBsAg loss and subsequently seroconversion. To improve the cure rate, agents with novel mechanisms of action are required. Starting from a phenotypic screening, RG7834, a compound from dihydroquino[lizinone (DHQ) chemical series, was discovered as a highly selective HBV inhibitor which can block both viral antigen and viral DNA production. Significant HBsAg reduction was observed in humanized liver mouse model after treatment with RG7834. The mechanism of action of RG7834 is clearly differentiated from the current therapies. Target identification efforts revealed that PAPD5 and PAPD7 are the target proteins for DHQs which had never been reported for HBV therapy. Herein we report the discovery of this first-in-class selective and orally bioavailable small molecule HBV expression inhibitor, as well as the identification of the novel targets.
SB 9200 (inarigivir), a selective oral immuno-modulator for chronic hepatitis B

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Over 250 million people worldwide are chronically infected with hepatitis B virus (HBV). Current therapies are life-long, using nucleotide and nucleoside analogs (Nucs) that only suppress viral replication; New antiviral agents that can reduce viral antigens, eliminate cccDNA and to effect viral clearance during a finite duration of therapy are urgently needed.

SB 9200 is an orally bioavailable dinucleotide that causes hepatoselective activation of RIG-I, an innate immune receptor, resulting in the induction of IFNs and ISGs. SB 9200 was discovered by phenotypic approach involving synthesis and screening of nucleotide libraries in HepG2.2.15 cell lines. The compound was shown to bind to RIG-I with a Kd of 12 pM. In reporter assays, SB 9200 was also shown to induce IRF3, and IFN in a RIG-I-dependent manner. SB 9200 showed potent antiviral activity against wild type-, as well as, nucleoside and polymorphic capsid variants of HBV and was synergistic with Nucs. Orally administered SB 9200 showed potent, dose-dependent antiviral activity in the transgenic mouse and woodchuck models of HBV, with significant reductions in viral DNA, RNA, and antigens that was associated with induction of host immune response.

The ACHIEVE Phase 2a clinical trial in treatment-naïve HBV patients evaluating safety and efficacy of ascending dose cohorts (25, 50 and 100 mg) of inarigivir monotherapy for 12 weeks, followed by switch to Tenofovir for 12 weeks, has been completed. Inarigivir monotherapy demonstrated a favorable safety profile with significant reductions in HBV DNA and RNA compared to placebo (ANOVA p < 0.0001) with a clear dose response especially in HBeAg-ve patients. In addition, 13 of 47 (28%) patients also showed mean and median HBsAg reduction of 0.8 log_{10} (range 0.5 – 1.4 log_{10}) with inarigivir alone or after Tenofovir switch. Inarigivir has been advanced to global Phase 2b clinical trials.

Hit to lead optimization of toll-like receptor agonists toward the treatment of hepatitis B virus

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Toll-like receptor (TLR) 7 and 8 agonists are potentially useful in the treatment of viral infections and are particularly promising for chronic hepatitis B virus (HBV) infection. An internal screening effort identified a pyrimidine TLR 7/8 dual agonist and permitted the
ligand-based design of other novel TLR agonists. This provided novel structures as alternatives over the previously reported imidazoquinoline, adenine and pteridone series. Structure activity relationship and lead optimization are presented.

MEDI 248

Discovery of the selective TLR8 agonist GS-9688 for HBV cure


Toll-like receptor (TLR) 8 recognizes pathogen-derived single-stranded RNA to trigger innate and adaptive immune responses. Published data suggest that TLR8 activation may augment hepatitis B virus (HBV)-specific T cell responses, activate natural killer cells and mucosal-associated invariant T cells, and suppress HBV via induction of antiviral cytokines. Therefore a selective TLR8 agonist has the potential to be a new treatment option for CHB.

GS-9688 is an oral, selective small-molecule agonist of TLR8 currently in clinical development for the treatment of chronic hepatitis B (CHB). Starting from a weakly active dual TLR7/8 agonist lead, potency and selectivity for TLR8 were optimized using a high throughput peripheral blood mononuclear cells (PBMC) assay measuring IL-12p40 production. The TLR8-ectodomain:GS-9688 complex X-ray structure was solved to confirm direct TLR8 binding. In HBV infected primary human hepatocytes, cytokines in the media of human PBMCs activated by GS-9688 reduced viral replication in HBV-infected primary human hepatocytes. The desired oral profile was high intestinal absorption leading to activation of TLR8 in the gut but also sufficient compound activating TLR8 in intrahepatic immune cells, combined with high first pass hepatic clearance, to minimize potential side effects resulting from systemic TLR8 agonism. GS-9688 demonstrated good absorption and high first pass clearance in multiple preclinical species, and stimulated a dose-dependent serum IL-12p40 response in monkeys. GS-9688 is therefore a promising, novel oral agent for the treatment of CHB.

MEDI 249

Hidden bias in the dataset leads to misleading performance of deep learning in structure-based virtual screening

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Recently much effort has been invested into using convolutional neural networks (CNN) models trained on 3D structural images of protein-ligand complexes to distinguish tightly binding from non-binding ligands. However, the dearth of reliable binding structure and affinity data has required the use of constructed datasets for the training and evaluation of CNN molecular recognition models. Here we outline sources of dataset bias and have constructed and performed tests to investigate whether CNN models are properly learning the underlying physics of molecular recognition or are instead learning biases inherent in the datasets themselves. We find that superior enrichment efficiency in CNN models can be attributed to the analogue and decoy bias hidden in the DUD-E datasets used to train and test the model rather than successful generalization of the pattern of protein-ligand interactions. Comparing additional deep learning models trained by PDBbind datasets, we found that their enrichment performances using the DUD-E dataset are not superior to the performance of the docking program AutoDock Vina.
Design and synthesis of Janus kinase inhibitors for inhaled delivery and the importance of aldehyde oxidase metabolism in the lung

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The Janus kinases (JAK1, JAK2, JAK3 and TYK2) are a family of intracellular tyrosine kinases that play an essential role in the signalling of numerous cytokines that have been implicated in the pathogenesis of inflammatory diseases. There is emerging interest in the development of small-molecule inhaled JAK inhibitors for severe asthma, as this approach targets multiple disease pathways to achieve broader efficacy compared to single cytokine approaches. Accordingly, this presentation describes the identification of a quinazoline lead series, and the optimisation of JAK potency, solubility and lung retention, aided by structure-based design. Two exemplars from the series were evaluated in an in vivo mouse model following intranasal administration to assess their ability to be retained in the lung, but only low lung concentrations of parent compound were measured which, after further investigation, was primarily due to metabolism by aldehyde oxidase (AO). Although AO is predominately expressed in liver and other tissues, the lower levels expressed in lung were significant enough to limit lung exposure. This, combined with the well-documented risk of advancing an AO substrate into the clinic, led us to identify compounds which were not metabolised by AO. We achieved this by incorporating specific substituents at the quinazoline 2-position and rationalised the lack of AO metabolism through computational docking studies in the AO binding site.
Discovery of a C-8 hydroxychromene as a potent inhibitor of estrogen receptor alpha with improved rat oral exposure over GDC-0927

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Breast cancer is the second leading cause of cancer death in women. Approximately 70% breast cancers are ER-positive. Despite the initial effectiveness of standard of care therapies, 20-30% of patients eventually relapse and become resistant. Among the recently discovered clinical candidates, GDC-0927 is a full ERα antagonist in breast and uterine tissues and is highly efficacious in tamoxifen-sensitive and -resistant xenograft models. However, GDC-0927 suffers from low oral exposure as a result of high clearance and low oral bioavailability. This is likely due to the presence of two electron-rich phenols in the molecule. The structural modifications identified several metabolically stable analogs, however, at the expense of potency. Subsequently, our crystal structure of GDC-0927 guided the design of a novel C8-hydroxy chromene in which the neighboring oxygen atom of the chromene was envisioned to shield the hydroxyl group from glucuronide conjugation and thereby improve clearance. Gratifyingly, this analog exhibited excellent enzyme potency and degradation efficiency with improved oral exposure in rat compared to GDC-0927. These efforts, the crystal structures of GDC-0927 and the novel C8-hydroxy chromene will be discussed.

MEDI 252

Process development and biological evaluation of antibody drug conjugate (ADC) based on a novel site-specific chemical conjugation platform

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Antibody–drug conjugates (ADCs) have become a major class of cancer biopharmaceuticals and traditional ADCs have a stochastic distribution of cytotoxic drugs linked across several different sites of the antibody. The heterogeneous nature of resulting stochastic ADCs can cause diminished efficacy and increased toxicity, thus limiting the corresponding therapeutic index. To improve on traditional ADC technology, we developed a novel chemical conjugation platform termed “AJICAP™” for the site-specific modification of native antibodies through the use of a class of IgG Fc-affinity reagents. Here we report the in vitro and in vivo activity of these resulting ADCs and assessed compared to the state-of-the-art ADC conjugation technology. Furthermore, we also report process optimization for the preparation of a “Gram-Scale” AJICAP™ conjugation batch by utilizing scale-down manufacturing and purification.
approaches. The minimum yield of each step was 91% and more than 1.4 g AJICAP™-ADC was synthesized to support the rodent safety studies. Toxicology studies revealed an enhancement of the maximum tolerated dose of AJICAP™-ADC, indicating an expansion of the comparative therapeutic index when compared to stochastic technology. These results presented herein indicate that AJICAP™ technology is an effective platform to enable next generation ADCs through the enhancement of dosing therapeutic index and this approach is amenable to relevant manufacturing production scales.

![AJICAP Technology Diagram](image)

**Figure 1. AJICAP™ Technology**

![Safety Study in Rats](image)

**Figure 2. Biological Evaluation of AJICAP™-ADCs**
MEDI 253

Directed meta C-H amination of benzyl picolates via FeCl₃-catalysis

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C-H bond functionalization offers considerable benefits in efficiency and economy. Impressive levels of regioselectivity have also been achieved by combining C-H functionalization with directing groups. However, direct arene meta NH₂ amination has been elusive. In this presentation, we report a high level of meta-selective NH₂ amination of benzyl picolates and related esters via FeCl₃-catalysis using commercial hydroxylamine-O-sulfonic acid (HOSA) at rt. Picolate esters are easily prepared/removed for operational simplicity and all of the reaction reagents are inexpensive. Mechanistic insights, scope, and applications to late-stage examples will be presented.

MEDI 254

Efficient synthetic approach for 3-acetamido phthalides: Complement inhibitor virtual screening hit

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The complement system is a self-amplifying proteolytic cascade that serves central role in the innate immune system. It is also recognized as an ideal target for treatment of certain inflammatory diseases like C3 glomerulopathies and age-related macular degeneration. Compound ¹ was identified from a virtual screen for small molecule ligands of complement component C3b. ¹ uniquely blocks downstream activation of
complement component C5 (Garcia et al., 2017). The existing approach to synthesize 1 and its related derivatives resulted in very low yielding reactions. In this endeavor we present our efforts leading to the development of a very efficient one-pot synthesis of the desired 3-acetamido phthalides (2). We further extend the approach to synthesize another potentially important class of compounds, 2-carboxycinnamamides (3) from the common intermediate (4) (Figure 1).

![Chemical structure of 1, 2, 3, and 4](image)

**Figure 1**

**MEDI 255**

**Efficacy of 4-oxo-4,5-dihydrothieno[3,2-c]quinoline CDK5 inhibitors as modulators of adipogenic insulin/metabolic pathways**

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Cyclin dependent kinase 5 (Cdk5) is a proline dependent serine/threonine kinase expresses primarily in neuronal cells. It regulates cellular migration, microtubule-dynamics and synaptic plasticity. In metabolic tissues, Cdk5 regulates insulin sensitivity and adipogenesis. Although Cdk5 is an essential enzyme in-vivo, its aberrant activation promotes obesity/type-2 diabetes (T2D) and Alzheimer’s disease (AD) via phosphorylation of various proteins including the adipogenic transcription factor PPARg and the tangle-forming protein Tau. Obesity/T2D induced insulin resistance also lead to neurodegeneration, particularly AD, which accounts for 60-80% of dementia cases. Thus targeting Cdk5 may ameliorate these diseases. However, potent and selective inhibitors of Cdk5 are not available.

Using virtual screening and structure-activity relationship studies, we identified a novel series of 4-oxo-4,5-dihydrothieno[3,2-c]quinoline compounds as selective ATP non-competitive Cdk5 inhibitors (1) (Chatterjee et al., 2014). In this current endeavor, we demonstrate that the compounds specifically inhibit Cdk5, increase glucose uptake and augment markers of insulin signaling and metabolic pathways in adipocytes. In summary, we discovered novel Cdk5 inhibitors that are active in a cell culture model. Our discovery poses a future therapeutic significance in obesity, diabetes and neurodegenerative diseases.

MEDI 256

Dual-acting compounds targeting the adenosine 2A receptor (A2AR) and histone deacetylases (HDACs) for cancer immunotherapy

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The adenosine A2A receptor (A2AR) has been demonstrated as a novel and promising drug target for cancer immunotherapy. A2A antagonists function as enhancers of the anti-tumor immunity of the host, but they display no direct anti-proliferative activity against the tumor cells. To enable the anti-proliferative activity of A2A antagonists, dual-acting compounds targeting both the A2AR and histone deacetylases (HDACs) have been designed and synthesized. Two series of chimeric A2A antagonists that incorporate a zinc-binding group such as the hydroxamic acid into the scaffold, through a proper linker, have been designed and synthesized. Many of these derivatives display potent activities in blocking A2AR and inhibiting HDACs, and also show potent anti-proliferative activity against cancer cell lines including HCT-116, CT-26 and MC-38. Remarkably, compound **IHCH-3066** showed potent and balanced activities against both A2AR ($IC_{50} = 29.7$ nM, binding assay) and HDACs (HDAC1, $IC_{50} = 43$ nM) and inhibited the proliferation of HCT116, CT-26 and MC-38 cancer cell lines in vitro ($IC_{50} = 0.26$ μM, 0.90 μM and 0.71 μM, respectively). Further PK profiling and in vivo efficacy study are ongoing, which results will illuminate whether A2AR-HDAC dual inhibitors would become novel candidates for the immunotherapy of cancer.

**MEDI 257**

**HER-2 kinase-targeted cancer therapy: Design, synthesis, and kinase profiling of novel quinazoline derivatives as selective antitumor hits**
In 2007, FDA-approved lapatinib in combination therapy for treatment of HER2 positive breast cancer. However, its effectiveness is limited by resistance that frequently emerges following treatment. T790M/L858R resistance is the most commonly reported EGFR-resistance and accounting for 60-60% of the acquired resistance. Inspired by this fact, we tackled T790M/L858R resistance through design, synthesis of 27 novel 4,6 disubstituted quiazoline derivatives with more structural flexibility at the solvent accessible region to avoid the steric clashes of the mutant M790. This design was conducted through multistep reactions to incorporate different flexible spacer at position 6 of quinazoline ring, namely, (propanoyl, acetamide or methylbenzamide), this followed by nucleophilic substitution with several polar fragments. At position 4, “N-(4-(3-chloro-4-(3-fluorobenzyl)oxy)phenyl)amino” fragment of lapatinib was replaced by “N-(4-(3-chloro-4-(3-substituted-phenoxy)phenyl)amino)” moiety to fit into the lipophilic back pocket with an enhanced selectivity against the target HER-2 kinase enzyme. Protein kinase profiling at 10 µM single measurements, using a radioactive assay method with [γ-33P]ATP was conducted for 7 compounds using lapatinib as a reference standard. The profiling data for compounds 12f, 23a, 23e, 23L, 18a, 18c, 25d, gave similar profiles with strong inhibitions ranging from (-90.9% to -93.4%) against the target HER-2 kinase, whereas lapatinib demonstrated an inferior inhibition (-52%). In addition, these compounds revealed significant reduction of ABL, EGFR, HER4 and JAK2 compared to the control values. Remarkably, the screened compounds exhibited insignificant activation or even mild inhibition of other kinases which are activated by lapatinib, anticipating lower side effects and toxicity of our designed compounds compared to lapatinib. NCI-60 cell lines single dose screening at 10⁻⁵ M was applied for 10 compounds, 5 compounds exhibited potent and wide spectrum of growth inhibition and were selected for 5 doses assay. In addition, the preliminary MTT assay in AU565 cells (HER2 +ve breast cancer cell line) revealed promising IC₅₀ values, 0.35 µM, 0.6 µM, 0.88 µM, 0.56 µM, 0.64 µM and 0.55 µM for compounds, 25c, 23a, 23d, 23b, 23e and 23g, respectively.

MEDI 258

Design, synthesis, and evaluation of O5 modified apramycin derivatives

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Apramycin, a unique broad spectrum aminoglycoside antibiotic, is only minimally susceptible to aminoglycoside modifying enzymes and has minimal ototoxicity compared to other aminoglycoside antibiotics. We have discovered that the O5 position can be modified without negatively affecting its interaction with the binding pocket in the decoding A site on helix 44 of the rRNA. In this poster we describe strategies for the derivatization at the O5 position of apramycin and present the subsequent structure-activity relationships resulting in significantly improved apramycin derivatives.

MEDI 259

Synthesis of a novel enzyme-activated nitric oxide prodrug for antibacterial applications

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Researchers predict that by 2050, bacterial infections will surpass both cancer and heart disease as the number one cause of death. The alarming increase in antibiotic-resistant bacterial infections demonstrates an urgent need for the development of new antibacterial materials.

Many antibiotics currently available target a specific gene or enzyme to kill bacteria, and mutations in bacteria quickly develop to circumvent the activity of these antibiotics. Nitric oxide (NO) is an excellent alternative antimicrobial agent, as it exhibits multiple mechanisms of action to kill bacteria, making resistance much more difficult to develop. However, targeted drug delivery is necessary when using NO as a therapeutic, as it has several unrelated functions throughout the body. In addition, exposure of bacteria to antibiotics unnecessarily exacerbates the problem of antibiotic resistance. Both of these
challenges can be addressed with an enzyme-activated NO prodrug that releases NO after exposure to a bacteria-specific enzyme.

In this presentation, the synthesis of an enzyme-activated NO-releasing antibiotic prodrug will be discussed. It will be shown that NO release is exclusively in the presence of a bacteria-specific enzyme that metabolizes the NO prodrug to release NO. Bacteria will be exposed to the synthesized NO-releasing compound to determine if it causes a decrease in viable bacteria, indicating antibacterial activity.

Applications of the synthesized antibacterial compounds to be added into polymer blends will be explored. These polymer blended materials could be used as coatings for medical devices to create devices that dispel bacterial infections as they form by releasing NO only when bacteria encounter the surface of the medical device.

MEDI 260

Novel pyrrolomycins as potential anticancer agents

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We previously reported ‘asymmetrical’ marinopyrroles that exhibited potent anticancer activities against Mcl-1/Bcl-2. Using fragment-based and structure-guided strategies, we performed calculations of physicochemical properties, SAR (Structure Activity Relationship) optimization and created a novel series of pyrrolomycins. After synthesizing these novel natural product derivatives, we carried out in vitro evaluations and molecular docking studies. Our results have revealed that some compounds exhibited sub-micromolar IC₅₀ values against a MYCN amplified neuroblastoma cell line. These active compounds also possess better physicochemical and drug-like properties, and pharmacokinetic profiles than asymmetrical marinopyrroles. This presentation will discuss fragment-based and structure-guided design, synthesis, evaluation of these novel pyrrolomycins on their anticancer activity.

MEDI 261

Synthetic and biological studies of benzazepine derivatives as dopamine receptor ligands
Despite the promise of selective dopamine D1 receptor (D1R) agonists as therapeutics to treat neuropsychiatric disorders and drug abuse, there is a lack of such compounds in the clinical armamentarium. The benzazepine scaffold has proven to be a rich source of D1R agonists. However, benzazepine D1R agonists all contain a catechol motif which presents pharmacokinetic liabilities, precluding their clinical use. Previous structure-activity relationship (SAR) studies have failed to identify suitable replacements for the catechol moiety that enable retention of D1R agonist activity in benzazepines. The goal of our project is to identify novel benzazepine-based and benzazepine-inspired D1R agonists that lack a catechol moiety, as leads for drug discovery efforts towards clinically useful neuroactive drugs. In keeping with that goal, we have designed, synthesized and evaluated a set of benzazepine-based compounds that contain a diverse array of substituents and substitution patterns in the phenyl rings and nitrogen atom of the benzazepine core. In addition, we have also examined the strategy of phenyl ring replacement with heterocyclic motifs as potential catechol bioisosteres in novel benzazepine-inspired chemotypes. SAR data appears to affirm the importance of the catechol motif for D1R binding and agonist activity. Most of the modifications attempted resulted in loss of affinity and/or D1R agonist activity. In general, the presence of hydroxyl groups in ring A is preferred over methoxy groups for D1R affinity. Similarly, an N-methyl is favored as compared to N-allyl or N-unsubstituted motifs in the analogs assayed. The heterocyclic groups examined lacked affinity for the D1R. This study provides further evidence that the catechol group of D1R-preferring benzazepines is sensitive to structural modifications and has also provided some important clues as to promising modifications for retaining D1R binding and activity. We will present details of our synthetic and SAR studies.

MEDI 262

Inhibitors of the KRIT1/HEG1 interaction as potential candidates for cardiovascular disease

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The inhibition of the interaction between HEG1 (also known as Heart of glass) and KRIT1 (Krev interaction trapped protein 1) protein complex is believed to upregulate the expression of KLF2/4. In turn, KLF2/4 differentially regulate the expression of factors
that confer anti-inflammatory, antithrombotic, and antiproliferative effects in endothelial cells. As a result, inhibitors of the KRIT1/HEG1 interaction may have therapeutic value for the treatment of cardiovascular diseases. A high-throughput screening assay was conducted, which identified Sirtinol (HKi001, Figure 1A) as a bona fide HEG1-KRIT1 inhibitor. Although this confirmed hit was found to exhibit suboptimal values in efficiency metrics, such as the ligand efficiency (LE) and the lipophilic ligand efficiency (LLE), structure activity and structure property relationship studies (SAR/SPR) led to the identification of smaller fragment-like molecules with comparable activity as Sirtinol but with significantly improved LE and LLE values (e.g., HKi002, Figure 1B). Furthermore, a representative example of these fragments has been co-crystallized with KRIT1 confirming that this small molecule occupies the same binding pocket within KRIT1 that is normally targeted by HEG1 (Figure 1C). Compounds of this type appear to be promising starting points in the development of inhibitors of the KRIT1/HEG1 interaction as pharmacological probes or therapeutic candidates.

Figure 1: A, B) The structure of HKi001 and HKi002; C) Crystal structure of KRIT1 bound to HKi002.

MEDI 263

Computational and experimental filtering of potential therapeutics using ADMET properties

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In silico approaches to predicting ADMET (absorption, distribution, metabolism, excretion, & toxicity) properties can aid in directing prioritization of the development of compounds as potential therapeutics. The main goal of this project is to both computationally predict and experimentally determine select ADMET properties for potential drug candidates relevant to ongoing collaborative projects. QSAR (quantitative structure-activity relationship) models have been generated and used to predict absorption and distribution of potential therapeutics. QSAR models predicting in vivo (human intestinal absorption, HIA) and in vitro (caco-2 permeability) aspects of absorption have been generated. These absorption models have both been internally & externally validated using a set of known compounds. QSAR models predicting protein binding have also been generated and both internally & externally validated. The best model for HIA prediction was found to accurately predict 49 of 60 compounds in the model development stage, 47 of 60 compounds in the internal validation stage, and 4 of 6 compounds in the external validation stage. The best model for caco-2 permeability was found to accurately predict 40 of 60 compounds in the model development stage, 37 of 60 compounds in the internal validation stage, and 4 of 6 compounds in the external validation stage. The best model for protein binding was found to accurately predict 52 of 57 compounds in the model development stage, 46 of 57 compounds in the internal validation stage, and 3 of 4 compounds in the external validation stage. Experimental validation of computational predictions for both absorption and protein binding is ongoing. This work includes validation using compounds with known ADMET properties, as well as enzyme inhibitors and GCPR ligands of interest in our lab.

MEDI 264

Developing chemical probes against falcilysin, an essential malarial metalloprotease

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The malaria parasite, *Plasmodium falciparum*, kills an estimated 445,000 people annually, with the most deaths occurring in African children. Previous studies show that falcilysin (FLN) is a metalloprotease essential to the parasite’s development in the human host, though its biological role is poorly understood. The parasite is notoriously resistant to genetic modification. To study the cellular roles of FLN, we are developing piperazine-derived hydroxamic acids to block FLN activity in cultured parasites in order to conduct loss-of-function studies. Previous data demonstrates that the active site of the metalloprotease is highly receptive to bulky non-polar substituents at the N4 position of the inhibitor scaffold. In this study, we synthesized several inhibitors with different combination of linkers and aryl substituents at the N4-position. Compound potency was determined against recombinant FLN and cultured *P. falciparum*. Tethering a phenyl ring through a lengthy alkyl chain with an N4-sulfonamide linkage resulted in
significantly increased potency against the protease target. These data will guide the further development of chemical tools to probe the function of this protease and to help evaluate FLN as a potential therapeutic target.

MEDI 265

Anti-fatty liver effects of 1-Hydroxy-2-naphthoic acid, a novel chemical chaperone

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Since non-alcoholic fatty liver disease (NAFLD) is being recognized as a primary cause of hepatitis and liver fibrosis/cirrhosis and increases worldwide, the development of effective anti-fatty liver drugs is clinically required. NAFLD is manifested by the excessive lipid accumulation in hepatocytes and sterol regulatory element-binding protein (SREBP)-1c plays an important role in de novo hepatic fatty acid synthesis. Endoplasmic reticulum (ER) stress can regulate the expression and activity of SREBP-1c, thus contributing to the pathogenesis of NAFLD. In the present study, we investigated the effects of 1-hydroxy-2-naphthoic acid (1-HNA), a novel chemical chaperone identified in high throughput screening (HTS) on the hepatic de novo lipogenesis in in vitro and in vivo mouse models. Pretreatment of 1-HNA reduced the protein expression of SREBP-1c enhanced by tunicamycin, an ER stress inducer in HepG2 cells in a concentration-dependent manner. Interestingly, 1-HNA also inhibited SREBP-1c expression induced by either insulin or a synthetic LXRα ligand (T0901317). We further investigated the inhibitory effects of 1-HNA in C57BL/6 mice fed high-fat diet (HFD) for 7 weeks. Oil Red O and H & E stainings showed that lipid accumulation in the liver were markedly reduced in the group orally treated with 1-HNA. Moreover, fasting blood glucose and serum total cholesterol levels were decreased by 1-HNA treatment. The ER stress marker proteins including CHOP and p-PERK were also reduced. To identify the underlying mechanism, we focused on the mTOR-p70S6K signaling which can regulate LXRα-SREBP-1c pathway. Rapamycin, an mTOR inhibitor suppressed tunicamycin-induced SREBP-1c expression. Surprisingly, 1-HNA blocked the mTOR/p70S6K signaling pathway activated by either tunicamycin or insulin and similarly, mTOR/p70S6K pathway was attenuated in HFD plus 1-HNA treated group compared to HFD alone. These inhibitory effects of 1-HNA explain, at least partly, its anti-fatty liver effects. Finally, our results suggest the potential of 1-HNA as a promising candidate for the treatment of NAFLD.

MEDI 266

Discovery and evaluation of potent orally bioavailable retinoic acid receptor-related orphan receptor-gamma-t (RORyt) inhibitors
T-helper 17 (Th17) cells produce the interleukin 17 (IL-17) family of cytokines in response to stimulation by interleukin 23 (IL-23), which is commonly associated with various human inflammatory and autoimmune disorders. The retinoic acid receptor-related orphan receptor-gamma-t (RORγt) is a nuclear receptor that has been identified as a key regulator of Th17 cell differentiation. Therefore, RORγt may be a potential drug target for IL-23/Th17-related autoimmune diseases and several inhibitors have been reported by groups in industry and academia. Our group has explored RORγt inhibitors based on a high-throughput screening campaign. Subsequent hit-to-lead optimization of several chemotypes led to the identification of methyl ester derivative 1. We will describe the identification of a novel series of a,a-dimethylphenylacetamide RORγt inhibitors, which were obtained by lead optimization of 1 through a structure–activity relationship (SAR) study and guided by a cocrystal structure analysis. These studies led to the discovery of a potent and orally bioavailable RORγt inhibitor, S18-000003. Oral administration of S18-000003 significantly inhibited IL-17 production in the skin of mice injected with IL-23 in a dose-dependent manner.
Synthesis of silibinin analogues targeting amyloid beta

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Alzheimer’s disease is an intractable disease; one of the pathological characteristics is the amyloid deposition in hippocampus. Reactive oxygen species (ROS) is known to be generated in the aggregation process of amyloid beta (Aβ), to injured nerve cells. In general, it is reported that polyphenol have the ability to inhibit aggregation of Aβ. Previously, a catechin analogue, called “planar catechin (PC)”, in which the geometry of (+)-catechin was constrained to be planar, was synthesized. Comparing with catechin, it exhibited potent radical scavenging activity, several novel biological activities and enhanced inhibitory activity against Aβ aggregation. Silibinin (Sib), extracted from milk thistle, is widely used as supplements. It has many biochemical functions, such as inhibitory activity of Aβ aggregation, anti-cancer and anti-inflammation activities. Interestingly, holding high planarity in Sib is the most stable, a certain researcher group hypothesize that planarity in the molecule is correlated with the inhibitory activity of Aβ aggregation. In this study, we designed the novel derivatives Sib-PC and Sib-EC in which the steric structure of Sib was constrained by introducing planar or nonplanar catechin, respectively, in order to clarify the effect of molecular planarity on biological activity. These derivatives will allow the protection of Aβ induced neurotoxicity by way of both potent inhibition of Aβ aggregation and antioxidation toward Aβ-induced intracellular ROS generation. Four step synthesis were accomplished for the preparation of these derivatives. The scavenging activity of these derivatives on hydroxyl radical were measured by electron spin resonance method (ESR). Furthermore, inhibition of oxidative DNA-damage for hydroxyl radical or singlet oxygen were measured by electrophoresis of agarose gel. These results indicated that they have weak radical scavenging activity and protective effects for oxidative DNA-damage. Next, we assessed the inhibitory effect on Aβ aggregation by Thioflavin-T assay. It was shown that Sib-PC having a planar structure has strong activity for inhibition of Aβ aggregating. These results revealed that the planar structure of Sib was essential for its inhibitory effect on Aβ aggregation. In this presentation, the details of these results will be reported.

Effect of bridged pyrrolidine rings on SAR and physicochemical properties in a series of Na+,1.6 selective aryl sulfonamide inhibitors

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Epilepsy is a condition characterized by excessive synchronous excitability in the brain that arises when the delicate balance of excitatory and inhibitory signaling falls out of equilibrium. It is the fourth most common neurological disorder in the United States and throughout the world. Nonselective antagonists of voltage-gated sodium channels (Na\textsubscript{v}) are among the most prescribed antiepileptic drugs despite their marginal therapeutic indices and dose-limiting side effects. Identification of sodium channel mutations and genetic studies in animals have enabled a deeper understanding of the involvement of various Na\textsubscript{v} isoforms in the etiology of epilepsies. Inhibition of Na\textsubscript{v}1.1 is expected to be proconvulsant since genetic loss-of-function of this channel in humans causes a serious childhood epilepsy, Dravet Syndrome. On the other hand, inhibition of Na\textsubscript{v}1.6 channels, which are primarily expressed in excitatory glutamatergic neurons, can be linked to anticonvulsant activity. Therefore, isoform-selective Na\textsubscript{v}1.6 inhibitors could provide a more effective treatment for epilepsy with the potential for seizure control with a greater safety margin compared to non-selective sodium channel blockers. We recently disclosed the design of a series of zwitterionic aryl sulfonamides as CNS-penetrant, isoform-selective Na\textsubscript{v}1.6 inhibitors with favorable ADMET properties. Here we discuss our optimization strategy for this series and the importance of the delicate interplay of lowering lipophilicity with other crucial properties. We show how a replacement of simple secondary amines with bicyclic versions enabled the balancing of lipophilicity, PXR activation, MDR1 efflux, and metabolic stability that ultimately led to the development of potent, isoform-selective Na\textsubscript{v}1.6 inhibitors with improved profiles.

MEDI 269

Novel pyrrolopyrimidine derivative DCBCO1601 as potent AXL kinase inhibitor with \textit{in vitro} and \textit{in vivo} biological activity

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AXL, a member of the TAM (TYRO3, AXL, and MERTK) subfamily of receptor tyrosine kinases, is overexpressed in a variety of cancer types which has been associated with poor prognosis. In the context of malignancy, evidence suggests that abnormal expression of AXL drives wide-ranging processes, including epithelial to mesenchymal transition, tumor angiogenesis, resistance to chemotherapy as well as targeted therapies, and decreased antitumor immune response. Therefore, AXL is a crucial prognostic biomarker in malignancy and also a promising therapeutic target for antitumor therapies. Herein, we introduce a novel pyrrolopyrimidine derivative DCBCO1601 as potent AXL kinase inhibitor with \textit{in vitro} and \textit{in vivo} biological activity. DCBCO1601 significantly inhibited ligand induce AXL signaling pathway activation and potentiated the cytotoxicity of docetaxel in AXL highly expressed H1299 NSCLC cells. The \textit{in vitro} inhibition activity of DCBCO1601 is superior to the lead AXL inhibitor.
BGB324, which is currently in phase II clinical trial for treating lung cancer. In addition, combination treatment of DCBCO1601 enhanced the in vivo antitumor activity of docetaxel in H1299 xenograft. DCBCO1601 is being developed as candidate for further clinical development and for IND submission.

MEDI 270

Studies on the design, synthesis, and antibacterial evaluation of new semisynthetic vancomycin derivatives reported

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Vancomycin is the last line of defense against Gram-positive bacterial infections in the clinic, and its resistant bacteria have caused the death of patients with bacterial infections posing serious challenges to humans. Therefore, more attention of governments and research institutions have been focused on finding and developing non-drug resistance new antibacterial drugs, and it will be a long-time research goal. Based on the structure-activity relationship of vancomycin, our research group modified vancomycin glycosamino moiety by introducing aliphatic hydrophobic side chains to obtain a series of derivatives and conducted their antibacterial activity studies. It was found that the target compound containing a length of aliphatic carbon chain between 7 and 10 showed high antibacterial activity and broad spectrum antibacterial. We believed that our present work is very significant and will bring new drug candidates for vancomycin antibiotic research.

MEDI 271

Development of novel ecto-5'-nucleotidase inhibitor with non-competitive mechanism

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The CD73, also known as ecto-5'-nucleotidase (NT5E), is a cell surface enzyme overexpressed on tumor cells. The CD73 catalyzes the conversion of AMP to ADO. In the tumor microenvironment (TME), binding of extracellular ADO to adenosine receptors (AR) promotes the proliferation of immunosuppressive cells and inhibits the cytotoxic immune response which diminishes the immune response towards cancer cells. Recently, antibody blockade of CD73 is shown to increase the therapeutic efficacy of clinically approved immunotherapies in preclinical models. This suggests the benefits of developing small molecular anti-CD73 inhibitor to enhance immunity or combination with immune checkpoint blockade immunotherapy. Here we have synthesized, characterized and evaluated a novel series of ecto-5'-nucleotidase inhibitors. The most potent compound was shown with IC50 values of 0.3 μM (APCP as 2.5 μM) on
recombinant protein. The competition assay was implemented to explain the non-competitive inhibition mechanism.

MEDI 272

OATD-01: Dual hAMCase and hCHIT inhibitor as a potential therapeutic agent for treatment of pulmonary diseases

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Acidic mammalian chitinase (AMCase) and chitotriosidase (CHIT1) are enzymatically active chitinases that have been implicated in the pathology of chronic lung diseases. Significantly elevated chitinolytic activity was demonstrated in asthma, chronic obstructive pulmonary disease (COPD) and interstitial lung diseases such as idiopathic pulmonary fibrosis (IPF) and sarcoidosis. Herein, we describe our studies on targeting chitinases with small molecules as a potential therapy for pulmonary diseases. In the course of our program 2500 compounds have been designed and synthesized, resulting in OAT-870 as our advanced lead compound. Further optimization of drug-like properties and selectivity of OAT-870 yielded a clinical candidate – OAT-889/OATD-01. The compound bears an additional methyl group at the morpholine ring, which abrogated undesired off-target activity towards dopamine transporter (DAT). OATD-01 is a nanomolar inhibitor of AMCase and CHIT1 with optimal pharmacokinetic profile in rodents and dogs. In addition to anti-inflammatory efficacy in asthma models, interestingly OATD-01 exhibited anti-fibrotic effects in a chronic HDM-induced airway remodelling model and in a bleomycin-induced pulmonary fibrosis model in mice. These data indicate that inhibition of chitinases might represent a novel therapeutic approach for pulmonary diseases as well as several fibrotic pathologies. Moreover, OATD-01 is the first-in-class chitinase inhibitor to have entered clinical trials (currently in phase 1b).
Planar catechin conjugated with DTPA as a promising antioxidant triggered by 
Fe$^{3+}$ coordination

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The main effects mediated by reactive oxygen species (ROS) relate to its potential to cause oxidative damage in cells and tissues. Therefore, a ROS burst contributes to cellular dysfunction and can cause a wide range of chronic diseases. Polyphenol such as catechin and resveratrol is capable of scavenging ROS resulting in the prevention of oxidative stress related diseases. In this study, planar catechin (PCat), in which the geometry of catechin is constrained to be planar, was conjugated to metal chelater DTPA. The antioxidative activity of the compound (PCat-DTPA) was evaluated in terms of the capacity to scavenge DPPH radical as an oxyl radical species. The compound (PCat-DTPA) showed weak antioxidative activity compared with planar catechin due to intramolecular hydrogen bonding between DTPA with catechol moiety of catechin structure. Alternatively, in the presence of Fe$^{3+}$, the antioxidative activity of PCat-DTPA greatly increased 345-fold, which was 3-fold compared to that of PCat. The strong antioxidative activity of PCat-DTPA in the presence of Fe$^{3+}$ was also shown by Fenton system and hypoxanthin-xanthine oxidase system. Enhanced radical scavenging activity of PCat-DTPA compared with PCat suggested that reduction of DPPH with PCat-DTPA accelerated by Fe$^{3+}$ mediated electron transfer. Transition metal ions, which have an ability to produce ROS by redox cycle, demonstrates the role of positive
oxidative stress in age-related diseases. However, PCat-DTPA exhibits more potent antioxidative activity by coordinating with Fe$^{3+}$. Therefore, the compound is a promising seed for the new antioxidant for the treatment of the oxidative stress-related diseases.

MEDI 274

Drug development and production for cardiovascular diseases & arrest (CDA/CDD) (Oxonitrogensic)

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Cardiac arrest is the abrupt loss of heart function in a person who may or may not have been diagnosed with heart disease. It can come on suddenly, or in the wake of other symptoms. Cardiac arrest is often fatal, if appropriate steps aren’t taken immediately. Most Cardiac arrest / Disease such as heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, heart arrhythmia, congenital heart disease, valvular heart disease, carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, and venous thrombosis will dealt with by using Oxonitrogensic, a new drug chemical therapeutics. Sudden cardiac arrest (SCA) and sudden cardiac death (SCD) occur when the heart abruptly begins to beat in an abnormal or irregular rhythm (arrhythmia). Without organized electrical activity in the heart muscle, there is no consistent contraction of the ventricles, which results in the heart’s inability to generate an adequate cardiac output (forward pumping of blood from heart to rest of the body. Oxonitrogensic is a cardiovascular arrest/ disease, (CDA/CDD) drug to be develop for counter measuring heart failure or suddenly muscles heart contract. Oxonitrogensic is been produce by reaction of propanalol with the nitric oxide and nitrogen (IV) oxide at a favorable temperature. It will helps to prevent harmful clots from forming in the blood vessels, prevent the clots from becoming larger and causing more serious problems, prevent clotting in patients who have had a heart attack,
unstable angina, ischemic strokes, TIA (transient ischemic attacks, or "little strokes") and other forms of cardiovascular disease. It will help lower blood & reduce swelling (edema) from excess buildup of fluid in the body. It will be use as therapy for cardiac arrhythmias (abnormal heart rhythms) and in treating chest pain (angina). Used to prevent future heart attacks in patients who have had a heart attack.

**Oxonitrogensic** is a chemical therapeutics drug for the cardiovascular arrest, which composition such as nitric oxide and nitrogen dioxide are used as an anesthetic agent in the CDA Drug. The composition of Propanalol with these agent helps for the Anti-cardiac arrest such as aiding instantaneous pumping of blood to the heart when there is arrest and letting the heart muscle when contracted to be relax and flexible. It won’t have an adverse effect as shown in the QSAR, QSTR and other relationship studies

**MEDI 275**

**Structure-activity and structure-metabolic stability relationship study of 1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridine and 3,4-dihydro-1H-pyranopyrano[4,3-b]quinoline phosphodiesterase 5 inhibitors for the treatment of Alzheimer’s disease**

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Alzheimer’s disease (AD) is a progressive neurodegenerative disorder that involves cognitive impairment, such as loss of memory and reasoning and decline in mental ability. The nitric oxide (NO) signaling pathway has been found to be perturbed in AD. NO stimulates soluble guanylyl cyclase, which increases the synthesis of second messenger cyclic guanosine monophosphate (cGMP) and activity of cGMP-dependent protein kinase. Activation of this signaling pathway leads to phosphorylation of the transcription factor cAMP-responsive element binding (CREB) protein, which induces the expression of memory-related genes. Thus, phosphorylated CREB (pCREB) has been linked to the improvement of learning and memory in mouse models of AD. Phosphodiesterase 5 (PDE5) is an enzyme that hydrolyzes cGMP, causing a decrease in pCREB levels. Therefore, inhibition of PDE5 represents a valid therapeutic strategy for enhancing learning and memory. Our goal is to develop novel PDE5 inhibitors (PDE5Is) with metabolic stability for the treatment of AD.

We previously discovered a PDE5I, namely JF14, which showed high PDE5 potency (IC50=56pM) but poor metabolic stability against human liver microsomes (half-life=6.0min). We designed and synthesized a library of new small molecules divided into two different chemical classes: 1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridine and 3,4-dihydro-1H-pyranopyrano[4,3-b]quinoline. All compounds were evaluated for their pharmacologic effects and metabolic properties. We have found that compound JF43 bearing two fluorine atoms at C-7 and C-9 of the 1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridine scaffold showed improved metabolic
stability (half-life=66.0 min) but PDE5 potency about 1100-fold lower (IC50=66.1nM) compared to JF14. Seven analogs (JF28, 32, 38, 41, 42, 45, and 46) retained PDE5 inhibitory effect in the picomolar range (IC50=320-49pM), however, did not possess improved metabolic stability. Four compounds (JF25, 29, 30, and 31) showed PDE5 inhibitory activity in the low nanomolar range (IC50=26.9-1.5nM) and did not show improved metabolic stability. Compound JF44 demonstrated poor metabolic stability and only 10% inhibition of PDE5 at 100nM. Further studies are undergoing to evaluate the soft spots of compound JF43 and design new PDE5Is with picomolar potency and in vitro metabolic stability greater than 60 minutes.

MEDI 276

Discovery of Praliciguat (IW-1973): Novel, once daily, orally bioavailable, stimulator of soluble guanylate cyclase with extensive tissue distribution

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Soluble guanylate cyclase (sGC) is a heme-containing enzyme and receptor of nitric oxide (NO). Binding of NO to the heme moiety activates sGC and catalyzes the conversion of guanosine-5′-tri-phosphate (GTP) to cyclic guanosine-3′, 5′-monophosphat (cGMP). Stimulators of sGC are a class of compounds that agonize sGC independently of NO concentration and synergistically with NO. A clinical approval from this class of molecules has resulted in developments of other sGC stimulators. Beyond the well-established cardiopulmonary effects of sGC stimulators, they have potential as anti-fibrotic and anti-inflammatory agents.

Praliciguat is the first sGC stimulator from a new pyrazole-pyrimidine series to enter clinical development. The structure-activity-relationship and lead optimization efforts that led to the discovery of praliciguat began with profiling of various amines, and in particular, amino alcohols, at the 4-position of the pyrimidine ring. The desired potency, stability, PK-PD parameters and drug-like properties were achieved through multi-parameter optimization. Praliciguat is novel, orally bioavailable, high volume of distribution sGC stimulator possessing a PK profile consistent with once-daily dosing. It is currently in Phase II clinical trials for diabetic nephropathy and heart failure with preserved ejection fraction.

MEDI 277

Compound selectivity evaluation in PPAR family using machine learning modelling
The peroxisome proliferator-activated receptor (PPAR) family belongs to the nuclear receptors superfamily. PPAR is responsible for regulating many different lipid-related genes, e.g. of the metabolism and transport of cholesterol and lipid. There are three different PPAR nuclear receptors, PPAGα, PPAGδ, and PPAGγ, with different localizations and specializations. There are many known agonists for these three subtypes and some of them are selective. For example, GW501516 is 1000 fold more selective for PPARδ than the other two.

Machine learning has been used successfully in many areas of drug discovery. For example, using pattern recognition and high-level statistical modelling to learn relationships among a large set of chemical compounds, their physical, chemical properties, and their biological data. In this study, we will employ both ligand-based, and structure-based approaches. Our aim is to train multiple machine learning models from existing PPAR agonists and their bioactivities retrieved from ChEMBL as well as X-ray crystal structures from the PDB to classify the selectivity of the subtypes. The results could help in filtering or screening potential compounds in future studies.

**MEDI 278**

**Cross-link breaking activity and inhibitory effect of *Moringa oleifera* leaf crude extracts on fructose-derived advanced glycation end products**

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Leaf extracts of *Moringa oleifera* (*M. oleifera*) have been shown to lower blood glucose levels in both human and animal models of type 2 diabetes. Whilst there is no report on the cross-link breaking properties of these extracts, their inhibitory effect against the formation of advance glycation end products (AGES) is also yet to be adequately investigated and confirmed. The objective of this study was to investigate the inhibitory effects of these extracts on the formation of AGEs in vitro and compare these effects with the inhibitory effect of aminoguanidine, a known inhibitor of AGEs formation and also assess their ability to break collagen-AGE-BSA cross-links. The polar extracts (methanol and water) significantly inhibited the formation of fluorescent AGEs (FAGEs) derived from fructose after incubation for both 20 and 40 days. In the case of total immunogenic AGEs (TIAGEs), at 20 days the highest inhibitory effect was observed in the hexane extract which was significantly higher than aminoguanidine whereas after 40 days’ incubation the highest inhibitory effect was obtained in the methanol extract and this was also significantly higher than that of aminoguanidine. All other extracts and aminoguanidine demonstrated similar inhibitory effect against TIAGEs as aminoguanidine after incubation for 40 days. After both 20 and 40 days’ incubation, the
polar extracts had comparable inhibitory effect as aminoguanidine against the formation of BSA-fructose derived carboxymethyllysine (CML). For cross-link breaking activity, all *M. oleifera* leaf extracts demonstrated the ability to break BSA-fructose derived collagen-AGE-BSA cross-links.

**MEDI 279**

**Synthesis and evaluation of a cinnoline-core type candidate radiotracer for positron emission tomography of brain macrophage colony-stimulating factor 1 receptor**

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Colony stimulating factor 1 receptor is a cell-surface class III tyrosine kinase receptor (CSF1R). In brain, CSF1R plays a pivotal role in regulating the development of microglia, the resident immune cells that are involved in neuroinflammation. Although activation of CSF1R promotes the survival and the proliferation of microglia, CSF1R overexpression is associated with several disorders. Positron emission tomography (PET) might be exploited with a suitably specific radioligand for non-invasively quantifying CSF1R levels in living human brains in biomedical research on neuropsychiatric disorders.

Several CSF1R inhibitors have been described. Among them, the potent (*IC*$_{50}$ = 3 nM) cinnoline-core type inhibitor 2 reported by AstraZeneca appeared to have very favorable physicochemical properties for development as a PET radiotracer, including molecular weight of 406 Da, TPSA of 76 Å, and clog*D*$_{7.4}$ of 2.9. In addition, the presence of potential sites for labeling with carbon-11 (*t*$_{1/2}$ = 20 min) or fluorine-18 (*t*$_{1/2}$ = 110 min) prompted us to consider this inhibitor for development as a PET radiotracer for CSF1R imaging.

The commercially available precursor 1 (2.5 µmol) was treated with [$^{11}$C]MeI in DMF (0.4 mL) in the presence of TMP base (1.1 eq.) at 100 °C for 5 min to give [$^{11}$C]2, which was purified with HPLC and formulated for intravenous injection. The whole radiosynthesis required 38 min. Evaluation of [$^{11}$C]2 in non-human primates and rodents with PET showed negligible brain uptake (SUV = 0.2). Furthermore, [$^{11}$C]2 appeared to be a weak substrate of the ATP-active efflux pumps at the blood-brain barrier. Therefore, [$^{11}$C]2 is ineffective as a PET radiotracer for CSF1R.
**Figure:** Synthesis of the radiotracer $[^{11}\text{C}]2$.

MEDI 280

**Metal-binding pharmacophores as scaffolds for the development of potent human arginase-1 inhibitors**

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Arginase-1 (Arg1) is the oldest known Mn$^{2+}$-dependent human metalloenzyme. It is a homotrimeric enzyme, with each subunit bearing a dinuclear Mn$^{2+}$ active site responsible for cleaving its substrate, L-arginine, to L-ornithine and urea. While the primary function of Arg1 is to complete the last step of the urea cycle in the liver, Arg1 is also distributed throughout the body where it plays various roles in maintaining homeostasis. Arg1 overexpression and subsequent L-arginine depletion have been linked to a number of diseases, including but not limited to cancer, hypertension, atherosclerosis, diabetic vascular disease, myocardial ischemia injury, ischemic stroke, Alzheimer’s disease, multiple sclerosis, diabetic retinopathy, and erectile dysfunction. Arg1 inhibition is proposed as a strategy for restoring L-arginine levels in these disease states, so that any new Arg1 inhibitor could be of great benefit to a range of conditions. Despite the known role of Arg1 overexpression in these diseases, there are currently no FDA approved therapeutics against this metalloenzyme. Reported inhibitor design has been sparse, and mainly limited to substrate analogues (oxidized guanidines) and transition state mimics (boronic acids). While these inhibitor classes have been useful as tool compounds, they have been found to have poor pharmacokinetic properties, stemming from limited bioavailability and in vivo stability, curtailing their potential for further therapeutic development.

The ultimate goal of this research is to rationally design new, potent inhibitors of Arg1. In order to meet this goal, we have synthesized and screened our in-house metal-binding pharmacophore (MBP) library against Arg1 to identify MBP fragments that selectively bind to the dinuclear Mn$^{2+}$ Arg1 active site. This screen has revealed multiple MBP small molecule scaffolds that selectively bind with sub 100 µM IC$_{50}$ values against Arg1. These scaffolds include oxazoline and hydroxamic acid based inhibitors, both of
which have never before been reported against Arg1. Moreover, rudimentary structure-activity relationship (SAR) derivatives of these MBP fragments has already yielded clear SAR trends identifying optimal positions for further compound elaboration. To this end, we are excited to report the development of new, metal-binding small molecule inhibitors of Arg1.

MEDI 281

Structure-based design and synthesis of novel DYRK1A inhibitors targeting inactive kinase conformation to induce human pancreatic β-cell proliferation

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Type 1 diabetes mellitus, an insulin-dependent diabetes, is an autoimmune condition resulting from pancreatic β-cell destruction leading to deficient insulin secretion. Inhibition of Dual-Specificity Tyrosine Phosphorylation-Regulated Kinase 1A (DYRK1A) has been reported to drive human pancreatic β-cell proliferation. However, previously reported DYRK1A inhibitors generally bind in the ATP-binding pocket, which is highly conserved among kinases, resulting in off-target kinase activities. Type II kinase inhibitors potentially have increased potency and selectivity relative to type I inhibitors due to their additional interactions with the allosteric pocket of the kinase. Recently, we reported a putative type II DYRK1A inhibitor, thiadiazine 3-5, with DYRK1A Kd = 71 nM, that induced human β-cell proliferation similar to the positive control type I DYRK1A inhibitor harmine. In order to advance this translational drug discovery effort, DYRK1A binding affinity and human β-cell proliferation activity require further improvement of this new lead scaffold. We have modified three parts of the compound 3-5, hinge binder, thiadiazine core and tail. Among that two novel DYRK1A classes exhibited DYRK1A Kd’s of <100 and <3 nM and one of them induces robust human β-cell proliferation comparable to or better than harmine at 10 μM. This presentation will report our medicinal chemistry approaches to enhance DYRK1A inhibition as well as β-cell proliferation activity.
Identification of a new class of proteasome inhibitors based on a naphthylcarbonyl-phenyl urea scaffold

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Proteasome plays an important role in protein degradation and regulation of many cellular pathways and as such, is a significant target for the treatment of many diseases, including cancer. Clinically used inhibitors of the proteasome have shown great success in the treatment of multiple myeloma and mantle cell lymphoma but yet exhibit side effects and toxicity, rendering the discovery of new inhibitors with higher therapeutic index, a necessity.

Virtual screening of a library of natural products (ZINC) led to the identification of a class of naphthyl carbonyl phenyl urea compounds as inhibitors of the β5 site of the proteasome. These compounds showed evidence of dose dependency through proteasome assays with IC₅₀ values in the low micromolar range. The inhibition mode of 3-(3-cyanophenyl)-1-(2-naphthylcarbonyl-oxo-BLAHyl)-urea (ZINC4258888) was further analyzed at a range of substrate and inhibitor concentrations the results of which revealed competitive binding at the β5 site with an estimated inhibition constant, Kᵢ 4μM. Molecular docking analysis of the binding mode of structural analogues identified the naphthyl and cyanophenyl groups to be important for activity.
The results of this study led to the identification of a potentially new class of proteasome inhibitors that can be further optimised through structure-activity relationship studies.

**MEDI 283**

**Structure-based design of dual AChE and BACE-1 inhibitors as potential therapeutics for neurodegenerative diseases**

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Inhibitors of β-secretase 1 (BACE-1) have demonstrated remarkable potential for development of multi-target-directed therapeutics for neurodegenerative diseases. In this study, donepezil analogues were developed as multifunctional inhibitors centered on BACE-1. Donepezil scaffold, a potent acetylcholinesterase (hAChE) inhibitor, is profiled to BACE-1 via introduction of backbone amide linkers which are capable of hydrogen-bonding with BACE-1 catalytic site. Enzyme inhibitory assays demonstrated the dual activity of the synthesized donepezil analogues against hAChE and BACE-1. Remarkably, the most active member of this study exhibited superior potency to donepezil with IC\textsubscript{50} values of 4.11 and 18.3 nM against hAChE and BACE-1, respectively. Molecular modeling studies were employed to investigate the key interactions between the active compounds and catalytic sites of hAChE and BACE-1. In addition, the demonstrated ability of these compounds to cross blood-brain barrier (BBB) by PAMPA-BBB assay and low cytotoxicity against SH-SY5Y neuroblastoma cells hold promise for their potential utility for future optimization in development of multi-target-directed therapeutics for neurodegenerative diseases.

**A. hAChE**

![Diagram of A. hAChE](image)

\textit{IC}_50 = 4.11 \text{nM}

**B. BACE-1**

![Diagram of B. BACE-1](image)

\textit{IC}_50 = 18.3 \text{nM}

Key interactions of the most active compound with catalytic sites of hAChE and BACE-1

**MEDI 284**

Amelioration of experimental autoimmune encephalomyelitis and DSS-induced colitis by thiadiazole derivatives of 6-aminopyridin-3ol through the inhibition of Th1 and Th17 cells differentiation
CD4+ T cells are the central players for the mammalian adaptive immune system. Naïve CD4+ T cells mainly differentiate into pro-inflammatory Th1, Th2 and Th17 cells upon antigenic stimulation. IFN-γ secreting Th1 cells and IL-17 secreting Th17 cells are found to play key roles in autoimmune diseases like multiple sclerosis (MS) and ulcerative colitis (UC). Previously, we have shown that some 6-aminotrimethylpyridin-3-ol analogues have anti-colitis activity both in vitro and in vivo models. In this study, we found 1,3,4-thiadiazole tethering 6-aminopyridin-3-ol derivatives have great inhibitory effect on in vitro differentiation of Th1 and Th17 cells without affecting regulatory T cells. Moreover, the derivatives had no effect on CD4+ T cell proliferation and viability. In vivo treatment has shown that the derivatives have ameliorated experimental autoimmune encephalomyelitis (EAE) and dextran sulfate sodium (DSS) induced colitis through the inhibition of Th1 and Th17 cells differentiation. Mechanistically, the derivatives suppressed Th1 and Th17 cells differentiation via the modulation of JAK/STAT signaling pathway. Thus, our data demonstrated that the derivatives ameliorated inflammation through the inhibition of Th1 and Th17 cells generation making it a potential therapeutic candidate for the treatment of inflammatory diseases.

MEDI 285

Identification and SAR studies of RhlR antagonists derived from 4-gingerol

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Pseudomonas aeruginosa (P. aeruginosa) is an opportunistic human pathogen that forms biofilms and produces virulence factors via quorum sensing (QS) network. QS is a bacterial cell–cell communication process that allows bacteria to share information against the change of environment. Therefore, blocking QS between auto-inducers and their cognate receptors is considered to be an effective strategy for attenuating its virulence factors in P. aeruginosa. The RhlR system plays an important role in the QS process of recognizing the ligand BHL. However, studies of RhlR antagonists competing with BHL have rarely been reported, despite their important role.

In an effort to discover new RhlR antagonists, we screened in-house gingerol derivatives (from 4-gingerol to 10-gingerol) and performed molecular docking studies. Gingerol analogs with shorter alkyl chain lengths at the tail part were more potent than...
ones with longer alkyl chains. Based on these results, 36 derivatives of 4-gingerol with variation of the head part and rotational flexibility of middle part were synthesized in 3 steps (up to 40% yield). RhlR agonism and antagonism activities of the compounds were determined using cell-based reporter strain assay and static biofilm formation assay. In addition, a molecular docking study of the compounds with the Rhl homology model exhibited that hydrogen bonding between the substituent at 4-position of the head section and Tyr 45 or His 61 at the active site was crucial for binding to RhlR. The information on comprehensive SAR studies of 4-gingerol analogs will be useful in designing and optimizing gingerol-based RhlR antagonists.

MEDI 286

Amphiphilic kanamycin for treatment and diagnosis of the fungal infection

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Amphiphilic kanamycin, synthesized by the introduction of hydrophobic group in kanamycin, is in great interest to the researcher due to their novel antifungal activity. The compounds synthesized by the modification of 4” or/and 6” hydroxyl group of kanamycin have wide spectrum antifungal activity against both plant pathogens and human pathogens. Despite excellent antifungal activity of these membrane-permeabilizing compounds, the requirement of multiple synthetic steps causes the cost of the compounds much higher than the commercial antifungal compounds in the market. To overcome this issue, we have newly synthesized amphiphilic compounds by the one-step modification 6’ amine group of the kanamycin. The new lead compounds have prominent antifungal activity as previously reported amphiphilic kanamycin with mild antibacterial activity. The cost of production of these new compounds are comparable to the marketed antifungal compounds and only consist of natural moieties; kanamycin and fatty acid. The fluorescent analogs synthesized using a similar synthetic procedure was used to study the fungal selective activity of amphiphilic kanamycin. The fluorescent imaging of the fungal, bacterial and human cells treated with the fluorescent analogs showed that the compounds can permeabilize the fungal cells at a faster rate and lower concentration relative to bacterial and human cells. The newly reported synthetic strategy opens the door for possible use of the amphiphilic kanamycin in the treatment of the fungal infection and the fungal selective properties of the fluorogenic amphiphilic kanamycin have potential to be used in the diagnosis of the fungal infections.

MEDI 287

Dopamine D1R-preferring ligands via structural modifications on apomorphine
Selective D1 receptor (D1R) agonists are promising for the treatment of a variety of neuropsychiatric disorders. However, the majority of available D1R agonists contain a catechol moiety which is associated with limited oral bioavailability. The anti-Parkinson’s disease drug apomorphine is a catechol-containing dual D1/D2 receptor agonist. We propose that isosteric modification of the catechol moiety of apomorphine, will allow for the identification of novel, selective and orally bioavailable D1 receptor agonists. Towards that goal, herein we examine the impact of structural modifications on D1R selectivity. The analogs contain variations in N-alkyl substituent groups on the tetrahydroisoquinoline moiety, alkoxy substituents in ring A as well as substituted aniline motifs in ring D that are designed to function as catechol group surrogates. Synthesis of the apomorphine analogs was achieved in 8-10 steps from readily available precursors via Bischler-Napieralski cyclization and intra-molecular direct arylation as key steps. The binding affinity of the analogs was assessed at dopamine D1-D5 receptors in standard radioligand binding assays. The acquired structure-affinity data indicates that most of the analogs display preferential binding to the D1 receptor over D2 and D5 receptors. In addition, alkyl group substitutions on the nitrogen atom of the tetrahydroisoquinoline moiety is generally favorable for affinity at all dopamine receptors. This study has provided valuable lead compounds that may be further tuned to achieve the required selective D1R agonist ligands. Details on our synthetic and pharmacological evaluations will be presented.

**MEDI 288**

**Discovery of clinical candidate, BMS-986235/LAR-1219: Design and optimization of selective 4-phenylpyrrolidinone FPR2 agonists**

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Formyl peptide receptors (FPRs), which belong to the G-protein coupled receptor (GPCR) family, play important roles in host defense and inflammation. In humans, three subtypes (FPR1, 2, 3) have been identified. FPR1 causes pro-inflammatory responses when activated with ligands such as N-formyl-methionyl-leucyl-phenylalanine produced from bacteria. In contrast, FPR2 has been reported to resolve inflammation when activated by ligands such as Annexin A1. Although FPR2 is a promising target for treatment of various inflammatory diseases, there are no compounds launched as therapeutic agents to date. In this context, we focused on the discovery of small molecule FPR2 agonists with selectivity over FPR1. A series of four to six membered lactam urea derivatives were synthesized that produced potent human FPR1 and 2 agonists. Further optimization of the pyrrolidinone scaffold led to selective FPR2
agonists with picomolar in vitro activity. Among the derivatives evaluated, highly potent and selective agonist, BMS-986235/LAR-1219, was identified as a promising clinical candidate.

MEDI 289

Development of novel synthetic TLR4 agonists

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Toll-like receptors (TLRs) are a family of pattern recognition receptors on innate immune cells that recognize pathogen-specific components of microbial invaders. Among the TLRs, TLR4 is the specific sensor of lipopolysaccharide (LPS, endotoxin), one of the molecular components of Gram-negative outer membrane. LPS binds TLR4 and its accessory molecule MD-2 to form a stable TLR-MD-2 receptor complex, triggering an initial innate immune response which protects the host against a wide spectrum of unrelated pathogens. This defensive reaction includes secretion of inflammatory cytokines that activate natural killer cells and initiates a cascade of signals to cells of the adaptive immune arm, preparing them for the development of antigen-specific immune responses. In this regard, molecules capable of stimulating innate immunity can also act as adjuvants leading to enhanced antigen-specific immunity.

In the course of our own structure-activity studies on Lipid A, the active component of LPS, we have developed a new class of chemically stable synthetic monosaccharide compounds capable of eliciting robust innate and adaptive immune responses. This new class of TLR4 agonists encompasses a new monosaccharide scaffold, the Diamino Allose Phosphate (DAP), which contains a non-hydrolyzable 3-amide bond instead of the classical 3-ester bond present in Lipid A derivatives. This new series of DAPs is more potent than the known TLR4 agonists benchmarks MPL and GLA, and retains equivalent TLR4 activity to the corresponding known synthetic TLR4 agonists CRX-524 and CRX-601. In addition, these new TLR4 agonists have a much-improved stability when formulated in aqueous formulations. These new synthetic TLR4 agonists were shown to protect mice against a lethal influenza challenge and are potent vaccine adjuvants.
Synthesis of N-cyclopropylbenzamide-benzophenone hybrids as novel and selective p38 mitogen-activated protein kinase inhibitors and their biological evaluation for neuroinflammation

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We recently reported a series of N-cyclopropylbenzamide-benzophenone hybrid molecules as novel and selective p38 mitogen-activated protein kinase (MAPK) inhibitors. Among of them, NJK14047 showed excellent p38 MAPK inhibitory activity and selectivity. To investigate the therapeutic usefulness of NJK14047, we evaluated its anti-inflammatory activity, especially in the aspect of neuroinflammation. P38 MAPK has been identified as an essential enzyme with inflammatory roles in several immune cells, and its regulation is important to be potential therapeutic agents for neurodegenerative diseases. In this study, we showed that NJK14047 attenuates lipopolysaccharide (LPS)-stimulated neuroinflammation in BV2 microglia cells and an LPS-injected mice model. NJK14047 reduced the production of prostaglandin E₂ and nitric oxide by downregulation of the expression of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), nitric oxide synthase (NOS) and cyclooxygenase-2 (COX-2) in LPS-stimulated BV2 microglia. Moreover, in vivo model studies showed that NJK14047 significantly reduced microglial activation in the brains of LPS-injected mice.
Design, synthesis, and biological evaluation of sulfamaoylbenzamide derivatives as hepatitis B virus capsid inhibitors

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Hepatitis B virus (HBV) remains the major health concern with 260 million people infected globally and 680,000 deaths by cirrhosis and liver cancer annually. HBV capsid assembly modulation has emerged as a promising therapeutic approach for the cure of HBV infection. The two major classes of small-molecule capsid modulators are HAPs (heteroaryldihydropyrimidines) and SBAs (Sulfamoylbenzamides). SBAs are known as capsid activators inhibiting viral replication by achieving the capsid assembly before polymerase encapsulation. Herein report a novel series of HBV capsid inhibitors based on the NVR 3-778, a class of SBAs. The compounds described exhibit improved pharmacological activity and we have explained this observation on the basis of molecular docking studies.

**MEDI 292**

Optimization of (8-quinolyloxymethyl)benzamide derivatives as potent and selective RORγ inhibitors

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RORγt (Retinoic acid-related Orphan Receptor γ thymus) is a nuclear receptor which is expressed in immune cells such as Th17 and γδ T cells. It is identical in sequence to RORγ with the exception of a few missing amino acids at the N-terminus of the protein. RORγt is a key player in the IL-17 pathway and is involved in the synthesis of pro-inflammatory cytokines such as IL-17A, IL-17F and IL-22. It is also implicated in the differentiation of naive T cells into Th17 cells where both RORα and RORγ are highly expressed.

Anti IL-17 antibodies such as secukinumab have shown robust efficacy in the treatment of psoriasis and psoriatic arthritis. A small molecule RORγt inverse agonist would, in theory, have an advantage over a targeted antibody by blocking the Th17/IL-17 cascade upstream at two different stages (differentiation and effector function). Not surprisingly,
the therapeutic potential of RORγt has drawn the attention of numerous research groups. Here we report on the optimization of a series of (8-quinolyloxymethyl)benzamide derivatives with the help of a co-crystal structure of one derivative in RORγ LBD (Ligand Binding Domain). The synthesis of these derivatives, their structure activity relationship (SAR) and in vitro biological activity is described herein. The compounds were first screened in a transactivation assay using a chimeric receptor Gal4 DNA-binding domain (DBD)-human RORγ LBD transiently transfected in COS-7 cells. The best derivatives were then evaluated in an IL-17A secretion inhibition assay in human Th17 cells. Finally the selectivity vs the other ROR isoforms was evaluated in a co-activator recruitment assay using the AlphaScreen™ technology. The most interesting derivatives were tested in vivo in a mechanistic model in mouse, where they reduced IL-17 cytokine production following immune challenge. One compound also proved to be active in a multiple sclerosis model (EAE) where it reduced the disease score.

**MEDI 293**

**Synthesis of novel bipyridine ligands as potential telomerase inhibitors**

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The search for novel chemotherapeutic approaches for cancer treatment is an active research field. An important target, the reverse transcriptase enzyme telomerase, has attracted a lot of attention because this enzyme is over expressed in several cancer cell types and inactive in normal somatic cells. Inhibition of telomerase, by G Quadruplex stabilization, induces cell senescence and death and, for this reason, it has become a very important target for cancer therapeutics. In this work we present the synthesis and telomerase inhibition studies of novel bipyridine ligands.

**MEDI 294**

**Flexible and integrated collaboration tools to aid, co-ordinate, and inspire medicinal chemistry**

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Modern drug discovery has draws on a vast array of information sources and resources to progress through the classic Design-Make-Test-Analyse cycle making the coordination of information and relevant tasks a challenging process. We present Torx, a new web-based application that joins molecule design and analysis to the tracking of molecule synthesis and testing to generate a single portal to coordinate all chemistry efforts.
Each stage of the cycle brings different demands of the users and diverse information. Equally different tasks and actions emanate from the varied nature of each stage of a project. Collaboration is central to all stages but is varied in meaning depending on the task in hand. To satisfy these demands requires a flexible, customizable application. However, success in drug discovery also relies on invention - the individual project teams must be inspired to take a novel step or gain a vital insight.

Torx is a new, web based application to address the needs of modern small molecule discovery. Each stage of the process has a dedicated interface to enable the specific workflows of that stage of the drug discovery process.

The Design and Analysis module enables collaborative 2D and 3D design by automatically converting molecules from a chemistry drawing application to a model inside the protein active site. Changes to the 2D structure are propagated 'live' to the 3D window enabling real-time 3D sketching in a simple chemistry drawing application. Molecule designers can choose to 'share' their session with other users enabling real-time collaboration on the selected design or analysis.

Tracking of successful designs through synthesis and testing, whether in-house or through an external partner, is achieved using a dedicated 'kanban' style tracking board with customizable workflow and business rules, detailed privacy and security settings, and easy visual feedback on the status of any single or set of molecules. Detailed labelling, alerting and priority settings enable users to gain exactly the information that they need whilst not compromising corporate security.

This poster will outline the current state of the application with an emphasis on the application of the Design and Analysis modules to the discovery of kinase inhibitors.

**MEDI 295**

**Toward a selective small-molecule antagonist of hyaluronan binding by CD44**

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CD44 is a cell surface hyaluronan (HA) binding protein implicated in a variety of different cancers because it can modulate tumor cell adhesion, tumor growth, and therapeutic resistance. High molecular weight-HA (HMW-HA; >10⁷ Da) in the extracellular matrix stimulates cancer progression by binding to CD44 and activating oncogenic signals which can be inhibited using very small (<10⁴ Da) HA fragments that disrupt HMW-HA/CD44 interactions. The goal of this study is to develop small molecules that selectively block binding of HMW-HA by CD44 to evaluate the potential of such antagonists to limit cancer progression and improve response to existing.
anticancer therapies.
In previous work, we identified an inducible subsite adjacent to the HA-binding groove of CD44 that has modest affinity for a tetrahydroisoquinoline (THIQ) pharmacophore. An exploration of SAR was undertaken to increase binding affinity and to explore extensions of this pharmacophore toward HA-binding subsites. Co-crystal structures with dozens of analogs and HA fragments have inspired the design of a short linker to connect a THIQ bound in this subset to saccharide units that occupy the Glc-5 and NaG-6 subsites of the CD44. We have undertaken the synthesis of a series of "THIQ-saccharide conjugates" that are computationally predicted to increase binding affinity with the addition of each saccharide unit. The first of the molecules in this series - a THIQ-glucuronic acid conjugate - has been prepared but shows no ability to antagonize HMW-HA binding by CD44 in vitro. Nevertheless, computational modeling of more extended analogs suggests that a N-acetylglucosamine saccharide appended to glucuronic-acid analogs will allow for additional H-bonding and afford a binding affinity sufficient to achieve antagonism of HMW-HA binding by CD44. Progress toward the design, preparation, and characterization of compounds in this series will be presented.

MEDI 296

3-Dimensional metal complexes as scaffolds for fragment-based drug discovery

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Fragment-based drug discovery (FBDD) has emerged as a powerful and efficient way to develop small molecule inhibitors. Though fragment libraries are typically small in size, they are able to concisely represent broad chemical diversity. However, one shortcoming associated with this approach is that most fragment libraries are biased toward small, flat molecules. Accordingly, there has been a recent concerted effort to improve the three-dimensionality of fragment libraries. In an attempt to improve the structural diversity of common fragment libraries, our lab has developed an innovative library designed to consist of more three-dimensional fragments than are typically employed in FBDD. By using small, inert metal complexes, we have developed a novel library of “metallofragments.” This modest library is highly three-dimensional, as demonstrated by a principle moment of inertia plot. To demonstrate the capacity of the metallofragment library it was screened against influenza endonuclease. Several classes of metallofragments were identified as hits. The structure-activity relationship around the metallofragment binding site is being explored in order to identify an elaborated, full-length inhibitor molecule.

MEDI 297
Identification of a β-hairpin peptide that disrupts growth arrest-specific gene 6 (Gas6)/Axl receptor interaction

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Growth arrest-specific gene 6 (Gas6) is a member of the vitamin K-dependent protein family, and is believed to play a role in platelet activation and endothelium dysfunction. Previous data suggested that Gas6 is a novel platelet and vessel wall target with a potential to improve clinical outcome of atherothrombotic diseases. Herein we present our structure-based design approaches using a crystal structure of the Gas6/Axl receptor complex to identify an Axl-derived β-hairpin millamolecule. The peptide was shown to bind Gas6 with high affinity and disrupt Gas6/Axl complex formation and inhibit platelet activation.

MEDI 298

Leveraging academic collaborations and expanding the millamolecular chemistry synthetic toolbox

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One of the key strategies to develop our Millamolecular platform is to leverage collaborations with academic research labs to expand the available collection of unnatural amino acids building blocks, to explore new methods for peptide modifications, and to advance new chemistry for bioconjugation. Advancement of these technologies is directed at enabling the discovery of millamolecular drug molecules, conjugates, and PET imaging agents. The academic research community is well positioned to discover new and innovative ways to access unnatural amino acids of high interest, in particular, those previously difficult or elusive to synthesize. In this presentation, we highlight our collaborative efforts that have enabled access to a diverse set of unnatural amino acids designed based on several program needs. The synthesis of these building blocks was achieved leveraging several cutting-edge
methodologies, namely Pd-catalyzed C(sp³)-H activation and radical enabled C-C cross-coupling reactions, developed under the Bristol-Myers Squibb (BMS) and The Scripps Research Institute (TSRI) collaboration.

MEDI 299

Discovery of APOBEC3B DNA cytosine deaminase ligands by protein observed fluorine NMR screening

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Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (A3) catalyzes C-to-U deamination in single-stranded (ss)DNA as a function of the innate immune defense against pathogenic DNA. A3s cause hypermutation leading to genomic instability and clearance by the host immune system. One A3 enzyme in particular, A3B, is overexpressed in various cancer types and is a source of genomic mutations that result in tumor evolution and the development of drug resistance. A3B is nonessential in humans making it an exciting new target for cancer therapy. High-throughput screening campaigns have identified covalent inhibitors of A3G, but no A3B small molecule inhibitors have yet been reported. Recently, a co-crystal structure of A3B with a fragment-sized molecule has been solved indicating that A3B can be targeted by fragments. Consequently, we have initiated a solution-phase fragment screening campaign to identify A3B-binding molecules. Our approach utilizes Protein Observed Fluorine (PrOF) NMR to identify A3B-binding ligands. PrOF NMR involves incorporating fluorinated amino acids into the target protein and observing changes in the ¹⁹F-NMR resonance shifts upon titration of ligands. These changes in resonance shifts not only indicates that a molecule is binding, but also gives information on where the molecule is binding, which yields a powerful tool for the discovery of enzyme ligands. This poster will highlight recent efforts to develop a PrOF-based assay for A3B ligand screening and preliminary chemical matter discovered through our efforts.

MEDI 300

GUNW-3 as a brain-targeting agent to improve the delivery of tamoxifen to the brain

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The Blood-brain barrier (BBB) protects the brain from harmful substances in the blood by restricting their entries. On the other hand, the barrier also prevents most therapeutic agents from reaching the brain leading to ineffectiveness of these therapeutics in treating brain diseases. Various strategies have been made to improve the delivery of therapeutic agents to the brain for the treatment of brain diseases.

The BBB is featured with various receptors and transporters. The ligands of some of these transporters and receptors have been exploited for brain-targeting delivery. Glutathione (GSH) is a three amino acid peptide and endogenous antioxidant. GSH enters the brain through the GSH transporter that is enriched in the BBB. GSH has been successfully used as a brain-targeting ligand in brain delivery nanoparticles. GUNW-3, a GSH-based derivative, has been confirmed to be an effective brain-targeting agent from our laboratory. This study was aimed to investigate how effective GUNW-3 could help deliver liposomes and micelles encapsulated with tamoxifen to the brain. The preparation and characterization of GUNW-3 liposomes and GUNW-3 micelles encapsulated with tamoxifen will be presented. The in vivo studies with mice demonstrating both GUNW-3 liposomes and GUNW-3 micelles significantly increased the brain delivery of tamoxifen will be reported as well.

MEDI 301

Small molecule-mediated degradation of BRAF-V600E for the treatment of melanoma

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BRAF is among the most frequently mutated oncogenes in human cancers, primarily due to mutations at codon 600. Three small molecule BRAF kinase inhibitors have been approved for treating melanoma patients carrying V600E/K mutations. Small molecule-mediated targeted protein degradation has recently emerged as novel technology for removal of disease causing proteins by hijacking the endogenous ubiquitin-proteasome system. In this study, we developed VHL-1 and thalidomide-based heterobifunctional compounds that selectively induced degradation of BRAF-V600E, but not the wild type BRAF. Reduced BRAF-V600E levels compromised the MEK/ERK kinase cascade and impaired melanoma cell growth in culture. Abolishing the interaction between degraders and cereblon or inhibition of proteasome greatly impaired the activities of these degraders. These findings demonstrated a novel strategy to modulate the functions of oncogenic BRAF and provide a framework to target non-catalytic functions of BRAF mutants.

MEDI 302
Design through computer-aided approach and synthesis of new benzimidazole derivatives as inhibitors of protein tyrosine phosphatase 1B

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Protein tyrosine phosphatase 1B (PTP1B) is a negative regulator of insulin signaling. Therefore, PTP1B is an attractive target to design new drugs against Type 2 diabetes. Our research group previously report a benzimidazole derivative that inhibits PTP1B (compound 1). Due to its Ki value in the low micromolar range (4.2 µmol) and drug like properties, it was selected for optimization. With the aim to design more potent and selective inhibitors, a computer-aided ligand-based strategy was applied. To this end, a detailed analysis of the interactions PTP1B-compound 1 was performed by molecular docking using Extra Precision and Induced Fit tools in Glide program from Maestro software (www.shrodinger.com). Additionally, in view of the high structural similarity among the catalytic domain of PTP1B and its closest homologous T-cell-PTP (TCPTP), the interactions showed by the selective inhibitors reported were taking into account also. This information was used to propose a series of 30 new compound 1 derivatives, modifying substituents at positions 2, 5 and 6 in the benzimidazole core. These compounds were docked into PTP1B and TCPTP catalytic sites. The data showed that compounds denominated MCα-1, MCα-2, MCβ-1 and ISα presented the best interactions to account for selectivity. These molecules were selected for synthesis and their inhibitory effect in PTP1B and TCPTP was evaluated. The results indicated that the compounds were able to inhibit PTP1B and their activity against TCPTP is being tested. Therefore, these molecules can be used to continue the optimization process in the search of more potent and selective PTP1B inhibitors.

MEDI 303

Nucleoside analogue inhibitors of GTP cyclohydrolase I (GCYH-I) as a potential new class of antibiotics

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This project seeks to develop a new class of antibiotic drugs to be used against resistant pathogens such as MRSA by targeting an unexploited enzyme in the folate biosynthesis pathway. GTP cyclohydrolase I catalyzes the first step in folate biosynthesis in bacteria and bioppterin biosynthesis in humans. Many pathogenic
bacteria use an essential GTP cyclohydrolase I enzyme, GCYH-IB, that bears little structural homology in the active site to the human form, GCYH-IA. The crystal structures of GCYH-IA and -IB reveal that the active site of GCYH-IB is significantly larger, suggesting that it can be inhibited selectively by molecules too large for binding to GCYH-IA. A known substrate analogue inhibitor of GCYH-IA, 8-oxo-GTP, inhibits bacterial GCYH-IB, but with similar or reduced potency. By modifying 8-oxo-GTP to exploit active site features unique to GCYH-IB, new inhibitors with high selectivity for the bacterial enzyme can be developed. We have synthesized an initial set of compounds to test structure-activity relationships in the inhibition of GCYH-IA and -IB. Two compounds, G1 and G2, showed lower inhibition of the bacterial enzyme than of the human enzyme. The third compound (S)-G3 showed no significant difference in the inhibition of the two enzymes. A further modification, G3, showed two-fold more inhibition of the bacterial enzyme than the human enzyme, demonstrating that these active site differences can be targeted. These results show that it is possible to design an inhibitor selective for the bacterial enzyme. With further modification, we expect to maximize the potency and differential inhibition, leading to a novel class of antibiotics that can act against resistant strains of bacteria.

MEDI 304

Discovery of IWP-597: Novel carboxylic acid-containing soluble guanylate cyclase stimulator

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Soluble guanylate cyclase (sGC) is an enzyme that plays a key role in the nitric oxide (NO)-sGC-cyclic-guanosine-monophosphate (cGMP) cell signaling pathway. Binding of the endogenous ligand NO to the prosthetic heme group of sGC results in increased cGMP production and downstream activation of targets including cGMP-dependent protein kinase (PKG), which ultimately regulates vasorelaxation, inflammation, fibrosis, and metabolism. In addition to the NO binding site, sGC contains an allosteric binding pocket where small molecule sGC stimulators bind and act in synergy with NO to amplify cGMP production. sGC stimulators have been clinically validated in two forms of pulmonary hypertension and have potential as therapeutic agents in other diseases associated with NO deficiency or where amplification of this pathway would be beneficial.

The discovery of a novel carboxylic acid-containing sGC stimulator, IWP-597, was initiated based on our desire to improve the potency of the previously reported IWP-051 and on key findings of an in-silico pharmacophore model. The SAR efforts led to improvement of the in vitro and in vivo metabolic profile and addressed potential liabilities associated with the formation of reactive, migrating acyl glucuronides found in related carboxylic acid containing analogs. IWP-597 is an sGC stimulator that
demonstrated good oral bioavailability and robust pharmacology in a normotensive hemodynamic rat model.

MEDI 305

Identification of a potent inhibitor of notch signaling

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Notch signaling is a pathway involved in cell proliferation and differentiation and is functional in regenerating tissues and cancerous cells. Therapeutic intervention of Notch signaling has been attempted with γ-secretase inhibitors (GSIs) and with antibodies to proteins involved in the Notch signaling cascade such as JAG and Notch-1. At issue with GSIs is their inherent non-selectivity and off-target effects that have led to the abandonment of the approach in several clinical studies. Racemic b-annulated dihydropyridines (DHPs) were reported to interfere with Notch signaling with EC₅₀ values in the 5 µM range. Screening of a focused proprietary library of substituted DHPs in a Notch reporter assay led to the identification of several inhibitors of Notch signaling with submicromolar potency. Synthesis of the individual enantiomers of the most potent compound gave the single enantiomer (+)-1, with EC₅₀ = 220 nM. The DHP (+)-1 also inhibited the proliferation of two different colon cancer tumor cell lines with EC₅₀ values of 200 nM for HCT-116 cells and 87 nM for SW480 cells. The expression of the HES-1 gene is increased as a consequence of Notch activation. It was observed that incubation of HCT-116 and SW480 cells with (+)-1 resulted in a statistically significant reduction of the expression of HES-1 in both cell lines, further supporting the idea that (+)-1 affects the Notch signaling pathway.

MEDI 306

Synthesis and spectroscopic characterization of analgesic drugs esters of poly-acrylic acid

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Prodrug is a class of drugs, in the begging it is in inactive form, that are converted into active form in the body by normal metabolic processes. Prodrug synthesis is an approach that can improve drugs and solve the problems such as solubility, stability, test, drug preparation, or bioavailability. Prodrug give a pharmacological response by binding with a receptor located at the site of action. In this project, polymers are used to form slow release drugs, by reacting poly acrylic acid with different hydroxyl containing non-steroidal analgesic drugs such as para-acetaminophen. This will form an ester drug derivative of the poly-acrylic acid. The latter are expected to easily convert to the active
drug after normal metabolic processes. The synthesized prodrugs are identified from their IR, 1H and 13C-NMR, and Mass Spectral data.

**MEDI 307**

**Synthesis, evaluation, and computational simulations of novel 1,2,3-triazole analogues of sitagliptin as DPP-4 inhibitors**

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Dipeptidyl peptidase-4 (DPP-4) inhibition is a new generation therapeutic approach to the treatment of type 2 diabetes. Precedent SAR studies of sitagliptin (Januvia™) performed to further improve its pharmacological profile demonstrate that the modification of 1,2,4-triazolopiperazine preserve the bioactivity. In an effort to find novel scaffolds as congeners of the 1,2,4-triazolopiperazine of sitagliptin, novel 1,2,3-triazole analogues were designed and efficiently synthesized using Click Chemistry in the key step, and evaluated in vitro. Two 1,2,3-triazole analogues with pyridyl substituent exhibited very promising inhibitory activities. Our results suggest that the position of the nitrogen atom in the pyridine ring might play an important role for the inhibitory activity (p-pyridyl > m-pyridyl > o-pyridyl). To obtain insights into potential binding modes of these analogues in the human DPP-4, we employed computational methods including docking simulations and molecular dynamics simulations. Our computational simulation results are consistent with the bioassay data, and suggest potential binding modes of the analogues in the human DPP-4 and its key amino acid residues for binding the analogues.

**MEDI 308**

**Synthesis and spectroscopy of binary prodrugs**

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Prodrug is the precursor of the active form of a drug. In more complex terms, a prodrug is an inactive form of a drug, but once administered, it undergoes a conversion by metabolic processes to become the active, pharmacological agent. Synthesis of prodrug is widely known and was validated to be a very good strategy amid approaches for refining and solving a wide range of problems associated with the drug. In this work, we designed the synthesis of a binary prodrug approach in which we connect two compatible drugs. Upon bio reverting the process, both drugs will be regenerated with possible synergetic activity for both. The new products are fully characterized using Infrared, Proton and Carbon-NMR Spectroscopy, and Mass Spectrometry.

**MEDI 309**
Background and Significance: Approximately 3.2 million people in the United States are currently living with hepatitis C virus (HCV). As a positive-sense RNA virus, HCV is prone to mutations, which makes it difficult to design drugs that can target either the viral proteins or the genome itself. It has been discovered that a small section of the 5' non-coding RNA, called the internal ribosome entry site (IRES) subdomain IIa acts as a molecular switch. The IRES recruits human ribosomes to bind, which causes a conformational change in the subdomain IIa, and allows for the ribosome to translate the RNA into viral proteins. Notably, this small section of RNA is highly conserved; as previously discovered, the virus showed only two point mutations in the subdomain IIa. Due to this high degree of conservation, it is an invaluable target for drug design that mimics the natural ligand and forces the IRES into a conformation that will not recruit ribosomes, rendering the virus unable to reproduce.

Methods: We have created an improved, efficient synthesis of diverse methylsulfoximine molecules using novel techniques developed in our laboratory. We have initiated synthesizing new analogs designed to improve affinity of the targets for the HCV RNA. We plan to conduct rapid assays of the new compounds against the IRES-IIa subdomain, allowing us to iteratively refine SAR and leverage our new synthetic route toward obtaining compounds with increased potency.

Results: It has been shown that precise shape complementarity based solely on hydrophobic interactions can significantly improve ligand binding even in hydrophilic target sites such as RNA. We have focused on synthesizing heterocyclic methylsulfoximine derivatives of the natural HCV IRES ligand that will take advantage of these space-filling interactions. The initial scaffold has been synthesized and tested on the RNA construct. We are currently working on modifying the scaffold to be more like the native ligand to further improve binding to the IRES.

Conclusions: The efficient new synthetic route we have developed has made it practical to obtain enough material to optimize for inhibition, replication and favorable pharmacokinetics and bioavailability, thus advancing the prospects of this class of compounds as potential anti-HCV medications.
Design and synthesis of novel CDK9-specific PROTACs for the treatment of leukemia

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The field of proteolysis targeting chimeras (PROTACs) has been rapidly expanding over the last twenty years due to its viability as an anticancer treatment approach. PROTAC development includes the design of a bifunctional molecule, including an E3 ligase ligand, target protein ligand, and “linker” region binding the two ligands together. Through these PROTACs, targeted protein degradation has been achieved for multiple proteins in a variety of cancer types. The PROTAC forms a ternary complex with the E3 ligase and target protein, with the E3 ligase ubiquitinating the target protein, leading to subsequent degradation by the 26S proteasome in the cell, removing the target protein altogether. Currently, our lab is focusing efforts towards targeted CDK9 degradation in treatment of leukemia. The CDK9 pathway plays a significant role in gene transcription and mRNA maturation whose dysregulation is associated with leukemia development. Both CDK9 inhibition and degradation have been established as viable options for leukemia treatment, with CDK9 degradation holding an immense amount of promise as a therapeutic route due to the long-lasting anti-proliferative effects seen in cancer cells. Utilizing the cereblon E3 ligase as the desired ubiquitinating machinery for CDK9, numerous PROTAC analogues have been created utilizing either 4-hydroxythalidomide or pomalidomide as the E3 ligase ligand. The distance between the E3 ligase ligand and CDK9 ligand were varied by placing a variety of linker types and lengths between the E3 ligase ligand and CDK9 ligand, allowing for determination of optimal linker length and composition to allow for CDK9 degradation. The synthesis of these CDK9 PROTAC analogues, as well as the biological data for this compound class, will be discussed.

MEDI 311

Synthesis of three fluoro-containing [¹¹C]ER176 analogs for PET imaging of TSPO in monkey brain

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ER176, when labeled with carbon-11 (t₁/₂ = 20 min), is a high-performing radioligand for imaging and quantifying TSPO, a biomarker of neuroinflammation, in human brain with positron emission tomography (PET). [¹¹C]ER176 ([¹¹C]1) analogs that might be labeled
with longer-lived fluorine-18 ($t_{1/2} = 110$ min) and provide comparable imaging performance would be more widely useful. We synthesized three new fluoro analogs (2a–2c) of ER176 and found them to be high-affinity TSPO ligands. We labeled them by $^{11}$C-methylation so that we could compare them with [${}^{11}$C]1 and guide our selection of ligand for evaluation with an $^{18}$F label.

Labeling precursors (4a–4c) were synthesized in good yields (55 to 80%) by amidation of 3 followed by Pd-catalyzed coupling with an appropriate fluorophenylboronic acid. $[^{11}$C]2a–[^{11}$C]2c were obtained by $^{11}$C-methylation of 4a–4c, respectively. PET was performed in rhesus monkey over 120 min after intravenous injection of radioligand, and in the same monkey after pre-treatment with the selective TSPO ligand, PK11195 (5 mg/kg, i.v.). Arterial input functions were determined in parallel. Brain radioactivity uptakes were comparable with those of [${}^{11}$C]1 and were strongly blocked with PK11195. $V_T$s, the indices of total binding in brain, were similar to that of [${}^{11}$C]1. They were decreased 69–84% by PK11195 (c.f., 85% for [${}^{11}$C]1), indicating high proportions of TSPO-specific binding. These new radiotracers merit evaluation after labeling with fluorine-18.

![Synthesis Scheme](image)

**Figure.** TSPO ligand structures (2a–2c), and synthesis of precursors (4a–4c) and radioligands ([${}^{11}$C]2a–[^{11}$C]2c).

**MEDI 312**

**Novel nanoformulation of Levofloxacin and antimicrobial efficacy**
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In this study, new levofloxacin loaded mesoporous silica nanoparticles were prepared by sol–gel technique using tetraethyl orthosilicate (TEOS) as silica precursor and cetyltrimethylammonium bromide (CTAB) as pore generating agent. The synthesis conditions were tailored by varying the molar ratio of water, NaOH and amount of CTAB used. The synthesized silica carriers were characterized by Scanning Electron Microscope (SEM) micrographs which showed that spherical particles with an average size between 80-87 nm were prepared. UV and Infra Red Spectroscopy (FTIR) confirmed the formation of levofloxacin-nano particulate system and showed the participation of carboxylic group in the synthetic process. This new nano particulate system exhibited better activity against 9 bacteria (\textit{Corynebacterium diptheriae}, \textit{Corynebacterium hofmanii}, \textit{Staphylococcus epidermidis}, \textit{Streptococcus fecalis}, \textit{Streptococcus pyogenes}, \textit{Acinetobacter baumanii}, \textit{Serratia marcesens}, \textit{Shigella dysenteriae} and \textit{Aeromonas hydrophila}) and three fungi (\textit{Microsporum canis}, \textit{Microsporum gypseum} and \textit{Penicillium sp}) compared to levofloxacin alone. The improved activity is associated with sustained-release properties and better penetration into the microbial cell of mesoporous silica nano particles.

MEDI 313

Structure-kinetics relationship study of CDK8 inhibitors with milestoneing

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Lead optimization using the relationship between compound structures and binding kinetics of a protein-ligand complex is an emerging paradigm. This presentation discusses use of computer modeling to reveals factors that determine ligand-binding kinetics and to assistant drug design. Using metadynamics simulations, we obtained plausible dissociation pathways of 5 type-II inhibitors of cyclin-dependent kinase 8 (CDK8). By mapping the high-dimensional protein-ligand dissociation process into 2-dimensional space, we proposed a novel strategy to define milestones and reaction coordinates. Rugged free energy landscapes computed by the milestoneing theory revealed multiple intermediates along the dissociation path. The protocol also obtained the correct rank of experimental residence times of the 5 compounds. Based on the high-resolution free energy profiles, we concluded that lacking multiple small energy barriers results in much short residence time than slower compounds. Furthermore, the milestones determined in this work retained the main interactions, conformation fluctuations, and solvent effects occurring during the dissociation. In accord with the unbinding free energy profiles, this information reveals potential interactions that may further stabilize the intermediate states, which are used to suggest modification in existing compounds. The agreement of the computed and experimental binding kinetics
suggests that this approach can be utilized in drug design projects aimed at optimizing the residence time of large and flexible systems.

**MEDI 314**

**Lewis acid-modified pyrophosphate bond synthesis via an improved phosphoramidite approach**

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Many diphosphate analogs are biological intermediates, important second messengers and natural substrates for enzymes in human bodies. Chemical synthesis of nucleoside diphosphate (NDP) analogs has been quite active in the area of nucleoside, nucleotide and nucleic acid chemistry. There have been a number of reports that phosphorous modified NDPs improved various enzymatic/biological activities. Therefore, the development of fast and efficient synthetic methods to ensure the availability of different nucleotide analogs for future bioassays is very important for new drug discovery. Here, a number of Lewis acid borane-modified NDPs were synthesized via an improved phosphoramidite approach where the addition of a non-nucleophilic base to deprotonate phosphor in an anhydrous condition is the key step. The mechanism proposed for P(V)-P(III) bond cleavage via phosphorus protonation-promoted nucleophile-exchange in synthetic reaction mixtures is discussed. Temperature, catalyst and reagent impacts on the final product yields are also reported. The yields of all the final products in the reaction mixtures were analyzed by HPLC using a reverse phase C-18 column and compared with earlier synthesized/reported compounds.

**MEDI 315**

**Combinatorial approach for synthesis of novel 1,3,5-triazine-2,4-diamines with potent and selective anti-proliferative activity**

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1,3,5-Triazine ring has a long history of successful implementation as a skeleton for the construction of bioactive compounds, including several marketed drugs. This heterocyclic ring became a privileged scaffold for the drug development. Among 1,3,5-triazine derivatives, *N*,6-disubstituted-1,3,5-triazine-2,4-diamines have found to be an
interesting scaffold for the construction of chemotherapeutic agents. In our study, we developed a new one-pot synthesis of $N_{6}$-disubstituted-$1,3,5$-triazine-$2,4$-diamines (1) by the three-component condensation of cyanoguanidine with aldehydes and primary amines in the presence of acid, followed by the Dimroth rearrangement and dehydrogenative aromatisation. The scope of the method was demonstrated by the successful synthesis of a representative library consisting of more than 100 targeted compounds 1. The anti-proliferative activity of the prepared compounds was evaluated using three breast cancer cell lines, namely MDA-MB-231, SKBR-3 and MCF-7. In general, MDA-MD-231 cells were more sensitive to the compounds as compared to MCF-7 and SKBR-3. Most active compounds have a 3-order selectivity towards the cancer cells as compared to normal breast cells (MCF-10A). Two compounds emerged as the most active in the prepared series against MDA-MB-231 cells. They were found to possess $IC_{50}$ values of 1.7 nM and 7.3 nM, respectively. Furthermore, a QSAR model was built to comprehend the structural requirements controlling the anti-proliferative activity and to assist in the further design of anticancer agents based on this scaffold.

![Reaction scheme]

**MEDI 316**

**New approach to preparation of RNA-targeted libraries**

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RNAs participate in more cell mechanisms than it has been thought before. Aside from transferring information from the DNA, this type of biomolecules appears to affect numerous cell processes: very small part of the transcripts actually codes proteins. Targeting RNA with small molecules was suggested after discovering “druggability” of the nucleic acids similar to that of proteins. The targeting could be aimed at cell processes in humans or blocking RNA functions in bacteria or viruses. For Chemspace RNA-targeted library, we focused on 15 binding motifs in different RNAs associated with bacterial and viral infections. We have selected the compounds from our Screening Compound Collection utilizing both ligand- and target-based approaches. Compounds similar to the known RNA binders have been scored using...
molecular docking, and only those with high predicted activity were picked. The annotations to the target and docking score are available.

**MEDI 317**

**Advantages of fluorinated fragment library in the discovery of novel specific binders and hit to lead optimization**

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Fragment-based drug discovery (FBDD) became an important strategy complementary to conventional high-throughput screening (HTS) campaigns in both academia and industry. The basic idea behind FBDD approaches is to initially identify, usually by screening small focused libraries of low molecular weight compounds (fragments) via biophysical methods, key chemical substructures or pharmacophores sufficient to confer a minimal yet specific interaction with the given target identified by structural studies using X-ray crystallography or nuclear magnetic resonance (NMR) spectroscopy. As a follow up, identified fragment hits could be converted into more potent binders by a variety of approaches using structural information of identified hits.

Chemspace reports variety of fluorine-containing molecules which satisfy criteria of fragments (122<MW<300; HbA≤3; HbD≤2; logP≤4; RotBonds≤3) and examples of follow up development into focused libraries of specific binders. There are distinct subgroups of molecules to identify specific interaction: aromatic compounds with small substituents in the pattern compounds with enriched Fsp^3 increased chirality dimensionality improved physico-chemical properties improved diversity in follow up Approaches to expand chemical space from Chemspace commercially available or de novo synthesis of new fragments and compounds from virtual 100M Chemspace chemical space is discussed. Fluorine atom serves as a marker for the identification of initial binders by NMR and may or may not be present in the final molecules as a structural feature.

**MEDI 318**

**Designing a compact plasmonic nanoparticle with enhanced fluorescence and potentially safer T1 magnetic imaging contrast**

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Engineering a small, near-infrared (NIR) plasmonic nanostructure for both imaging and therapy is a critical nanomedical challenge. Recently, we demonstrated that the
plasmonic core-shell nanostructure consisting of Au core, SiO$_2$ spacing layer, and outer Au shell, known as nanomatrJoshkas (NM), is a highly promising compact nanostructure with a NIR photothermal therapeutic response. Here, we demonstrate that near-infrared-resonant NM can provide simultaneous contrast enhancement for both T1 magnetic resonance imaging (MRI) and fluorescence optical imaging (FOI) by simultaneously encapsulating various contrast agents in the internal silica layer between the Au core and shell. The internalization of Gd(III)-DOTA within the NM would reduce potential exposure of Gd(III) in future clinical applications, ameliorating mounting Gd(III) toxicity concerns while enhancing MRI contrast. Here we also demonstrate that this method of T1 enhancement is even more effective for Fe(III) DOTA doped within NM. Fe(III)NM are found to have relaxivities 2× greater than those found in the widely used gadolinium chelate, Gd(III) DOTA, providing a practical alternative that would eliminate Gd(III) patient exposure entirely. The photobleaching rate of the fluorescent dye is also significantly reduced when sequestered within NM, potentially lengthening the viable imaging time. This multifunctional nanostructure could enable not only tissue visualization aided by MRI but also fluorescence-based nanoparticle tracking for quantifying nanoparticle distributions in vivo, in addition to a near-infrared photothermal therapeutic response.

MEDI 319

**Fatty acylated CGKRK conjugated cell-penetrating peptide for targeted delivery of siRNA in tumor**

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Tumor-targeted carriers provide efficient delivery of chemotherapeutic agents to tumor. siRNA offers innovative therapeutics for cancer treatment; however, siRNA delivery is challenging due to short *in vivo* stability and negligible interaction with cell membrane. CGKRK is one of the well-known peptides which targets heparin sulfate receptor in the tumor cells. Therefore, it could be used for targeting chemotherapeutic agents to tumor. Cell-penetrating peptides containing alternate arginine and histidine amino acids (HR) are demonstrated to be efficient molecular transporters. We hypothesize that conjugation of fatty acylated CGKRK peptide with cell-penetrating peptides will provide efficient delivery and targeting of siRNA to the tumor cells. Several peptides with sequences (HR)$_4$, [HR]$_4$, C$_{20}$-KH(HR)$_3$, C$_{20}$-KH(HR)$_3$-CGKRK, [HR]$_4$C$_{20}$-CGKRK, CGKRK-C$_{20}$ and (HR)$_5$, where () indicates linear peptide and [ ] indicates cyclic peptide, were synthesized using Fmoc/tBu solid-phase peptide synthesis (SPPS), purified by preparative reverse-phase high-performance liquid chromatography (RP-HPLC), and analyzed by matrix-assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry. Peptides were tested for their binding affinity to siRNA using a standard SYBR Green II dye exclusion assay at different N/P ratios. The ratio required for 50% binding (termed BR50) of all the peptides studied were in the range of 0.06 to
0.20, and the maximum binding was observed with cyclic [HR]₄ peptides (BR50 = 0.06). The HR peptides showed a highly significant binding and it can be inferred from the results that all modified peptides would completely bind the siRNA at N/P ratio of 1. Zeta potential, particle size, cytotoxicity, serum stability and gene silencing efficiency of peptide-siRNA complexes will be investigated and reported soon. Since the modified peptides being investigated have been shown to be effective molecular transporters, they are expected to efficiently deliver siRNA to the tumor cells.

MEDI 320

Synthesis and evaluation of bicyclic peptides containing arginine and tryptophan residues as molecular transporters

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We have previously reported two bicyclic peptides [W₅G]-(triazole)-[KR₅] and [W₅E]-(β-Ala)-[KR₅] as molecular transporters, indicating the importance of flexible linker in improving cellular uptake. In continuation of our efforts to develop novel bicyclic peptides, two new bicyclic peptides, [W(WR)₄K]-GFLG-[W(WR)₉E] and [W(WR)₄K]-[W(WR)₄E], composed of alternate tryptophan and arginine residues in each monocyclic peptide building blocks connected through lysine or a short tetrapeptide were synthesized. The bicyclic peptides did not show any significant cytotoxicity at a concentration of 3 µM against human leukemia adenocarcinoma (CCRF-CEM). The peptides were evaluated as cellular delivery agents and found to be significantly more effective molecular transporters when compared with the corresponding monocyclic peptide [WR]₅. The peptides enhanced the cellular delivery of fluorescein (F')-labeled phosphopeptide F'-GpYEEI (F'-PP) (5 µM) by 6.5- and 4.5-fold, respectively, in CCRF-CEM cells after 3 hours incubation, when used at a concentration of 25 µM. While monocyclic peptide [WR]₅ improved F'-PP uptake by 1.4-fold only under a similar condition after 3 hours incubation. These data suggest that these new class of bicyclic peptides containing monocyclic peptides composed of alternate tryptophan and arginine residues can be utilized as a new class of cell-penetrating peptides and cellular delivery tools.

MEDI 321

Synthesis and evaluation of cyclic peptide-dasatinib conjugates as antimelanoma agents

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The adverse drug effects associated with dasatinib treatment as an anticancer agent is mainly due to its nonspecific targeting of normal cells. In our study, we hypothesized that the combination of a cell penetrating peptide and Cat B sensitive group could improve the cellular uptake and targeted delivery towards cancer cells, therefore ultimately results in the reduction of adverse drug events. Herein we synthesized two amphiphilic cell-penetrating cyclic peptide containing tryptophan and arginine residues attached to dasatinib, using a suitable Cathepsin B (Cat B) sensitive tetrapeptide moiety (Gly-Phe-Leu-Gly). Since the steric interaction between the cyclic peptide and Cat B has a significant impact on the release of dasatinib from the pro-drug, two different linkers, succinate and glutarate, were integrated between the drug and the peptide to decrease the steric hinderance. A solid-phase strategy was used to synthesis the cell-penetrating peptide attached Cat B sensitive moiety that was subsequently reacted with the different spacers. Conjugation of the peptide with dasatinib was conducted in the presence of N-methylmorpholine and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), generating the novelly designed pro-drugs. The synthesized compounds were characterized by high-resolution mass spectrometry MALDI, and the purity was confirmed by analytical HPLC. The synthesized cyclic peptide-dasatinib conjugates containing glutarate and succinate linkers were further evaluated against human melanoma A375 cells, which exhibited differential anti-cancer activities with IC\textsubscript{50} of 4.2 µM and 8.8 µM, respectively. The difference of cytotoxicity may be explained by the nature of the linker, which results in differential intracellular release of the drug or cellular uptake of the pro-drug.