Yao Yuan

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UIC UNIVERSITY OF ILLINOIS AT CHICAGO

Emerging Therapeutics: A Fundamental Driver of Pharma's Future Growth

The 8th Yao Yuan Biotech-Pharma Symposium

University of Illinois at Chicago, College of Pharmacy Auditorium
833 South Wood St., Chicago, IL 60612

APRIL 23 TH 2016

Chaired by

Dr. Xueqing Wang
Sr. Group Leader
Discovery Chemistry
And Technology (DCAT)
AbbVie, Inc.

Dr. Hyunwoo Lee
Assistant Professor
Department of Biopharma-
ceutical Sciences
University of Illinois at Chicago

Dr. Alexander Mankin
Professor and Director
Center for Biomolecular
Sciences

TO ATTENDANTS

Welcome to the 8th Yao Yuan Biotech-Pharma Symposium. This is the eighth in a series of annual Yao Yuan conferences, and this year is co-sponsored with SAPA (Sino-America Pharmaceutical Association) and University of Illinois at Chicago, College of Pharmacy.

Despite the high cost and low probability of success associated with drug discovery and development, we are at a time that new drugs with improved profiles and new mechanisms of action are still emerging. As a result of better understanding fundamental biology, rigorous academic and industrial research, and fruitful collaborations, scientists are discovering breakthrough therapies for hard-to-treat diseases and greatly benefitting patients. In this forum, case studies on early discovery research and clinical development of compounds that are on or at the brink of being brought to the market will be presented. Progress in the exciting field of oncology (*e.g.*, CAR-T cells, IDO and BCL-2 inhibitors), which is at the tipping point of producing revolutionary therapies, will also be discussed.

Continuing with last year's emphasis on students, there will be a poster session with TEDA (Tianjin Economic-Technological Developemnt Area)-sponsored awards and a panel discussion relevant to students hoping to find a future in drug discovery.

This event provides a valuable opportunity for learning amongst professionals, academicians and students, and serves as a platform for discussions around many themes central to the world of drug discovery. Though primarily intended to be a Midwest regional gathering, *e.g.*, Illinois, Indiana, Iowa and Wisconsin, this symposium has attracted participants from other regions as well as international attendees.

We hope that you enjoy the day. We're all looking forward to it!

Dr. Xueqing Wang Prof. Hyunwoo Lee Prof. Alexander Mankin

ACKNOWLEDGEMENT

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Dr. Gui-Dong Zhu
President, Yao Yuan—
Academy for Pharma Innovation

Agenda

7:30 – 8:30	Registration/Poster setup
8:30 – 11:30	**MORNING SESSION** Moderator: **Dr. Alexander Mankin,** Professor and Director, Center for Biomolecular Sciences, University of Illinois at Chicago
8:30 – 8:40	Opening Remarks: **Dr. Xueqing Wang,** Sr. Group Leader, AbbVie, Inc.
8:40 – 9:30	Novel Therapeutics for Treating Viral Diseases, Cancers and Inflammatory Disorders **Dr. Dennis C. Liotta**, Samuel Candler Dobbs Professor and Executive Director, Emory Institute for Drug Development, Emory University
9:30 – 9:50	Coffee break/Networking/Vendor displays
9:50 – 10:40	Selective BCL-2 family inhibitors: Potential therapeutics and powerful research tools **Dr. Andrew Souers**, Sr. Research Fellow and Project Director, AbbVie, Inc. Introduced by **Dr. Joel Leverson**, Associate Director of Clinical Science, AbbVie, Inc.
10:40 – 11:30	Inventing INCB24360 (epacadostat), An Indoleamine-2,3-dioxygenase-1 (IDO1) Inhibitor for immuno-oncology **Dr. Andrew P. Combs**, Vice President, Incyte Corporation
11:30 – 2:15	**NOON SESSION**
8:30 – 5:00	**AbbVie Recruiting Booth** (Rm 111, Accepting Resumes)
11:30 – 12:00	**Lunch/Networking/Vendor displays**
12:00 – 1:30	**Poster Presentations** (Presenters on board)
11:30 – 5:00	**Poster Session/Exhibition/Networking**
1:30 – 2:15	**Pharma Panel Discussion**: Career Opportunities in Pharmaceutical Industry Moderator: **Dr. Thomas von Geldern**, Independent Consultant, Former Research Fellow at Abbott Laboratories **Panelists:** Dr. Andrew Combs, Vice President, Incyte Corporation Dr. Xiaochang Dai, President, KPC Pharmaceutical Dorth Korst, Postdoc Program Manager, AbbVie, Inc. Dr. Michael Michaelides, Senior Research Fellow and Head of Oncology Chemistry, AbbVie, Inc.
2:15 – 5:00	**AFTERNOON SESSION** Moderator: **Dr. Hyunwoo Lee, Assistant Professor, Department of Biopharmaceutical Sciences and Center for Biomolecular Sciences**
2:15 – 2:25	**TEDA Awards Ceremony** (presented by Director from TEDA)
2:25 – 2:40	Award Poster Talk: Novel Strategy for The Treatment of Asthma by Targeting the α4 Subunit of GABAA Receptors in Airway Smooth Muscle **Rajwana Jahan**, Department of Chemistry, University of Wisconsin, Milwaukee
2:40 – 3:30	Drug Discovery in Academia: Successful Case Studies **Dr. Michael Jung**, Distinguished Professor of Chemistry, University of California at Los Angeles
3:30 – 4:20	Building and Driving CARs: A Novel Platform For Cancer Immunotherapy **Dr. Samuel Blackman, Sr. Medical Director, Juno Therapeutics**
4:20 – 4:50	**Poster Session/Exhibition/Networking continues**
4:50 – 5:00	Acknowledgement/Closing ceremony **Dr. Joel Leverson**, Conference Vice Chair (Chair-2017)

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BIOGRAPHICAL SKETCH

Samual Blackman, MD, Ph.D

Senior Medical Director, Juno Therapeutics

Dr. Blackman is a physician-scientist trained in pediatric hematology-oncology and pediatric neuro-oncology at the Dana-Farber Cancer Institute and Children's Hospital Boston. For the past 8 years he has been focused on the clinical development of novel cancer therapeutics and has held various positions of increasing responsibility within the pharmaceutical and biotechnology industry. In his present role at Juno Therapeutics he is the Senior Medical Director, and is responsible for clinical development of novel immunotherapeutics for cancer, including chimeric antigen receptor (CAR) T cell therapies and high-affinity T cell receptor (TCR) therapies. Prior to his current role he served as Head of Translational Medicine at Seattle Genetics where he was responsible for preclinical and early clinical development of novel antibody drug conjugate (ADC) therapeutics for cancer and lead a group of 30 physicians and scientists. Earlier he was a Director in the Oncology Early Development Unit at GlaxoSmithKline where he focused on the development of targeted therapeutics for cancer and also lead the pediatric development of GSKs BRAF and MEK inhibitors. At Merck Research Laboratories, Dr. Blackman was Associate Director of Experimental Medicine/Oncology and was responsible for developing novel proof-of-concept platforms and clinical validation of biomarkers in association with several early stage drug development programs and designed the pediatric development strategy for Merck's mTOR inhibitor program.

He currently serves on the scientific advisory boards of the Pediatric Low Grade Astrocytoma Foundation, CureSearch, and the Cravat Foundation. He is a member of the Board of Trustees of Bright Water School in Seattle. He as done extensive fundraising on behalf of the Dana-Farber Cancer Institute and was a founding member of Pedals For Pediatrics, which has raised over $2.7 million dollars for pediatric oncology. In addition, he is a strong advocate for science education. He was a faculty member at Columbia College Chicago for 3 years, and continues to lecture regularly to college, graduate, and lay audiences on a variety of scientific topics related to oncology and drug development.

Dr. Blackman is a graduate of the pediatric residency program at Cincinnati Children's Hospital Medical Center. He received his MD and PhD degrees at the University of Illinois at Chicago College of Medicine and Department of Pharmacology, and his undergraduate degree in philosophy from the University of Chicago.

Andrew P. Combs, Ph.D

Vice President, Incyte Corporation

Andrew P. Combs, Ph.D. joined Incyte in 2003 where he is currently a Vice President of Discovery Chemistry. Prior to Incyte, Dr. Combs was a Director at Bristol-Myers Squibb and Dupont-Merck. He has led several medicinal chemistry programs in oncology to novel candidates, three of which are currently in human clinical trials. The most advanced is epacadostat, a first-in-class IDO1 inhibitor, which is expected to enter pivotal phase 3 trials in combination with pembrolizumab, an anti-PD1 mAb, for advanced melanoma in 2016. His passion for research embraces the application of innovative technologies to expedite the invention of new chemical entities. He has co-authored >60 research articles/book chapters, an inventor on >30 patents, co-chaired >10 conferences and served on editorial advisory boards of several scientific journals (currently *J. Med. Chem. Letters*). Dr. Combs was a HHMI postdoctoral fellow in the laboratories of Prof. Schreiber at Harvard from 1994-1996 and holds a Ph.D. in Organic Chemistry from UCLA and BS degrees in Chemistry and Molecular Biology from the UW-Madison.

Michael E. Jung, Ph.D

Distinguished Professor
University of California at Los Angeles

Prof. Jung received his BA in 1969 from Rice University and his PhD in 1973 from Columbia University, where he worked with Gilbert Stork as an NSF Fellow. After a one-year NATO postdoctoral fellowship with Albert Eschenmoser at the ETH in Zurich, he joined the faculty at UCLA in 1974, where he is now a Distinguished Professor of Chemistry. He currently consults for 21 industrial laboratories in both biotech and big pharma settings and has founded six companies. He is an authority on synthetic organic and medicinal chemistry and has 64 patents and/or applications arising from both his consulting activities and his own research.

His current synthetic chemistry research interests include the easy preparation of hindered cyclohexenes via Diels-Alder reactions using new acid catalysts, the use of several epoxide rearrangements in synthesis (e.g., the non-aldol aldol reaction), and new types of gem-disubstituent effects. Recently he has expanded his role in medicinal chemistry and drug discovery at UCLA and has more than 15 ongoing collaborations. One of his compounds, Xtandi, was approved in September 2012 for the treatment of castration-resistant prostate cancer while several others are in various clinical and pre-clinical stages. He has supervised 90 PhD and 8 Masters theses and has taught 130

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BIOGRAPHICAL SKETCH

postdoctoral scholars. He has published more than 335 articles and given over 590 lectures on his research.

Prof. Jung has received the American Chemical Society Arthur C. Cope Scholar Award, the Team Science Award from American Association of Cancer Research, and was named a Fellow in the National Academy of Inventors. He recently was the Carl M. Franklin Lecturer on Science and Society at the University of Southern California. He will soon be the Glenn T. Seaborg Award Medalist at UCLA (November 2016). He is an excellent teacher and has won every teaching award offered at UCLA: the Departmental Hanson-Dow Teaching Award, the University Distinguished Teaching Award, and the inaugural Gold Shield Faculty Prize.

Dennis C. Liotta, Ph.D

Samuel Candler Dobbs Professor,
Executive Director, Emory Institute for Drug Development, Emory University

Professor Dennis Liotta has helped to transform HIV/AIDS from a death sentence to a chronic infection in which patients are able to live active, near normal lives. The Emory University Office of Technology Transfer estimates that greater than ninety per cent of all of the HIV-infected persons in the United States take (or have taken) one of the drugs he invented. In his current role as Executive Director of the Emory Institute for Drug Development, Dennis oversaw the discovery and development of another novel nucleoside analogue, EIDD-2023, for treating hepatitis C infections. His research group has also recently discovered the first potent, dual tropic (CCR5/CXCR4) HIV entry inhibitors.

Over the past two and a half decades Dr. Liotta's research has focused on the discovery and development of novel antiviral, anticancer and anti-inflammatory therapeutic agents. He is one of the leaders of the Emory team that discovered the antiviral drug, Emtriva (emtricitabine), which was approved for treating HIV in July 2003. Emtriva is a component of the ground breaking, once a day, triple combination therapy, Atripla, which is now universally accepted as the drug combination of choice for treating HIV infected patients. In addition, he is the inventor of record for several clinically important antivirals, including Lamivudine, Reverset, Racivir and Elvucitabine. He is also the lead inventor of Q-122, a safe, orally available clinical agent for controlling hot flashes in post-menopausal women.

Andrew Souers, Ph.D

Sr. Research Fellow & Project Director,
AbbVie, Inc.

Dr. Souers is currently a Senior Research Fellow and Project Director of Oncology Discovery at AbbVie, Inc. He received his B.S. degree in chemistry from the University of Wisconsin, where he worked in the laboratories of Professor Laura Kiessling. Shortly after graduation, Andrew joined the laboratories of Professor Jon Ellman at the University of California at Berkeley. After completing his doctoral degree in organic chemistry, he accepted a medicinal chemistry role with Abbott Laboratories which spun off AbbVie, Inc. in January of 2013. Dr. Souers has been in the Oncology Discovery organization since 2007, where he primarily focuses on apoptosis.

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ABSTRACTS-Plenary Presentations

Inventing INCB24360 (epacadostat), an indoleamine-2,3-dioxygenase-1 (IDO1) inhibitor for immuno-oncology

Andrew P. Combs, PhD
Incyte Corporation, Wilmington, DE 19803

Immunotherapy agents, such as anti-CTLA-4, anti-PD1 and anti-PDL1, have provided unprecedented efficacy in a broad range of tumor types and paved the way for a new paradigm in cancer treatment through inhibition of innate mechanisms subverted by tumors to suppress the immune response. Indoleamine-2,3-dioxygenase-1 (IDO1) emerged as an immunotherapy target due to its role in regulating local T-cell response. In this presentation, we will focus on our data centric medicinal chemistry decision making that culminated in the invention of epacadostat, a first-in-class, potent, selective and orally bioavailable small molecule IDO1 inhibitor. The novel molecular structure provides yet another example of a "rule -of-5 breaking" clinical candidate. Epacadostat in combination with anti-PD1 mAb (pembrolizumab) as a first-line treatment for advanced melanoma is scheduled to enter a pivotal phase 3 clinical trial in 2016.

Drug Discovery in Academia: Successful Case Studies

Michael E. Jung

Department of Chemistry and Biochemistry, University of California at Los Angeles

The process of drug discovery in academia will be discussed with examples of prior and ongoing collaborations, including at least one success story. The areas of research include antitumor agents, osteogenic materials for spinal fusion and osteoporosis, and anti-leukemic agents. In particular, the biology and chemistry leading to the approved drug, enzalutamide (Xtandi) will be described.

Novel Therapeutics for Treating Viral Diseases, Cancers and Inflammatory Disorders.

Dennis Liotta, PhD, DSc,
The Emory Institute for Drug Development and the Department of Chemistry, Emory University, Atlanta, GA 30322 USA

The chemokine receptors, CCR5 and CXCR4, are the primary co-receptors responsible for mediating HIV-1 cell entry. Small molecules that modulate these receptors utilize a fundamentally different approach for controlling viral replication than most other classes of antiretroviral agents in that they act on host factors, rather than viral enzymes. While CCR5 entry inhibitors that demonstrate clinical efficacy against HIV have now become available (Maraviroc), the development of CXCR4 entry inhibitors is currently at a more nascent stage. Due to the ability of HIV to switch between CCR5 and CXCR4 entry co-receptors, the availability of a CXCR4 entry inhibitor that could be used in combination with Maraviroc or other ARVs could prove to be important in prolonging the effectiveness of HIV therapies in patients. Unfortunately, the complexities associated with the multiple CXCR4 signaling pathways (which include, inter alia, expression of survival and proliferation genes, as well as induction of chemotaxis) create a major challenge for identifying efficacious compounds that also possess a safety profile suitable for dosing every day of a patient's life. Alternatively, exploitation of selective aspects of the CXCR4 signaling pathways can be used for other important medical applications, such as hematopoetic stem cell mobilization and chemosensitization.

My lab has discovered a series of CXCR4 modulators that, depending on their their binding profiles, can act as either an antagonist or an inverse agonist. In addition, we have discovered a series of dual tropic antagonists that simultaneously block HIV entry through both CXCR4 and CCR5. In this presentation I will discuss some of the issues and challenges associated with the development of these series.

Selective BCL-2 Family Inhibitors: Potential Therapeutics and Powerful Research Tools

Andrew J. Souers
AbbVie, Inc. North Chicago, Illinois, USA

AJS is an AbbVie employee. The design, study conduct and financial support were provided by AbbVie and Genentech. AbbVie and Genentech participated in the data generation, interpretation of data, review and approval of this publication.

Many cancer cells maintain survival through over-expression of anti-apoptotic BCL-2 family proteins, making them compelling targets for the development of cancer therapeutics. However, disrupting protein-protein interactions, such as the BCL-2 or BCL X_L interactions with pro-apoptotic BH3 proteins, has been a major challenge for the field. The BCL-2/BCL-X_L inhibitor ABT-263 (navitoclax) has shown promising activity in the clinic but its efficacy has been limited by thrombocytopenia caused by BCL-X_L inhibition. This clinical result led to the design of ABT -199/GDC-0199, a BCL-2-selective inhibitor that maintains efficacy in hematologic malignancies while sparing platelets. The challenging path to ABT-199/GDC-0199 will be presented, as will clinical data that represents validation of the hypothesis behind selectively targeting BCL-2. While ABT-199/GDC-0199 has helped establish the importance of targeting BCL-2 in hematologic malignancies, expression of BCL-X_L has been linked with drug resistance and disease progression in multiple solid tumors. Efforts towards the development of novel BCL-X_L-selective inhibitors will also be discussed.

Building and Driving CARs: A Novel Platform For Cancer Immunotherapy

Samuel C. Blackman, MD, PhD
Juno Therapeutics, Inc.

Stimulation of the immune system in order to mount an anti-tumor response has been an area of scientific investigation for over 100 years. The major challenge to the field has been overcoming the immunosuppressive response generated by the tumor and tumor microenvironment. Recent developments in cancer immunotherapy have shown that de-repression of T cells (via checkpoint inhibition) can lead to substantial tumor regression and improvements in progression-free and overall survival. Recently it has been shown that a focused anti-tumor T cell response can also be generated by by stable gene transfer of a chimeric antigen receptor (CAR) consisting of a single chain variable fragment (scFv) directed towards a tumor-specific antigen, a T cell costimulatory domain, and the CD3 zeta chain. CAR-modified T cells allow for substantial expansion and activation of tumor-directed T cells and represent an emerging and important platform for cancer therapy. This talk will provide an overview of cancer immunotherapy leading up to the development of first- and second-generation T cells. Phase 1 clinical trial data from CD19-directed CAR T cells in B cell malignancies will be reviewed, and determinants of CAR T cell efficacy and CAR T cell-specific toxicities will be discussed. Finally, feasibility of CAR T cell clinical scale manufacturing will be discussed, along with current areas of focus for this field such as solid tumor directed CAR T cells, next-generation CAR constructs, and combination immunotherapy.

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About KPC

KPC Pharmaceuticals,Inc.(KPC) identifies, manufactures, and markets herb-based therapeutic products and small molecule drugs in China and internationally. There are a series of drug products marketed in China and some counties in Asia and Africa. The Institute of Drug Discovery and Development is a company based research center, and the core component and engine for new drug development in KPC. KPC is dynamically expanding its pipelines towards the Bio-Medical area in aspect of diagnostic technologies and biological drug production. KPC is a listed company with trading code 600422 on the Shanghai Stock Exchange (China) since 2000. KPC is located in Kunming, ("Spring City"), in South Western of China.

Welcome to Kunming

KPC is seeking potential partners to co-develop and market their novel biomedical products in China; and cordially inviting the scientists from different area to join our research team and identify new therapeutic using our unique compound resources.

Contact

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TEDA AWARDS

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WINNING POSTERS

TEDA AWARD
First Place

Poster #7: Novel Strategy for The Treatment of Asthma by Targeting the α4 Subunit of GABAA Receptors in Airway Smooth Muscle

Rajwana Jahan[1, 2], *Michael Stephen*[1, 2], *Gene T. Yocum*[3], *George Gallos*[3], *Yi Zhang*[3], *Revathi Kodali* [1, 2] ,*Zdravko Varagic*[4], *Roshan Puthenkalam*[4], *Margot Ernst*[4], *Leggy A. Arnold*[1, 2], *Douglas Stafford*[2], *Charles Emala*[3], *James M. Cook*[1, 2]

[1] *Department of Chemistry, University of Wisconsin, Milwaukee, Wisconsin- 53211, United States;.*[2] *Milwaukee Institute for Drug Discovery, University of Wisconsin, Milwaukee, Wisconsin- 53211, United States;* [3] *Department of Anesthesiology, College of Physicians and Surgeons of Columbia University, New York, New York-10032, United States;* [4] *Department of Molecular Neuroscience, Center for Brain Research, Medical University of Vienna, Vienna, Austria.*

TEDA AWARD
Second Place

Poster #8: Metabolic Regulation of Gene Expression by Histone Lysine β-hydroxybutyrylation

Zhongyu Xie[1], ***Di Zhang***[1], *Dongjun Chung*[2,4], *He Huang*[1], *Lunzhi Dai*[1], *Shankang Qi*[1], *Xiaoyong Yang*[3], *and Yingming Zhao*[1]

[1]*Ben May Department for Cancer Research, The University of Chicago, Chicago, IL 60637, USA;* [2]*Department of Biostatistics, Yale School of Public Health, New Haven, CT 06520, USA;* [3]*Section of Comparative Medicine and Department of Cellular and Molecular Physiology, Yale University School of Medicine, New Haven, CT 06520, USA;* [4]*Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC 29425, USA*

TEDA AWARD
Second Place

Poster #19: Investigating the Role Of IDO1 During Immune Checkpoint Blockade in A Mouse Model of Glioblastoma

Lijie Zhai[1], *Kristen L. Lauing*[1], *Jun Qian*[1], *Galina Gritsina*[1], *Erik R. Ladomersky*[1], *Carlos Dostal*[2], *Robert H. McCusker*[2], *Craig M. Horbinski*[1], *David James*[1], *Derek A. Wainwright*[1]

[1]*Northwestern University, Feinberg School of Medicine, Department of Neurological Surgery, Chicago, IL 60611,* [2]*University of Illinois, Department of Animal Sciences, Urbana-Champaign, IL 61801*

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Northwestern University

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Hepalink

Established in 1998, Shenzhen Hepalink Pharmaceutical Co., Ltd (Hepalink) distributes its product, Heparin Sodium API in the global market to internationally renowned pharmaceutical companies, such as Sanofi-Aventis, Fresenius -Kabi, and Novartis. Hepalink went public and was listed on the Shenzhen Stock Exchange on May 6, 2010 (stock code "002399").

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Hepalink, as a leading high-tech enterprise, has received numerous awards, including the National Award for Technology Innovation and Outstanding New Products, the award for the Enterprise with Outstanding Contributions for the Past 30 Years in the Shenzhen Special Economic Zone, the Shenzhen Excellent Private Enterprise award, the Shenzhen Excellent and Strong SME award, and the Shenzhen Leading Private Enterprise award.

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ABSTRACTS-Poster Presentations

Poster #1: Co-Administration of Hydroxyurea and a Specific AKT2 Inhibitor Has Beneficial Effects on Acute Vaso-Occlusive Events

***Jing Li*[1], *Andrew Barazia*[1], *Kyungho Kim*[1], *and Jaehyung Cho*[1,2]**

[1]Department of Pharmacology, [2]Department of Anesthesiology, University of Illinois College of Medicine, Chicago, IL

Intravtial microscopy has provided compelling evidence that neutrophil-platelet interactions on the activated endothelial cells (ECs) mediate microvascular occlusion under inflammatory conditions. Sickle cell disease (SCD), an inherited blood disorder, mediate recurrent vaso-occlusive events through heterotypic cell-cell adhesion/aggregation, which causes pain crises and increased mortality due to organ damage, acute chest syndrome, and cerebrovascular injury. Decreased nitric oxide (NO) bioavailability and increased oxidative stress contribute to the pathophysiology of SCD. Hydroxyurea (HU), the only FDA-approved drug for treatment of SCD, stimulates HbF production, serves as an NO donor, and inhibits tissue factor expression in leukocytes. However, it is unclear whether the short-term treatment with HU has immediate benefits on acute vaso-occlusive events in SCD patients. We recently identified AKT2 as a critical regulator for heterotypic cell-cell interactions during vascular inflammation. Importantly, we found that the basal level of AKT phosphorylation is significantly increased in neutrophils and platelets isolated from SCD patients compared with those cells from healthy donors and that specific inhibition of AKT2 impairs heterotypic cell-cell aggregation in SCD patient's cells in vitro and in venules of SCD (Berkeley) mice in vivo.

In the present study, we investigated whether combination therapy of HU and Akti XII, an AKT2 specific inhibitor, has beneficial effects on acute vaso-occlusive events and survival in Berkeley mice. Using intravital microscopy, we demonstrated that co-administration of HU (100 μg/g body weight (BW), iv) and Akti XII (3 μg/g BW, iv) efficiently reduced neutrophil-EC and platelet-neutrophil interactions in cremaster venules of TNF-α-challenged Berkeley mice. Importantly, compared with HU or Akti XII treatment alone, treatment with both agents significantly improved survival rates in the mice. Further, similar results were obtained in Berkeley mice challenged with hypoxia and subsequent reoxygenation. As determined by histochemistry of cremaster muscle sections after intravital microscopy of Berkeley mice, the expression of endothelial E-selectin and intercellular adhesion molecule 1 (ICAM-1) was significantly decreased by treatment with either HU or Akti XII. Neutrophil transmigration in the lung section of Berkeley mice was also inhibited by either agent, and the inhibitory effect was potentiated by co-administration of HU and Akti XII. Using the plasma and isolated cells from Berkeley mice treated with the inhibitor, we found that the level of plasma NO species (NOx) was elevated by treatment with HU but not Akti XII and that the level of AKT2 phosphorylation in neutrophils and platelets was reduced by treatment with Akti XII but not HU.

Taken together, these results suggest that short-term treatment of Berkeley mice with either HU or Akti XII inhibits inflammatory conditions: treatment with HU significantly increases plasma NOx levels, treatment with Akti XII decreases AKT2 phosphorylation in neutrophils and platelets without affecting plasma NOx levels, and administration of either agent reduces the surface expression of ICAM-1 and E-selectin on activated ECs. Thus, our results provide evidence that combination therapy with HU and a specific AKT2 inhibitor has immediate benefits on acute vaso-occlusive events and survival in SCD mice exceeding those seen for single therapy.

Poster #2: A Novel Vitamin D Receptor Modulator, VS-105, Improves Bone Mineral Density in an Estrogen-deficient Rat Model of Osteoporosis

***J. Ruth Wu-Wong**, Yung-wu Chen, Jerry L. Wessale.*

Vidasym, Chicago, IL

Vitamin D is essential for bone health; vitamin D receptor modulators (VDRMs) such as calcitriol have been used as therapeutic agents for osteoporosis since 1983 in some countries outside of the US. VDRMs increase bone mineral density (BMD) and reduce the incidence of bone fracture in patients with osteoporosis. However, VDRMs are not widely used for treating osteoporosis, in part due to the hypercalcemic side effects of current VDRMs. It is not well studied whether VDRMs at non-hypercalcemic doses have effects on bone mineral density (BMD). VS-105, a novel VDRM with an exceptionally wide therapeutic index (TI) at >50-fold (vs. TI of calcitriol at 1-fold) offers a unique opportunity for answering the aforementioned question. The effect of VS-105 on BMD was evaluated in an ovariectomized (OVX) rat model of osteoporosis. Treatment of OVX rats by VS-105 at three doses (0.1, 0.2 or 0.5 μg/kg, i.p., 3x/week, for 12 weeks, n=8-12 per group) significantly improved BMD in the L3 lumbar vertebra in a dose-dependent manner (sham: 324 ± 14 mg/cm2; OVX/vehicle: 279 ± 10 mg/cm2; VS-105 at 0.1, 0.2 and 0.5 μg/kg: 306 ± 9, 329 ± 12, and 327 ± 10 mg/cm2, respectively) without affecting serum calcium (Ca). In comparison, calcitriol at 0.1 μg/kg significantly increased BMD, but it also increased serum Ca (13.8 ± 0.3 mg/dL vs. sham at 11.3 ± 0.5 mg/dL). VS-105 significantly suppressed serum PTH without affecting serum Ca at all doses tested, results attributable to its lack of effects on inducing the expression of intestinal Ca transporter genes such as Calb3 and TRPV6, and on stimulating intestinal Ca transport. VS-105 increased serum osteocalcin (a marker for osteoblast activity) in a dose-dependent manner, and reduced the expression of receptor activator of nuclear factor kappa-B ligand (RANKL) in tibia. In a mouse calvaria bone primary organ culture system, VS-105 was ~2-fold less effective than calcitriol in stimulating net Ca release from calvaria (a measurement of osteoclast activity). These results demonstrate that VS-105 is effective in improving BMD in a dose range that does not affect serum Ca in OVX rats. The overall preclinical profile of VS-105 supports future clinical development for its use in treating osteoporosis.

Poster #3: Novel Non-Absorbed, Calcium-Free, Highly Effective Phosphate Binders Derived From Gum Arabic

***J. Ruth Wu-Wong**, Yung-wu Chen, Jerry L. Wessale*

Vidasym, Chicago, IL

Inadequate control of serum phosphate in chronic kidney disease can lead to pathologies of clinical importance. Effectiveness of on-market phosphate binders is limited by safety concerns and low compliance (high pill size/burden and gastrointestinal (GI) discomfort). We have developed a series of novel, highly effective phosphate binders from metal ions and gum Arabic (GA), ingredients commonly used in food. In vitro studies show that VS-505 (Fe-GA), VS-605 (Mg-GA) and VS-705 (Zn-GA) have high density (e.g. 1.95 g/cm3 for VS-505 vs. 1.27 g/cm3 for sevelamer) and a low swell volume when exposed to simulated gastric fluid (e.g. 0.4 cm3/0.1g for V-505 vs. 4 cm3/0.1g for sevelamer) or a phosphate buffer. VS-505, VS-605 and VS-705 bind phosphate within a wide physiologically relevant pH range, enabling them to bind phosphate along much of the GI tract. In normal SD rats on high-phosphate diet, increasing dietary phosphate led to an increase in serum phosphate, which was prevented in

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ABSTRACTS-Poster Presentations

rats treated with VS-505, VS-605, or VS-705 (0.2 - 5% in food). Urinary phosphate increased by >10-fold in the vehicle-treated group; VS-505, VS-605 or VS-705 reduced urinary phosphate, and also increased fecal phosphate in a dose-dependent manner. No significant changes were observed for serum calcium, while urinary calcium increased from 1.4 +/- 0.2 mg/24 hr before dosing to 9.2 +/- 1.0 mg/24 hr in the 5% sevelamer group, and to 3.6 +/- 0.5, 3.0 +/- 0.7, and 5.2 +/- 1.6 mg/24 hr in the 5% VS-505, VS-605, and VS-705 groups, respectively. In uremic SD rats induced by 5/6 nephrectomy fed a high phosphate diet (5/6 NX rats), urinary and serum phosphate levels were significantly elevated in untreated rats, which were decreased by VS-505 and sevelamer. VS-505 increased fecal phosphate levels in a dose-dependent manner. More aortic calcification was observed in 5/6 NX rats treated with 5% sevelamer, but not for VS-505. These results demonstrate that these metal ion-GA phosphate binders effectively controls phosphate imbalance in the rats by carrying phosphate from GI tract to feces. VS-505 is currently being evaluated in a clinical study in Australia involving hemodialysis patients (ClinicalTrials.gov Identifier #: NCT02469467).

Poster #4: Cardiac Glycoside A06920D2F13K1 Blocks Cell Growth And Induces Apoptosis In Human Ovarian Cancer Cells

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Epithelial ovarian cancer is the most lethal gynecological malignancy and fifth leading cause of cancer death among US women. Nearly 75% of patients are diagnosed with advanced stage disease at which point the five year survival drops to under 30%. Thus, there is an urgent need to find new molecular targets to treat first line and relapsed ovarian cancer. For decades, secondary metabolites from plants, fungi and bacteria have been found to contain powerful anticancer activity. A06920D2F13K1 was isolated from the stem bark of Streblus asper in Southeast Asia, and its chemical structure shares a common cardiac glycoside structural motif. The new structure compound A06920D2F13K1 was identified as exhibiting nM potency against human melanoma, breast cancer and ovarian cancer cell lines by screening for cytotoxic compounds. Next, A06920D2F13K1 was studied in a hollow fiber assay to determine if it had any potency in vivo. A06920D2F13K1 was able to dose-dependently inhibit the growth of ovarian cancer cell model OVCAR3 and also triple negative breast cancer cell model MDA-MB-231. From these data, ovarian cancer models were chosen due to its high response to A06920D2F13K1. To further verify that this compound was active against high-grade serous ovarian cancer, several cell models were treated. A06920D2F13K1 was more potent in OVCAR3 than the other cell lines. Next experiments were designed to define the mechanism of action that A06920D2F13K1 uses to inhibit cell growth in high-grade serous ovarian cancer. A06920D2F13K1 blocked cell progression through the cell cycle at the G2-phase in OVCAR3 cells after 72 h treatment at 500 nM. A06920D2F13K1 treatment also induces PARP cleavage indicating apoptosis activation in OVCAR3 after 48 and 72 h at 500 nM. The mechanism of A06920D2F13K1 blocking cell proliferation and inducing apoptosis deserves further investigation. Future direction will focus on genome profiling and validating potential targets.

Poster #5: Paper Test Card For Quantifying Beta-Lactam Antibiotics

Nicholas M. Myers*, Jamie Luther, Doa'a Aldulaimi, and Marya Lieberman*

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN 46556

Finding low-quality pharmaceuticals in the developing world is challenging because assaying finished products requires a sophisticated lab setting. At the University of Notre Dame, we performed HPLC analysis on pills containing amoxicillin, clavulanic acid, and ampicillin that were collected in Kenya. About 20% (n = 90) of the pills did not meet the regulatory specification of containing 90-120% of the labeled active pharmaceutical ingredient (API). The pills contained anywhere from 0-150% of the labeled API, with most failures being below specification. Having a portable and inexpensive paper-based test card that can analyze beta-lactam antibiotics over this range could help monitoring agencies perform market surveys or even empower manufacturers to do more quality control testing in the developing world.

The United States Pharmacopeia method <425> describes the use of an iodometric back-titration to quantify beta-lactam antibiotics. The back-titration was translated to a paper test card format. The titration reagents, which are mutually incompatible, could be stored separately and recombined through surface-tension enabled mixing. Good visual distinction is achieved among amoxicillin or ampicillin solutions that differ by 0.05 mg/mL over the range of 0.80-1.15 mg/mL. For example, pills containing either 95% or 100% of the labeled amount of amoxicillin can be differentiated from one another. Each beta-lactam antibiotic responds differently to iodometry, so the test card must be calibrated accordingly. For analyzing amoxicillin pills, the accuracy of the test card was 2 ± 2% (n=23), and for ampicillin pills it was 4 ± 2% (n=20). The test card was engineered using the World Health Organization's ASSURED criteria, with an emphasis placed on cost and usability, to keep the technology widely accessible.

Poster #6: Branching Out: γ-Methylated Hydrocarbon Stapled Peptides for the Estrogen Receptor/Coactivator Interaction

Thomas E. Speltz,[a] *Sean W. Fanning,*[b] *Christopher G. Mayne,*[c] *Colin Fowler,*[b] *Emad Tajkhorshid,*[c] *Geoffrey L. Greene,*[b] *Terry W. Moore*[a]

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"Stapled" peptides are typically designed to replace two non-interacting residues with a constraining, olefinic staple. To mimic interacting leucine and isoleucine residues, we have created new amino acids that incorporate a methyl in the γ-position of the stapling amino acid S5. We have incorporated them into a sequence derived from steroid receptor coactivator 2, which interacts with estrogen receptor α. The best peptide (IC50 = 89 nM) replaces isoleucine 689 with an S-γ-methyl stapled amino acid, and has significantly higher affinity than unsubstituted peptides (390

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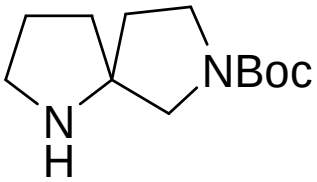

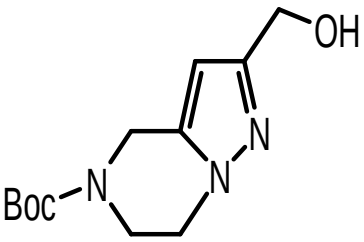

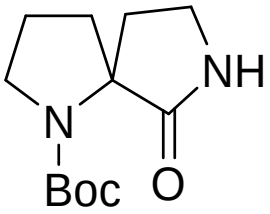

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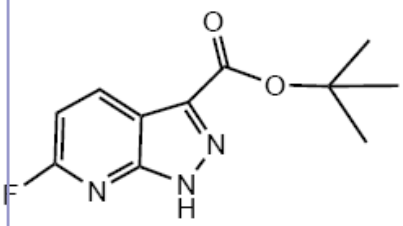

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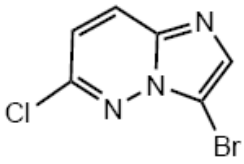

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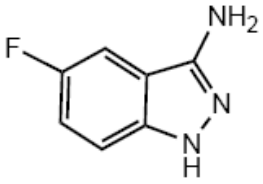

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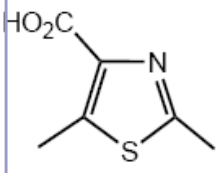

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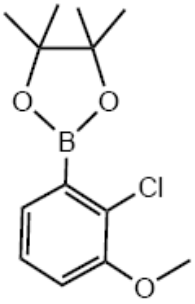

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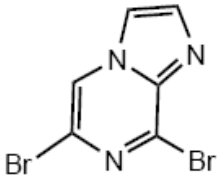

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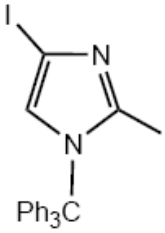

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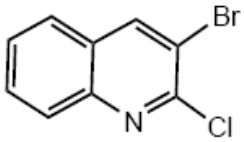

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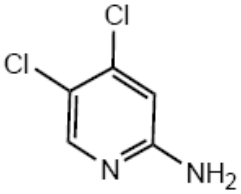

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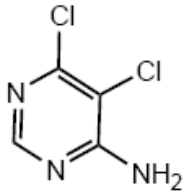

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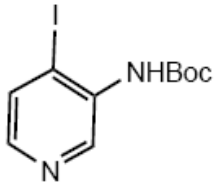

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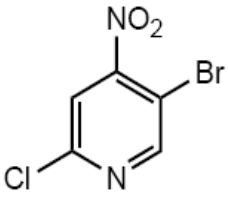

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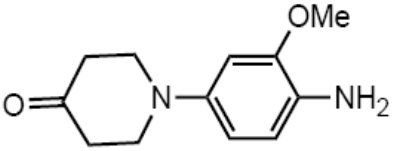

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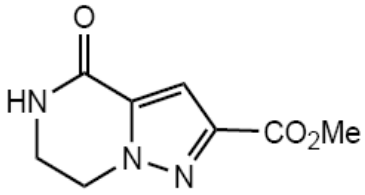

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ABSTRACTS-Poster Presentations

and 760 nM). Through x-ray crystallography and molecular dynamics studies, we show that the conformation taken up by the S-γ-methyl peptide minimizes syn-pentane interactions between α- and γ-methyl groups.

Poster #7: Novel Strategy for The Treatment of Asthma by Targeting the α4 Subunit of GABAA Receptors in Airway Smooth Muscle

Rajwana Jahan[1, 2], *Michael Stephen*[1, 2], *Gene T. Yocum*[3], *George Gallos*[3], *Yi Zhang*[3], *Revathi Kodali* [1, 2] ,*Zdravko Varagic*[4], *Roshan Puthenkalam*[4], *Margot Ernst*[4], *Leggy A. Arnold*[1, 2], *Douglas Stafford*[2], *Charles Emala*[3], *James M. Cook*[1, 2]

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Asthma is a major health concern and millions of individuals XHe-III -74 CMD-45 are affected. Current asthma treatments, both chronic maintenance and acute rescue therapy, use β2-agonists and corticosteroids, both of which suffer from inadequate efficacy and safety issues. As a result, there is an unmet demand for more effective and safer treatments for asthma. Our previous studies demonstrated that airway smooth muscle (ASM) cells express GABAA receptors (GABAARs) of the α4 and α5 subunits and agonists of GABAAR can relax ASM acutely. Targeting the limited and overlapping α subunits with subtype selective GABAAR agonists would cause both ASM relaxation and suppression of inflammation without having any off-target CNS activity. Bz/GABAAergic agents have been proven to be safe and have a long clinical safety record. As a result targeting Bz/GABAAR in the lung would be a novel and effective strategy in asthma management. Novel GABAAR positive allosteric modulators designed for α4/α6 subunit selectivity were synthesized using iterative computational analyses. Two compounds from our library, namely CMD-45 and XHe-III-74 have shown α4 subtype selectivity and serve as leads for designing novel drugs for treating asthma. Recent results in this area will be presented.

Poster #8: Metabolic Regulation of Gene Expression by Histone Lysine β-hydroxybutyrylation

Zhongyu Xie[1], ***Di Zhang***[1], *Dongjun Chung*[2,4], *He Huang*[1], *Lunzhi Dai*[1], *Shankang Qi*[1], *Xiaoyong Yang*[3], *and Yingming Zhao*[1]

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Besides serving as an energy source, β-hydroxybutyrate has been used to treat epilepsy and plays a neuro-protective role in models of neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease, Moreover, it has been reported that β-hydroxybutyrate contributes to cancer cell 'stemness'. Ketogenic diets are under evaluation as adjunctive treatments for patients with brain tumors and other malignancies. These lines of evidence suggest a regulatory role for ketone bodies beyond serving as an energy source. However, the mechanisms underlying these physiological and pharmacological effects of ketone bodies remain largely unknown.

Here we report the identification and verification of a β-hydroxybutyrate-derived protein modification, lysine β-hydroxybutyrylation (Kbhb), as a new type of histone mark. Histone Kbhb marks are dramatically induced in response to elevated β-hydroxybutyrate levels in cultured cells, and in livers from mice subjected to prolonged fasting or streptozotocin-induced diabetic ketoacidosis. In total, we identified 44 histone Kbhb sites, a figure comparable to the known number of histone acetylation sites. By ChIP-seq and RNA-seq analysis, we demonstrate that histone Kbhb is a mark enriched in active gene promoters, and that the increased H3K9bhb levels that occur during starvation are associated with genes up-regulated in starvation-responsive metabolic pathways. Histone β-hydroxybutyrylation thus represents a new epigenetic regulatory mark that couples metabolism to gene expression, offering a new avenue to study chromatin regulation and the diverse functions of β-hydroxybutyrate in the context of important human pathophysiological states, including diabetes, epilepsy, and neoplasia.

Poster #9: Novel Selective Estrogen Receptor Downregulators Developed Using Endocrine-Independent Breast Cancer Cells Lines

Rui Xiong,[1] *Jiong Zhao,*[1] *Lauren Gutgesell,*[1] *Hitisha Patel,*[1] *Yueting Wang,*[1] *Longjiang Li,*[1] *Debra Tonetti,*[2] *Gregory R. J. Thatcher*[1]

[1]*Department of Medicinal Chemistry & Pharmacognosy, University of Illinois, Chicago,* [2]*Department of Biopharmaceutical Sciences, University of Illinois at Chicago*

Approximately 70% of breast cancer patients are estrogen receptor positive (ER+). Aromatase inhibitors and the selective estrogen receptor modulator (SERM), tamoxifen, are the first line treatments for these patients; however, almost 50% of patients either do not respond or acquire resistance. Multiple mechanisms, including mutations of the ESR1 gene, contribute to resistance via ligand-independent constitutive activation of ER. Selective estrogen down-regulators (SERDs) that block ligand-dependent and independent ER signaling by ablation of ER, offer a therapeutic approach to treatment-resistant, advanced stage and early stage ER+ breast cancer. Therapeutic use of the first generation SERD, fulvestrant (Faslodex), has largely remained 2nd and 3rd line, because of poor physiochemical/pharmacokinetic properties. Novel benzothiophene based SERDs were designed, synthesized, and optimized and assayed in three tamoxifen-resistant (TR), endocrine-independent ER+ MCF-7 and T-47D cell lines. Cell viability, ERE-luciferase response, and ER degradation was measured and compared to parent endocrine-dependent MCF-7 and T -47D cell lines in 2D and/or 3D spheroid cell cultures and compared to SERDs, fulvestrant and GDC-0810. Pharmacokinetic analysis was used to select novel SERDs for xenograft studies.

Poster #10: Synthesis of Novel β-carbolines as a GABAA subtype Selective Agents for the Treatment of Alcohol Abuse. Regiospecific Solution to the Problem of 3,6-Disubstituted β- and Aza-β-carboline Specificity

V. V. N. Phani Babu Tiruveedhula,[1] *Kaitlin T. Warnock,*[2] *Harry L. June,*[2] *Xenia Simeone,*[3] *Margot Ernst,*[3] *Marjorie C. Gondre-Lewis,*[2] *and James M. Cook*[1,*]

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版块		序号	岗位	工作地点	人数	备注
生物	生物研发	1	生物发现总监（杂交瘤）	新泽西	2	
		2	生物发现总监（Phage Display）	新泽西	2	
		3	生物工艺总监（培养基开发）	成都/新泽西	2	
		4	生物工艺总监（细胞工艺开发及放大）	成都	2	
		5	生物工艺总监（纯化工艺开发与放大）	成都	2	
		6	生物质量总监（活性测定）	成都	2	
	生物生产车间	7	生物生产总监	成都	1	要具备工程经验
		8	生物工艺总监（大规模培养）	成都	1	技术经验
		9	生物工艺总监（大规模纯化）	成都	1	技术经验
		10	生物工艺总监（制剂 GMP 生产）	成都	1	技术经验
		11	生物质量总监	成都	1	GMP 体系建设的经验
创新小分子		12	计算化学总监	成都	1	
		13	药效研究总监	成都	2	
		14	药代研究总监	成都	2	
		15	毒理研究总监	成都	1	
		16	创新制剂总监	成都	2	
		17	创新工艺总监	成都	1	
		18	临床前开发总监	成都	1	
临床		19	临床研究总监	成都	2	
		20	医学总监	成都	1	
		21	数据管理总监	成都	1	
		22	临床大区经理	苏州/天津	2	苏州、天津各 1
仿制药	化学	23	原料出口研发总监	成都及新泽西	1	
		24	合成工艺总监	成都	1	
		25	晶型研究总监	成都	1	
	制剂	26	口服固体制剂总监	成都/天津/苏州	3	成都、苏州、天津各 1
		27	注射剂研究总监	成都/天津/苏州	3	成都、苏州、天津各 1
		28	新型给药系统总监	成都	3	脂质体、微球、纳米粒 1 人
		29	膜材研究总监	成都	1	
		30	油料 API 研究总监	成都或天津	1	
	质量	31	质量分析总监	成都/天津/苏州	3	成都、苏州、天津各 1
		32	质量分析总监（纳米粒、脂质体等）	成都	2	
	国际车间	33	生产总监（口服/注射剂）	成都	2	口服及注射剂各 1 人
		34	质量总监	成都	1	QA

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ABSTRACTS-Poster Presentations

Department of Psychiatry and Behavioral Science, Howard University College of Medicine, Washington, DC; [3]Department of Molecular Neuroscience, Center for Brain Research, Medical University of Vienna, Vienna, Austria

β-carbolines are found in a large number of natural products, many of which demonstrate important biological activity, especially in regard to the reduction of alcohol-self administration [binge drinking (BD)], due to the activity at the benzodiazepine site of the GABAA receptor. Surprisingly, BD kills six people a day, most of which are men, and approximately 88,000 people die from alcohol related issues annually making it the third leading preventable cause of death in the United States. In 2006, this alcohol misuse costs approximately $223.5 billion to the US government. BD (blood-alcohol level ≥ 0.08 g% in a 2 hour period) is one form of excessive drinking and because of it, alcohol addiction and dependence remain a significant public health concern. A novel two step protocol was developed to gain regiospecific access to 3-substituted β- and aza-β carbolines, 3-PBC (1), 3-ISOPBC (2), βCCt (3), 3-AZA-PBC (4) and 3-AZA-ISOPBC (5). These β-carbolines (1-3) are potential clinical agents to reduce alcohol self-administration, especially 3-ISOPBC·HCl (2·HCl) which appeared to be a potent anti-alcohol agent active against binge drinking in maternally deprived (MD) rats. The method consists of two consecutive palladium-catalyzed reactions: a Buchwald-Hartwig amination followed by an intramolecular Heck-type cyclization. This two-step protocol decreased the number of steps, eliminated the unwanted δ-regioisomer, improved the overall yields, 43 % to 84 % in the case of β-carbolines 1-2 and from 16 % to 66 % for Aza-β-carbolines 4-5 respectively and ultimately provided a regiospecific solution to the synthesis of 3,6-disubstituted β- and aza-β carbolines. These ligands are available now on multigram scale for in vivo research into treatments for alcoholism. The development, application of this synthetic route and in vivo studies will be presented.

Poster #11: Synthesis and Evaluation of Neo-Glycopolymers, Heparan Sulfate Mimetics, As Potential Inhibitors of Heparanase

***Ravi Sankar Loka**, Fei Yu and Hien Nguyen*

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Heparan sulfate (HS) glycosaminoglycans are ubiquitously found on cell surfaces and extracellular matrices (ECM); play a vital role in adhesion, inflammation, proliferation, metastasis and angiogenesis. Heparanase, an endo-δ-glucuronidase enzyme, is involved in degrading HS chains by hydrolyzing specific glucuronosyl-glucosaminyl linkages. Heparanase over expressed in various tumor types is found to promote cell invasion and angiogenesis associated with cancer metastasis by cleaving HS chains. Therefore, inhibitors of heparanase are attractive and promising therapeutic targets for cancer. So far, only one compound, PI-88, a sulfated mannose oligosaccharide mimetic of HS, has reached phase III clinical trials.

Heparin, a glycosaminoglycan similar to HS shows good inhibitory activity towards heparanase, however it's strong anticoagulation properties due to abundant iduronic acid moiety limits its use as antitumor agent. Anticoagulation is a common side effect encountered in most of the HS mimetics. We envisioned that a polymer of glucosamine-δ(1→4)-glucuronic acid, important epitope required for heparanase binding, without any iduronic acid moiety could serve as potential heparanase inhibitor and minimize anti-coagulation. We have successfully synthesized glucosamine-δ(1→4)-glucuronic acid utilizing nickel-catalyzed 1,2-cis-δδaminoglycosylation method developed by our group by directly coupling glucoronic acid acceptor to glucosamine donor yielding exclusively δδ product with excellent yields, Later This disaccharide has then been tethered to anorbornene scaffold utilizing click chemistry. Finally the disaccharide attached norbrnene scaffold was subjected to ring-opening metathesis polymerization with Grubbs III catalyst to generate glycopolymers of different lengths by varying catalytic loading. Neo-glycopolymers with 12, 20 and 50 repeating units were synthesized with excellent polydispersity index (~1). These polymers were tested for heparanase inhibition using a FRET assay. The longest polymer, n = 50, showed good inhibition of heparanase activity (IC50, 40 nM).

Poster #12: Novel Substituted Tetrahydropyran Polymers as Potential Drug Releasing Agents in the Oral Cavity

***R.P. Pesavento**, [ϕ]H.M. Nguyen,*

*University of Iowa, Iowa City, IA, *College of Dentistry and Dental Clinics, [ϕ]Department of Chemistry*

Current mucoadhesive films offer mostly palliative treatment and little therapeutic effect in the oral cavity. The newly proposed substituted tetrahydropyran polymers share structural similarities with naturally occurring polysaccharides, however, the current polymers are linked via carbon-carbon bonds which afford more chemical stability in the oral cavity. The increased chemical stability of the new polymers is proposed to provide enhanced therapeutic efficiency, as well as the capacity for localized drug delivery in the oral cavity.

Objectives: To synthesize novel polymers with varying functionality and promote mucoadhesion in the oral cavity. To test the adherence of the new polymers to epithelial tissue as well as their capacity to bond and release known therapeutic substances.

Methods: New polymers bearing the carbon-carbon linked tetrahydropyran backbone were synthesized by reacting substituted 3,4,-dihydropyran monomers with a catalyst under mild conditions. New compounds were purified by either precipitation or thin layer chromatography, and characterized by known spectroscopic methods (i.e., Nuclear Magnetic Resonance (NMR), Infrared Spectroscopy (IR), etc.) The new polymers varied in the polarity of the functional group (i.e., acetate, sulfonamide, alcohol, etc.) present in the 2-position of each repeating unit. Preliminary mucoadhesion studies with the newly synthesized polymers and epithelial cells are currently underway.

Results: Substituted tetrahydropyran polymers have been synthesized with varying levels of aqueous solubility and polarity. Preliminary results suggest the polymers have the capacity to release known therapeutic agents in the oral cavity with the addition of mild nucleophilic agents.

Conclusions: Changing the pendant functional group in each repeating unit dramatically affected the polarity and water solubility of each polymer. The carbon-carbon bound backbone present in the new polymers is stable under hydrolytic conditions and may be used as a scaffold to release known therapeutic agents in the oral cavity.

Poster #13: Absolute Binding Free Energies Between T4 Lysozyme And 112 Small Molecules: Calculations Based On Multiple Rigid Receptor Structures

***Bing Xie**, Trung-Hai Nguyen, David Minh**

Illinois Institute of Technology

Free energy calculations predict binding affinities of noncovalent binding partners, which can play an important role in drug design. However, the calculations are difficult due to insufficient sampling, solvation

effects, and limited time. Our group is developing a new free energy prediction program, AlGDock, which is based on implicit ligand theory. This approach combines advantages of molecular docking and alchemical free energy calculations, obtaining results more accurate than the former and more quickly than the latter. Here, we apply this new method to estimate the affinity between T4 lysozyme and 112 different small molecules. Calculated binding free energies are highly correlated to results from YANK, which uses a flexible receptor. Primarily due to a more advanced force field, the method is better than DOCK6 in distinguishing active and inactive molecules.

Poster #14: A Novel Device for Convenient Therapeutic Drug Monitoring of Tacrolimus

***JingJing Zhang**, Tian Lan,* Yi Lu,* Xinxin Feng and Steve Mayer*

University of Illinois at Urbana-Champaign, GlucoSentient, Inc.

Today there is an ideological shift in the development of next generation medical therapies occurring. It is the movement from "one size fits all" therapy regimes to optimal results achieved through "personalized medicine." One aspect of personalized medicine focuses on addressing the innate highly variable inter- and intra- patient response to the same therapy. In order to optimize a patient's therapy, clinicians employ a process called "therapeutic drug monitoring (TDM)" to measure an individual drug's bioavailability for a particular dosage over time.

Our goal is to design and develop a simple, user friendly POC device that quantifies tacrolimus concentrations using a novel assay being developed by GlucoSentient, Inc. (GSI). This technology is based on a patented method that converts the concentration of tacrolimus in body fluids into a proportional concentration of glucose. The glucose concentration is then quantified via commercially available electrochemical methods, and a tacrolimus concentration is made available to the user.

The device will be simple, reliable and affordable, and it will meet regulatory criteria such that it can be used by patients in their homes or at their bedsides. Notably, our device will only require a finger prick sample of blood instead of today's standard requirement, a tube full of the patient's venous blood drawn at a qualified clinic. By dramatically improving patient outcomes through better adherence and more accurate dosing, the device will play a key role in realizing significant cost savings for organ transplant patients and payers.

Poster #15: Targeting the proteolytic and nucleolytic pathways to enhance the activity of topoisomerase II-targeted anticancer agents

***Yilun Sun**, John Nitiss*

Department of Biopharmaceutical Sciences, College of Pharmacy, University of Illinois at Chicago, Rockford, IL

DNA topoisomerases play a critical role in many nuclear processes such as replication and transcription. Type II topoisomerases (Top2) function in the processes by cleaving both strands of the DNA helix. Top2 is also a molecular target for a number of FDA-approved anti-cancer agents such as doxorubicin and etoposide, which act by blocking a step in the enzyme reaction. This leads to accumulation of Top2-DNA covalent complexes (Top2 cc) that interfere with DNA metabolism and trigger cell death. The mechanisms causing tumor-specific killing by Top2-targeting drugs remain poorly understood, and have been hypothesized to result from DNA repair defects in tumor. Therefore, targeting the DNA repair pathways could be developed as a strategy to enhance the activity of Top2-targeting agents. It has been implicated that pathways processing Top2 cc include proteolytic and nucleolytic activities, both of which remove trapped Top2 from DNA. To gain insight into the pathways, we optimized the ICE (in-vivo complex of enzyme) bioassay to detect and quantitate Top2 cc in cultured cancer cells. Of note, we also developed a biochemical method for detection of post-translational modifications on DNA-linked topoisomerases such as ubiquitylation and SUMOylation. We found that inhibition of 26 proteasome by MG132 or FDA-approved anticancer proteasome inhibitor carfilzomib increased Top2 cc levels and conferred hypersensitivity to etoposide in yeast and human cells, suggesting an important role of the proteasome system in repair of Top2-medidated DNA damage. Treatment with MG132 in etoposide-exposed cells abolished γH2AX foci formation and Dss1/Brca2 interaction, a vital step to facilitate homologous recombination. Next, we found in yeast that deletion of genes encoding ubiquitin ligase Slx5/Slx8 complex and DNA strand break repair protein Mre11 led to elevation in Top2 cc levels, respectively. Importantly, deletion of Slx5/Slx8 reduced ubiquitylation of Top2 cc. In consistence with these findings, knockdown of Rnf4 (the human ortholog of Slx5/Slx8) or Mre11 in human cells resulted in increased Top2 cc levels. Rnf4 was also found to be required for Top2 cc ubiquitylation via interaction with the trapped enzyme. Taken together, our work sheds light on mechanisms of Top2 inhibitor action and resistance by elucidating a DNA damage signaling network that is governed by the proteasome system. Carfilzomib therefore could be combined as a repair inhibitor in concert with Top2-targeting drugs. Rnf4, Mre11 and other enzymes that we identified as repair factors of Top2-mediated DNA damage in this study are promising drug targets that could be utilized to specifically enhance the action of anti-cancer agents targeting Top2.

Poster #16: Synthesis of Indoline-7-Sulfonamide Inhibitors of the Bacterial Enzyme DapE

***Rachel Torrez**, Tahirah Heath, and *Daniel P. Becker*

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The alarming increase of antibiotic resistant bacterial strains emphasizes an urgent need for research to identify new classes of antibiotics. One promising enzymatic target is DapE (N-succinyl-L,L-diaminopimelic acid desuccinylase enzyme), which is found in all Gram-negative and most Gram-positive bacteria. DapE is part of the succinylase biosynthetic pathway, which is critical to the production of lysine and meso-diaminopimelate (mDap). Lysine and meso-diaminopimelate (mDap) are essential in protein synthesis and bacterial peptidoglycan cell wall remodeling. The deletion of the gene DapE is lethal to bacteria, which is very encouraging in support of the hypothesis that inhibitors of DapE will function as antibiotics. Another appealing aspect of targeting DapE is that this enzyme is not found naturally in the human body. Therefore inhibitors that target DapE could potentially provide selective toxicity against bacteria with no mechanism-based toxicity in humans. After the completion of a high-throughput screen of over 33,000 compounds, two indoline sulfonamides demonstrated promising inhibition of DapE. The objective of this project is to identify successful methods to synthesize medicinally relevant analogs of the two lead indoline compounds, and to test their antibiotic activity. This presentation will describe our current ortho-directed lithiation synthesis and the previously used cyclization synthetic step that has been used to synthesize indoline analogs and discuss the limitations and benefits of each synthetic route.

ABSTRACTS-Poster Presentations

Poster #17: Protection of Islet Function Through Bromodomain Inhibition in Type 1 Diabetes

Michael D. Olp *and Brian C. Smith*

Department of Biochemistry, Medical College of Wisconsin, Milwaukee, WI

Type 1 diabetes (T1D) is an autoimmune disease characterized by the destruction of insulin-secreting pancreatic β-cells. Low concordance rates of T1D incidence between monozygotic twins indicates a role for epigenetic mechanisms in disease progression. It was recently demonstrated that early inhibition of the bromodomain and extraterminal domain (BET) family of transcriptional regulators irreversibly prevents onset of insulitis and overt T1D in non-obese diabetic (NOD) mice. The BET family of proteins, consisting of BRD2, BRD3, BRD4, and BRDT bind to sites of lysine acetylation on chromatin or other nuclear proteins and influence gene transcription in a cell-type specific manner. Here, we demonstrate that BET bromodomain inhibition reduces inflammatory islet damage and prevents pro-inflammatory gene transcription in macrophages. In addition, BET inhibitors protect β-cells from cytokine-induced cell death, possibly through increasing expression of the NAD+-dependent deacetylase Sirt1.

As epigenetic therapies targeting BET proteins in T1D would likely be most useful in young patients to protect against predisposition to disease, it is imperative that potentially long-lived negative side effects are avoided. However, current small molecule pan-BET bromodomain inhibitors that target all four BET proteins with similar potency were recently associated with impaired learning and memory in mice. The BET family member BRD4 is uniquely implicated in promoting inflammatory gene transcription. As a result, BRD4-selective inhibitors are desired as potential epigenetic therapies for autoimmune and inflammatory disease that would lack off-target effects caused by inhibition of other three BET family members. Here, we covalently target a unique nonhomologous cysteine residue on the second bromodomain of BRD4 (BRD4-BD2). Using intact protein mass spectrometry (MS), we identified five cysteine-reactive fragments out of 200 initial compounds that selectively modified BRD4-BD2 over other BET bromodomains. Top-down MS analysis revealed all five fragments covalently modify one of the unique cysteine residues on BRD4 -BD2. In addition, thermal shift analysis was used as an orthogonal method for hit validation. Moving forward, we are developing methods to assess the selectivity of our cysteine reactive fragments in cells by modifying the cysteine-reactive fragments with bioorthogonal reporter groups. To improve potency, the covalent compounds will be elaborated through NMR-based fragment screening of adjacent binding sites and subsequent fragment linking. Ultimately, BRD4-selective chemical probes will be instrumental in improving current understanding of BET bromodomain biology in inflammation and autoimmunity, and potentially contribute to the future design of epigenetic therapies for type 1 diabetes.

Poster #18: Fragment-based Screening in an Academic Setting: A semi-automated approach for identification of lead fragments using 1H-15N sofast-HMQC experiments and principal component analysis

John Egner[1]*, Davin Jensen[1], Francis Peterson, Nolan Kennedy, Michael Olp, Brian Smith, Brian Volkman, and Blake Hill

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Fragment-based screening (FBS) on a clinically important protein target is a powerful tool in drug discovery. We have implemented a medium-throughput approach, accessible to academics, to rapidly identify chemical fragments through use of liquid and sample handling robotics and automated data analysis using NMRPipe system. Fragment libraries (~1000 fragments total, 352 fragments initially screened) are multiplexed in matrices containing 6 fragments each, which greatly reduces instrument time and costs. The fragment library is screened using protein-detected 1H-15N sofast-HMQC NMR experiments rather than ligand-detected experiments. Hit identification from HMQC data is performed using principal component analysis (PCA) to rapidly identify compounds that perturb HMQC spectra and rescreening of individual fragments contained within each matrix hit to discriminate false from true positives. Hit validation is based on concentration dependent titrations using 1H-15N sofast-HMQC experiments to determine apparent binding affinities (Kd) and verify binding pockets on the target protein. Due to the nature of 2D NMR experiments, we are already in a position to develop structure- activity relationships with validated hits that will aid computational and medicinal chemistry efforts in fragment elaboration. Herein, we validated our approach by screening against CXCL12, a chemokine that can suppress cancer metastasis with validated ligands. First, we evaluated whether to use 1H-15N sofast- HMQC or 1H-13C HSQC NMR experiments as our primary screening method. We determined that minimal information was gained by 1H-13C HSQC experiments whereas 1H-15N experiments yielded useful data. For CXCL12, NMR screening with PCA successfully identified 8 matrices with possible hits. After rescreening of all 48 possible fragments, we identified 7 lead fragments to begin fragment elaboration and preliminary SAR studies. Use of CXCL12 validated our approach since we identified chemical fragments that bound in a similar manner to previously identified ligands. This approach has been extended to several colleagues' targets including the mitochondrial fission protein Fis1. Screening of Fis1 revealed 14 fragment hits to use in titration experiments for hit validation. PCA consistently identified false positive binders (same 3 matrices) across all targets screened. Our FBS by NMR approach allows for rapid identification of lead compounds for drug discovery efforts and is being applied to several clinically relevant targets of our colleagues.

Poster #19: Investigating the Role Of IDO1 During Immune Checkpoint Blockade in A Mouse Model of Glioblastoma

Lijie Zhai[1], *Kristen L. Lauing[1], Jun Qian[1], Galina Gritsina[1], Erik R. Ladomersky[1], Carlos Dostal[2], Robert H. McCusker[2], Craig M. Horbinski[1], David James[1], Derek A. Wainwright[1]*

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Glioblastoma multiforme (GBM) is the most aggressive primary brain tumors with an average survival of 14.6 months post-diagnosis. Coincidently, we have discovered that the mRNA expression level for indoleamine 2,3-dioxygenase 1 (IDO1), a tryptophan (Trp) catabolic enzyme expressed in patient-derived glioma, correlates to overall patient survival. Our preclinical data also demonstrate that tumor cell-derived IDO1 is essential for local GBM immune suppression and genetical depletion of this molecule results in significant survival benefit, indicating IDO1 as a promising target for brain tumor immunotherapy. However, it remains unclear whether and how the IDO1-mediated Trp catabolic pathway functions in both the GBM-induced immunosuppression and the GBM-targeted immunotherapy. Here, using orthotopic GL261 mouse

GBM model in combination with CTLA-4/PD-L1 immune checkpoints therapy, we analyzed the level of both systemic (serum) and local (GBM) Trp and one of its major bioactive metabolites, kynurenine (Kyn) and revealed that depletion of GBM cell-derived IDO1 has no effect on tumor local Trp->Kyn catabolism. In contrast, global depletion of IDO1 via IDO1-/- mice showed significantly decreased Trp->Kyn catabolism in blood, GBM and cervical lymph nodes (cLNs) when compared to IDO wild-type (IDO1+/+) mice in the presence or absence of immunotherapy. Moreover, there is no significant difference of Trp and Kyn levels in blood and brain tissues between tumor-free and GBM-bearing mice regardless of IDO1 expression. The dual immune checkpoint blockade has no effect on Trp-Kyn level in IDO1+/+ mice when compared to untreated mice although it significantly increases the survival rate. In contrast, IDO1-/- mice treated with CLTA-4/PD-L1 blockade showed slightly decreased Kyn level in the cLN tissues compared to untreated group although no survival benefit was observed in IDO1-/- mice. Role of IDO1 in GBM-induced immunosuppression is further investigated using a tamoxifen-inducible transgenic mouse GBM model, which closely mimicking the primary GBM development in patients. Both systemic and glioma cell-specific depletion of IDO1 in this model shows no survival benefit when compared to IDO1 competent transgenic GBM mice. Preliminary analysis indicates no difference of Trp and Kyn levels in the sera between IDO1-competent and tumor IDO1 deficient transgenic GBM mice. However, orthotopic implantation of glioma cells isolated from these transgenic GBM mice partially recapitulates previous results from the GL261-based GBM model, that deprivation of tumor-derived IDO1 enlongates mice survival in contrast to mice receiving IDO1 competent glioma cells. Interestingly, in this alternative orthotopic GBM model, mice injected with IDO1-deficient glioma cells showed increased Kyn level in contrast to the mice receiving IDO1 competent glioma cells in GBM tissues but not in sera. Collectively, these data for the first time suggest that, in the settings of orthotopic GBM model, tumor-derived IDO1 plays its immunosuppressive role via Trp-Kyn catabolism-independent mechanisms, which differs from IDO1's essential role in maintaining systemic Trp catabolism. Tumor local Trp-Kyn catabolism seems irrelevant to GBM formation under the orthotopic GBM conditions. Chronic loss of tumor-derived IDO1 (transgenic GBM) might lead to activation of compensatory pathways, while acute loss of that (GL261 GBM) has insufficient time for this compensation to occur. Finally, dual immune checkpoints blockade has beneficial effect on orthotopic GBM mice survival rate and this effect depends on the global expression of IDO1.

Poster #20: Synthesis and Biological Activity For Novel Inhibitors of Aurora Kinase A and Epidermal Growth Factor Receptor Kinase

Robert Senones,[1] *Stephen Zych,*[1] *Bradley McAllister,*[1] *Trusha Mistry,*[1] *Alexander Hollein,*[2] *Ulrich Keller,*[2] *Sonali Kurup*[1]

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Simultaneous inhibition of multiple kinases has been suggested to provide synergistic effects on inhibition of tumor growth and tumor resistance. In a recent study, researchers have reported that resistance against approved kinase inhibitors targeting epidermal growth factor receptor kinase (EGFR) could be overcome if given in combination with aurora kinase inhibitors. Additionally, the mitotic kinase, aurora kinase A (AURKA) provides an alternative target that could also be explored to develop novel antimitotic agents that act by a different mechanismcompared to traditional antimitotic agents such as vincristine and paclitaxel. Compounds 3-20 incorporating a pyrrolo[2,3-d]pyrimidine scaffold have been synthesized and evaluated as dual inhibitors of EGFR and AURKA. Compounds 3-20 demonstrated nanomolar inhibition of EGFR and micromolar inhibition of AURKA. Compound 5 the most potent EGFR inhibitor of the series was evaluated in squamous cell head and neck cancer cells and caused cell cycle arrest in the G2/M phase.

Poster #21: Dissecting the Influence of Protein Flexibility on the Location and Thermodynamic Profile of Explicit Water Molecules in Protein-Ligand Binding

Ying Yang*, Markus A. Lill*

Department of Medicinal Chemistry and Molecular Pharmacology, College of Pharmacy, Purdue University

Drug companies spend on average $2.6 billion and 10~15 years to bring a single drug to market which is the main reason for the high cost of new drugs today. The objective of drug design is to find a chemical compound that can fit into a specific cavity of a protein target both geometrically and chemically. The conventional drug design methods are usually time-consuming and laborious. With the increasing computer power, computer-aided drug design (CADD) has emerged as an important set of tools to speed up the drug discovery process. The most fundamental goal in CADD is to accurately and efficiently predict whether a given ligand will bind to the target protein, and if so, how strongly it will bind. Water, as the most important molecule in all living systems, plays an essential role being the solvent of most biological molecules. However, water molecules complicate the calculation of binding affinities since they may either be displaced by a binding ligand or may mediate protein-ligand interactions via hydrogen bonds. Thus, how to efficiently and accurately account for the solvation effects caused by the water molecules still remains one of the most significant challenges in CADD. First, the localized positions of water molecules, i.e. hydration sites, need to be identified and their thermodynamic profiles, i.e. enthalpy and entropy of desolvation, need to be computed. These hydration sites and their properties can be predicted using our previously developed program WATsite. In this study, I investigate the influence of protein flexibility on water locations and thermodynamic profiles. This is the first study aiming to predict the influence of protein conformational change on hydration site position and thermodynamic profile. This study will also allow for a more accurate prediction of protein desolvation, which is an important component of the binding free energy of a ligand.

Poster #22: Metabolic Studies of Drug Candidates for Neurological Disorders and Asthma Based on GABAA Receptor Subtype Selective Ligands using Mass Spectrometry

Revathi Kodali,[a] *Margaret L. Guthrie,*[a] *Michael M. Poe,*[a] *Michael R. Stephen,*[a] *Rajwana Jahan,*[a] *Charles W. Emala,*[b] *James M. Cook,*[a] *Douglas Stafford,*[a] *and Leggy A. Arnolda,**

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Development of pre-clinical experimental models to understand the in vivo metabolic performance of a drug is important in the field of drug discovery. GABA-ergic drugs are historically used for the treatment of neurological disorders such as neuropathic pain, schizophrenia and anxiety but recently have shown potential to treat asthma. In the present study, an in vitro microsomal assay was designed to evaluate the metabolic stability of GABAA receptor subtype selective ligands using microsomes and S9 fractions of human and mouse liver extracts. A LC-MS/MS method was developed to quantify the amount of drug degrading over a period of time using verapamil as internal standard. Herein, we will report the development, analysis and standardization of a liver microsome stability assay using the Shimadzu LCMS-8040 triple quadrupole instrument at the MIDD.

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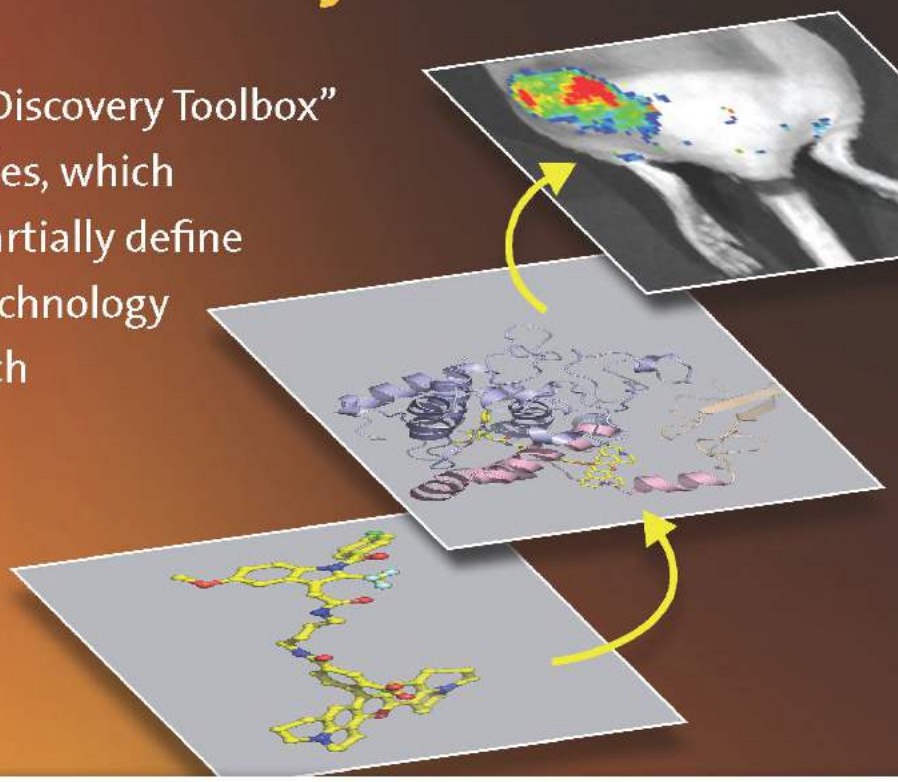

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