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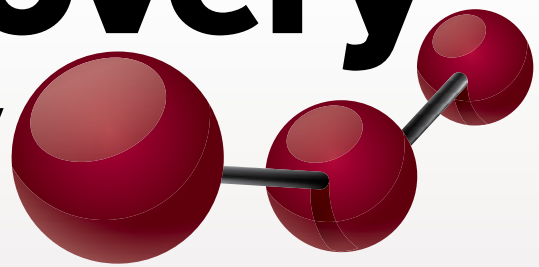
Drug Discovery Chemistry



APRIL 19 - 22, 2016 HILTON SAN DIEGO RESORT & SPA | SAN DIEGO, CA

OPTIMIZING SMALL MOLECULES FOR TOMORROW'S THERAPEUTICS

PLENARY KEYNOTES

A Chemist's Foray into Translational Research
Peter G. Schultz, Ph.D.,
The Scripps Research Institute

Cell-Penetrating Miniproteins
Gregory L. Verdine, Ph.D.,
Harvard University

EVENT FEATURES

- More than 125 presentations
- 600+ high-level participants
- 70+ posters
- Interactive roundtable, breakout & panel discussions
- "Track-hop" between concurrent meetings
- Exclusive exhibit & poster viewing hours
- Dedicated networking opportunities
- 10 interactive short courses

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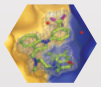
April 19 - 20

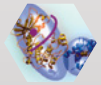
Inflammation Inhibitors



Protein-Protein Interactions

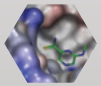
Epigenetic Inhibitor Discovery

April 20 - 21



Kinase Inhibitor Chemistry

Macrocyclics & Constrained Peptides



Fragment-Based Drug Discovery

SYMPOSIA Friday, April 22

Brain Penetrant Inhibitors

Biophysical Approaches for Drug Discovery

Antivirals: Small Molecule Inhibitors of Viral Targets

Cambridge Healthtech Training SEMINARS

Applying Pharmacology to New Drug Discovery

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CONFERENCE-AT-A-GLANCE

MONDAY, APRIL 18	PRE-CONFERENCE SHORT COURSES*		
TUESDAY, APRIL 19	INFLAMMATION INHIBITORS	PROTEIN-PROTEIN INTERACTIONS	EPIGENETIC INHIBITOR DISCOVERY
	Combined Plenary Keynote Session		
	Welcome Reception in the Exhibit Hall with Poster Viewing		
WEDNESDAY, APRIL 20	Continental Breakfast & Breakout Discussions		
	INFLAMMATION INHIBITORS	PROTEIN-PROTEIN INTERACTIONS	EPIGENETIC INHIBITOR DISCOVERY
	KINASE INHIBITOR CHEMISTRY	MACROCYCLICS AND CONSTRAINED PEPTIDES	FRAGMENT-BASED DRUG DISCOVERY
	Breakout Discussions		
	Dinner Short Courses*		
THURSDAY, APRIL 21	Combined Plenary Keynote Session		
	KINASE INHIBITOR CHEMISTRY	MACROCYCLICS AND CONSTRAINED PEPTIDES	FRAGMENT-BASED DRUG DISCOVERY
FRIDAY, APRIL 22	Symposium 1: Brain Penetrant Inhibitors		
	Symposium 2: Biophysical Approaches for Drug Discovery		
	Symposium 3: Antivirals: Small Molecule Inhibitors of Viral Targets		
	Training Seminar: Applying Pharmacology to New Drug Discovery		

Separate registration is required

TRACK-HOPPING Attendees at **Drug Discovery Chemistry** are encouraged to "track-hop" between concurrent conference tracks.

Though you register for a particular conference(s) or symposium, in reality you gain access to all concurrent meeting or symposia tracks. For the best value, register for a conference in each half of the event and a symposium, and gain access to all nine conference/symposia tracks to customize four days of presentation programming that best fits your research needs. Add some pre-conference short courses and spend the week in San Diego!

PLENARY KEYNOTES

Tuesday, April 19 - 4:30 pm

A Chemist's Foray into Translational Research

Peter G. Schultz, Ph.D., Professor, Department of Chemistry, The Scripps Research Institute and Director, California Institute for Biomedical Research

Our research program combines the tools and principles of chemistry with the molecules and processes of living cells to synthesize new molecules and molecular assemblies with novel physical, chemical and biological functions. By studying the structure and function of the resulting molecules, new insights can be gained into the mechanisms of complex biological and chemical systems.

Thursday, April 21 - 8:30 am

Cell-Penetrating Miniproteins

Gregory L. Verdine, Ph.D., Professor, Departments of Stem Cell and Regenerative Biology, Chemistry and Chemical Biology, and Molecular and Cellular Biology, Harvard University

It has been estimated that as few as 10-15% of all potential targets are targetable *in vivo* by either biological or small molecules. To address this deficiency, we and FOG Pharmaceuticals are developing cell-penetrating mini-proteins, molecules that combine the ability of proteins to target large flat surfaces, with the ability of small molecules to penetrate cells. Progress on the development of cell-penetrating mini-proteins will be reviewed in this talk.

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WELCOME TO DRUG DISCOVERY CHEMISTRY

Cambridge Healthtech Institute's **Drug Discovery Chemistry,** now in its 11th year, has established itself as a leading conference for medicinal chemists working in pharma and biotech. The event focuses on discovery and optimization challenges of small molecule drug candidates, and offers many exciting opportunities for scientists to move between concurrent conference tracks to create a unique program according to personal interests.

New this year are Symposia on the last day of the event. The three symposia are: Brain Penetrant Inhibitors, Biophysical Approaches for Drug Discovery, and Antivirals. The symposia represent areas of drug discovery with recent upticks in their pace of progress which nicely complement the event's established conference tracks.

The 2016 conference tracks remain, due to last year's record attendance and overwhelming positive delegate feedback: Inflammation Inhibitors, Protein-Protein Interactions, and Epigenetic Inhibitor Discovery as the first set of concurrent meetings. The second set of conference tracks include: Kinase Inhibitor Chemistry, Macrocyclics & Constrained Peptides, and Fragment-Based Drug Discovery.

Event highlights include roundtable breakout discussion groups as part of each meeting track and two Plenary Keynote sessions where participants across the concurrent meetings come together to hear a renowned scientist discuss pioneering work of interest to all discovery chemists and biologists. More information on our Plenary Keynotes can be found on page 2. In addition, we have dedicated and robust poster sessions in an exhibit hall that features cutting-edge chemistry, technologies, and services.

We also offer more than ten pre-conference and dinner short courses which are designed to be instructional and interactive. The short courses aim to introduce researchers to a particular discipline and to serve as a refresher for those familiar with the topic, but who want to brush-up on the most current advances. They also serve as an opportunity for the attendees to meet and ask questions of instructors and peers in a small group setting.

We invite you to review this brochure to see how our great roster of speakers and synergistic topics blend to create the leading event in drug discovery chemistry where scientists from all levels and settings can enjoy networking and spontaneous face-to-face interactions with one another. We look forward to meeting you in San Diego!

Anjani Shah, Ph.D.
Conference Director and
Lead Director for Drug Discovery Chemistry
ashah@healthtech.com

Kip Harry
Conference Director
kharry@healthtech.com

Carolyn Benton
Business Development Manager
cbenton@healthtech.com

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SHORT COURSES

Separate registration is required

MONDAY APRIL 18, 2016

MORNING COURSES | 10:00 AM – 1:00 PM

SC1: Trends in Physical Properties of Drugs

Instructors: Terry Stouch, Ph.D., President, R&D, Science for Solutions, LLC

Robert Fraczkiewicz, Ph.D., Team Leader, Simulations Plus, Inc.

John Comer, Ph.D., CSO, Sirius Analytical Ltd.

- Properties important for enhanced efficacy, delivery, and formulation
- pKa, tautomerism, crystallization, others
- Computational prediction: What works - what doesn't
- Experimental best practices

SC2: GPCR Structure-Based Drug Discovery

Instructors: Matthew Eddy, Ph.D., Postdoctoral Fellow, Ray Stevens Laboratory, The Bridge Institute, University of Southern California

Huixian Wu, Ph.D., Senior Scientist, Groton Center of Chemistry, Pfizer Inc.

- Review of recent GPCR structures and their lessons
- Approaches for crystallization of GPCRs
- GPCR conformational dynamics
- Application of nuclear magnetic resonance (NMR) to study GPCR structure and dynamics

SC3: Designing Peptide Therapeutics for Specific PPIs

Instructors: Nir Qvit, Ph.D., Postdoctoral Associate, Chemical & Systems Biology Operations, Stanford University School of Medicine

Opher Kornfeld, Graduate Student, Chemical&Systems Biology Operations, Stanford University

- Designing novel modulators of protein interactions based on sequence homology, domain conversation and protein structure
- Synthesis of novel inhibitors to target specific protein-protein interactions
- Development of peptidomimetics that derive from an active site to improve stability, activity and bioavailability

AFTERNOON COURSES | 2:30 – 5:30 PM

SC4: Immunology Basics for Chemists

Instructors: Seng-Lai "Thomas" Tan, Ph.D., Senior Director, Immunology, FORMA Therapeutics

Songqing Na, Ph.D., Senior Scientist, Biotechnology & Autoimmunity Res-AME, Eli Lilly and Company

- Review of immune system's cellular players
- Review of inflammatory process
- Autoimmune & inflammation-related diseases
- Current treatment landscape and promising drug targets

SC5: Phenotypic Screening and Chemical Probe Development

Instructor: Samarjit Patnaik, Ph.D., Research Scientist, Probe Development Center, NCATS, NIH

- Overview of modern phenotypic drug discovery using examples from literature and NCATS
- Screening assay designs and phenotypic systems
- Strategies to elucidate MOA and options for de-convoluting molecular targets
- Development of chemical probes at NCATS

DINNER COURSES | 6:00 - 9:00 PM

SC7: Molecular Interactions and Drug Design

Instructor: Maricel Torrent, Ph.D., Senior Scientist, AbbVie

- Drug design principles generally applicable to all medicinal chemistry programs
- Interpretation of atomic-level protein X-ray and modeled structures of binding modes
- Understanding the relative amounts of potency gain from different interactions
- Case studies illustrate all of the design strategies

SC8: Inhibitor Design using MOE SBDD Applications

Daniel Chang, Ph.D. Applications Scientist Chemical Computing Group

Alain Ajamian, Ph.D. Director Chemical Computing Group

- Analyzing protein active sites with molecular surfaces and maps
- Generating pharmacophore models to capture essential ligand binding features
- Application of docking to determine ligand poses in the active site
- Fragment-based design applications for scaffold replacement
- A virtual reaction-based combinatorial approach for R-group screening

WEDNESDAY APRIL 20, 2016

DINNER COURSES | 6:30 – 9:00 PM

SC10: Enabling Macrocyclic Compounds for Drug Discovery: Opportunities, Challenges and Strategies

Instructors: Mark L. Peterson, Ph.D., COO, Cyclenium Pharma, Inc.

Eric Marsault, Ph.D., Professor, Medicinal Chemistry and Pharmacology, University of Sherbrooke

- Unique characteristics of macrocycles
- Factors affecting cell permeability and PK/ADME properties
- Synthetic strategies for macrocyclic compound libraries & macrocyclization challenges
- Drug discovery and development examples and future perspectives

SC11: Advancing Tools and Technologies for Fragment-Based Design

Instructors: Daniel A. Erlanson, Ph.D., Co-Founder, Carmot Therapeutics, Inc.

Ben Davis, Ph.D., Research Fellow, Biology, Vernalis Research

- Why fragments – pros and cons
- What makes a good fragment, and a good fragment library
- Finding, validating and characterizing low affinity ligands
- The importance of using orthogonal screening methods
- What to do with a fragment – growing, linking, and more

SC12: Introduction to Targeted Covalent Inhibitors

Instructors: Mark Schnute, Ph.D., Associate Research Fellow, Biotherapeutics Chemistry & Immunoscience Research, Pfizer Global R&D

Christoph Zapf, Ph.D., Senior Principal Scientist, Worldwide Medicinal Chemistry, Pfizer Research Labs

- Overview of covalent drugs, irreversible and reversible inhibitors including recent clinical examples
- Biochemical analysis of covalent inhibitors
- Design considerations for targeted covalent inhibitors
- De-risking covalent inhibitors
- Mechanism of drug resistance

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DISTINGUISHED FACULTY of Drug Discovery Chemistry 2016

Plenary Keynotes:
Peter G. Schultz, Ph.D., The Scripps Research Institute and Director
Gregory L. Verdine, Ph.D., Harvard University

Andrew Andrews, Fox Chase Cancer Center
Paola Arimondo, CNRS
C. Glenn Begley, TetraLogic Pharmaceuticals
Ashok Bhandari, Protagonist Therapeutics
Ann Boriack-Sjodin, Ph.D., Senior Director, Protein and Structural Sciences, Lead Discovery, Epizyme, Inc.
Jark Böttcher, Boehringer Ingelheim RCV GmbH & Co KG
Michael Bradshaw, Principia Biopharma
Stacie Bulfer, University of California, San Francisco
Chris Burns, Walter and Eliza Hall Institute
Eric Campeau, Zenith Epigenetics
Philip Chamberlain, Celgene
Huifen Chen, Genentech
Alessio Ciulli, University of Dundee
Derek Cole, Takeda
Philip Collier, Vertex Pharmaceuticals
John Comer, Sirius Analytical
Stuart Conway, University of Oxford
Chitta Das, Purdue University
Tom Davies, Astex Pharmaceuticals
Ben Davis, Vernalis Research
Iwan de Esch, VU University & Griffin Discoveries BV
Jerome Deval, Alios BioPharma (J&J)
Paola Di Lello, Genentech
George Doherty, Abbvie
Alexander Dömling, University of Groningen
Donald Durden, SignalRx Pharmaceuticals
Matthew Eddy, University of Southern California
William Elmquist, University of Minnesota
Istvan Enyedy, Biogen
Daniel Erlanson, Carmot Therapeutics
Umar Faruk Mansoor, Merck Research Laboratories
Evelyne Fontaine, Sanofi
Robert Foster, Ciclofilin Pharmaceuticals
Robert Fraczkiewicz, Simulations Plus
Matthias Frech, EMD Serono
Matthew Fuchter, Imperial College London
Robert Gish, Robert G. Gish Consultants
Eric Goedken, AbbVie
Val Goodfellow, Califia Bio
Fan Hao, A*STAR
Mary Harner, Bristol Myers Squibb
Michael Hewitt, Constellation Pharmaceuticals
Robert Hughes, Boehringer-Ingelheim
Alexander (Sandy) Hurd, Lycera
Radhakrishnan Iyer, Spring Bank Pharmaceuticals
Matthew Jacobson, University of California, San Francisco
Yutao Jiang, Genentech
Ramon Jimenez-Moreno, ASINEX
Ted Johnson, Pfizer Oncology
Tim Kaminski, AstraZeneca
Jan Kihlberg Uppsala University
Thomas Kodadek, The Scripps Research Institute, Scripps Florida
Roman Kombarov, ASINEX
Alexandr Kornev, University of California, San Diego
Irina Kufareva, Univeristy of California, San Diego
Shenping Liu, Pfizer Global R&D
Paul Lockman, West Virginia University Health Science Center
Scott Lokey, University of California, Santa Cruz
Kevin Lumb, Janssen R&D
Doug Marcotte, Biogen
Jose Marquez, (EMBL) Grenoble Outstation
Eric Marsault, University of Sherbrooke
Elisabeth Martinez, University Texas Southwestern Medical Center
Andreas Marzinzik, Novartis Institute BioMedical Research
Alan Mathiowetz, Pfizer Worldwide Medicinal Chemistry
Larry Mattheakis, Protagonist Therapeutics
Matthew McClure, Alios BioPharma (J&J)
Essam Metwally, Chemical Computing Group
Christian Montalbetti, Inventiva
Gerhard Mueller, MercaChem BV
Songqing Na, Eli Lilly and Company
James Naismith, St. Andrews University
Radek Nowak, University of Oxford
Daniel Obrecht, Polyphor
Feroz Papa, University of California, San Francisco
William Pappano, Ph.D., Senior Scientist, Oncology Discovery, AbbVie, Inc.
William Pardridge, ArmaGen
Jighar Patel, Roche NimbleGen
Samarjit Patnaik, NIH
Dehua Pei, The Ohio State University
Juan Jesus Perez, Technical University of Catalonia
Kevin Peters, Aerpio Therapeutics
Mark Peterson, Cyclenium Pharma
Christopher Phelps, GSK
Jason Pickens, Takeda
William Pomerantz, University of Minnesota
John Quinn, Genentech
Nir Qvit, Stanford University School of Medicine
Shahrooz Rabizadeh, NantBioScience
Murali Ramachandra, Aurigene Discovery Technology
Adam Renslo, University of California, San Francisco
Michael Reutershan, Merck Research Labs
Martin Scanlon, Monash Institute for Pharmaceutical Sciences
Joerg Scheuermann, ETH Zurich
Mark Schnute, Pfizer Global R&D
Eric Schwartz, Celgene Avilomics Research
Phillip Schwartz, Takeda California
Qiang Shi, National Center for Toxicology Research, FDA
Laura Silvian, Biogen
Dan Sindhikara, Schrödinger
Dhanalakshmi Sivanandhan, Jubilant Biosys
Chris Smith, COI Pharmaceuticals
Michael Sofia, Arbutus Biopharma
Oliver Sperandio, Inserm
Terry Stouch, Science for Solutions
Yongchao Su, Merck Research Laboratories
John Sullivan-Bólyai, ContraVir Pharmaceuticals
Takayoshi Suzuki, Kyoto Prefectural University of Medicine
Seng-Lai "Thomas" Tan, FORMA Therapeutics
Leticia Toledo-Sherman, CHDI Foundation
Maricel Torrent, AbbVie
Andrew Vaillant, Replicor
Michael Vazquez, Pfizer
Sandrine Vendeville, Janssen Infectious Diseases (J&J)
Hari Venkatesan, Janssen R&D
Florence Wagner, The Broad Institute
Jakob Wallner, University of Vienna
Xiaolun Wang, Takeda San Diego
Patrick Woster, Medical University of South Carolina
Huixian Wu, The Broad Institute
Ryan Wurz, Amgen
David Wustrow, Cleave Biosciences
Wendy Young, Genentech
Christoph Zapf, Pfizer Research Labs
Rumin Zhang, Merck Research Laboratories

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April 19-20, 2016 *7th Annual*

Inflammation Inhibitors

Small Molecule and Macrocyclic Approaches

TUESDAY, APRIL 19

7:00 am Registration and Morning Coffee

INHIBITING PRO-INFLAMMATORY PATHWAYS: RORγ AND OTHER TARGETS

8:00 Chairperson's Opening Remarks
Eric Schwartz, Ph.D., Executive Director, Medicinal Chemistry, Celgene

» 8:10 FEATURED PRESENTATION: Small Molecule Modulators of RORgamma

Robert Hughes, Ph.D., Senior Associate Director, Small Molecule Discovery Research, Boehringer-Ingelheim

RORγt is a nuclear hormone receptor expressed in Th17 cells and distinct subsets of lymphoid cells, including innate lymphoid cells (ILC), and γδ T-cells. RORγt is required for Th17 cell and innate lymphocyte differentiation and regulates the transcription of the effector cytokines genes such as IL17A. We describe our approach, including screening, structure-based design and optimization, which led to the discovery of potent, selective ROR g modulators with favorable ADME properties.

8:40 Quinoline Tertiary Alcohols as Modulators of Retinoic Acid Receptor-Related Orphan Receptor gamma t (RORγt)
Hari Venkatesan, Ph.D., Principal Scientist, Discovery Chemistry, Immunology, Janssen Research & Development

Differentiation of naïve T-cells into IL-17 producing Th17 cells is regulated by the nuclear receptor transcription factor retinoic acid receptor-related orphan receptor gt (RORgt). Blocking the production of pro-inflammatory cytokines by RORgt modulation has the potential to be a first-in-class treatment of autoimmune diseases. High-throughput screening identified a promising series of quinoline tertiary alcohols. The subsequent optimization efforts that resulted in the identification of compounds for *in vivo* profiling will be discussed.

9:10 Sponsored Presentation *(Opportunity Available)*

9:40 Coffee Break

10:05 Inducing RORgamma-Specific Inverse Agonism Using a Synthetic Benzoxazinone Ligand
Doug Marcotte, Associate Scientist, Physical Biochemistry, Biogen

RORγ regulates transcriptional genes involved in production of pro-inflammatory interleukin IL-17 which is linked to autoimmune diseases. We have discovered a series of synthetic benzoxazinone ligands having either an agonist (BIO592) or inverse agonist (BIO399) mode of action. We demonstrate that upon binding of BIO399 the AF2 helix of RORγ become destabilized. The X-ray structures of RORγ with BIO592 and BIO399 demonstrates how small modifications modulate the mode of action for achieving RORγ-specific inverse agonism.

10:35 Small Molecule Inhibitors of RORgamma and IRAK4 for the Treatment of Autoimmune Disorders
Susanta Samajdar, Ph.D., Director, Medicinal Chemistry, Aurigene Discovery Technologies Limited

Although biologics such as anti-TNFα antibody are fairly successful in the treatment of autoimmune disorders, there is significant unmet need due to heterogeneity in diseases and lack of response to established therapies in some patients. While biologics typically target one cytokine signaling pathway, small molecule therapeutics directed towards intracellular target(s) can interfere in the signaling from multiple cytokines potentially leading to improved response. Development of small molecule oral inhibitors of IRAK4 and RORgamma to target TLR/IL-R and Th17 pathway respectively will be discussed.

11:05 Structure-Based Design of Macrocyclic IL-17A Antagonists
Shenping Liu, Ph.D., Associate Research Fellow, Structural Biology and Biophysics, Pfizer Global Research and Development

IL-17A is a pro-inflammatory cytokine that has been implicated in many autoimmune and inflammatory diseases. Monoclonal antibodies targeting the IL-17A pathway have shown significant efficacies in treating psoriasis and Psoriatic arthritis in late stage clinical trials, and one of them was approved recently. We are interested in developing small molecule IL-17A antagonists for oral medication. We have determined several IL-17A/antagonists complex structures. These structures enabled us to design macrocyclic IL-17A antagonists with much improved potencies.

11:35 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

12:05 pm Session Break

INTRACELLULAR KINASE INHIBITORS FOR INFLAMMATION

1:15 Chairperson's Remarks
Jennifer Venable, Ph.D., Associate Scientific Director, Medicinal Chemistry, J&J

1:20 Discovery of Potent, Selective, and Non-Covalent BTK Inhibitors for Clinical Development
Wendy B. Young, Ph.D., Vice President, Discovery Chemistry, Genentech

We developed a series of highly potent, selective, non-covalent Btk inhibitors that are efficacious in several rodent models of RA and lupus. Compounds in this chemical series remain highly active against the C481S Btk mutant identified in patients that have relapsed on Imbruvica®. We describe the SAR, preclinical DMPK and toxicology investigations leading up to the discovery and selection of our lead clinical candidate, GDC-0853. Results from our Phase 1 clinical trials will be shared.

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Inflammation Inhibitors

Small Molecule and Macrocyclic Approaches

1:50 A Covalent BTK Inhibitor for Inflammation
Eric Schwartz, Ph.D., Executive Director, Medicinal Chemistry, Celgene
This presentation will discuss the identification and characterization of a covalent BTK inhibitor with *in vitro*, *in vivo* and preliminary toxicity data presented.

2:20 BTK and other Case Studies: Fragment Hit Prioritization and Optimization for Immunology Targets
Jason Pickens, Ph.D., Senior Scientist, Medicinal Chemistry, Takeda
As cutting-edge methods for fragment screening evolve into a series of best practices, the question of how to prioritize fragment hit sets to select the "best" fragments for initial chemistry follow-up elicits wide-ranging levels of analysis and opinion among FBDD practitioners. Through select case studies of immunology targets including BTK, this presentation will illuminate some specific strategies employed recently by medicinal chemistry teams at Takeda California in the pursuit of high-quality drug candidates derived from fragment starting points.

2:50 Structure-Activity-Relationships around Lead Series of Selective Jak1 Inhibitors for Inflammation
Michael L. Vazquez, Ph.D., Associate Fellow, Medicinal Chemistry, Pfizer, Inc.
Our research efforts have identified a series of potent and selective JAK1 inhibitors. Our lead, PF-04965842, is currently in clinical trials for the treatment of autoimmune diseases. This talk will discuss learnings from our clinical experience with tofacitinib a pan-JAK inhibitor with respect to potency and selectivity, SAR, the preclinical evaluation of our lead, and crystallographic data which has enabled us to build a structural hypothesis for the JAK1 selectivity.

3:20 Sponsored Presentation *(Opportunity Available)*

3:35 Refreshment Break in the Exhibit Hall with Poster Viewing

» 4:30 PLENARY KEYNOTE PRESENTATION

A Chemist's Foray into Translational Research
Peter G. Schultz, Ph.D., Professor, Department of Chemistry, The Scripps Research Institute and Director, California Institute for Biomedical Research
(Please see page 2 for details.)

5:30 Welcome Reception in the Exhibit Hall with Poster Viewing

6:30 Close of Day

WEDNESDAY, APRIL 20

7:30 am Continental Breakfast Breakout Discussions
In this session, attendees choose a specific roundtable discussion to join. Each group has a moderator to ensure focused conversations around key issues within the topic. The small group format allows participants to informally meet potential collaborators, share examples from their work and discuss ideas with peers. Check our website in February to see the full listing of breakout topics and moderators.

TREATING DISEASE-SPECIFIC INFLAMMATION

8:30 Chairperson's Remarks
Kamal Puri, Ph.D., Senior Principal Scientist, Immunology & Inflammation, Celgene Corp.

8:35 PTG-100: An Oral Peptide Antagonist of $\alpha 4\beta 7$ Integrin for Ulcerative Colitis
Larry Mattheakis, Ph.D., Senior Director, Biology, Protagonist Therapeutics
PTG-100 is an oral peptide antagonist of the gut homing integrin $\alpha 4\beta 7$. Its potency and selectivity are similar to that of the FDA-approved antibody vedolizumab. PTG-100 was chemically engineered to be orally stable within the harsh proteolytic and reducing environment of the human gastrointestinal tract. In preclinical animal models, PTG-100 exposure is largely restricted to GI tissues, whereby it alters the trafficking of gut homing T cells to reduce local inflammation. Together, these results provide the rational for investigating PTG-100 in human trials, specifically ulcerative colitis.

9:05 ATPase Modulators for Treating Inflammatory Bowel Disease
Alexander (Sandy) Hurd, Ph.D., Associate Director of Chemistry, Chemistry, Lycera Corp
Autoimmune diseases occur in part as a result of dysregulation of the natural immune response. Autoimmune disease is characterized by chronic activation of lymphocytes that recognize and attack naturally occurring, endogenous targets. These chronically activated lymphocytes exhibit a distinct bioenergetic profile in comparison to acutely activated immune cells, which provide a target for therapeutic intervention. Lycera is developing modulators of the mitochondrial ATPase to treat autoimmune conditions such as inflammatory bowel disease (IBD). The talk will include a description of the identification and characterization of Lycera's current lead candidate for treating IBD.

9:35 Coffee Break in the Exhibit Hall with Poster Viewing

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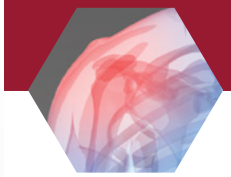

Inflammation Inhibitors

Small Molecule and Macrocyclic Approaches

10:30 AKB-4924: Targeting Hypoxia Inducible Factor 1 for Therapy of Inflammatory Bowel Disease

Kevin Peters, M.D., CSO and Senior Vice President, R&D, Aerpio Therapeutics, Inc.

Emerging evidence shows that hypoxia inducible factor 1 (HIF-1) is an important regulator of the immune response. AKB-4924 is a novel small molecule inhibitor of HIF prolylhydroxylases (PHDs), a family of enzymes that promotes HIF degradation. AKB-4924 preferentially stabilizes HIF-1 over HIF-2 and has profound beneficial effects in multiple models of inflammatory bowel disease by either parenteral or oral administration without concomitant increases in erythropoiesis. These data support advancement of AKB-4924 into the clinic.

11:00 CHDI-00340246: A Potent and Selective Kynurenine Monooxygenase Inhibitor as a Potential Therapeutic Agent for the Treatment of Huntington's Disease

Leticia Toledo-Sherman, Ph.D., Director of Medicinal Chemistry, CHDI Foundation

Deregulation of the kynurenine pathway, has been implicated in the pathophysiology of Huntington's Disease (HD). This talk will describe CHDI's medicinal chemistry efforts that lead to the identification of CHDI-00340246, a highly potent and selective KMO inhibitor that has been nominated as clinical candidate for the treatment of HD. We will describe the pharmacokinetic/pharmacodynamics effects of CHDI-00340246 in several species, as well as its biological effects in various disease models.

11:30 Towards Third Generation Antihistamines as Potent Inflammation Inhibitors

Iwan de Esch, Ph.D., Professor, Medicinal Chemistry, VU University Amsterdam & Griffin Discoveries BV

The histamine receptor consists of four subtype GPCRs. The histamine H1 receptor has been successfully targeted by two generations of blockbuster drugs. With the emerging insights into the role of the other histamine receptor subtypes in the different mechanisms of inflammatory responses, there is now a growing interest in poly-pharmacological approaches. We will disclose how fragment-based approaches and computer-aided drug design have resulted in series of compounds with well defined activity profiles for histamine receptor subtypes. These compounds proof potent anti-inflammatory compounds in various preclinical studies.

12:00 pm Close of Track

"Speakers were great and presented valuable data. Comprehensive conference and overview of most current inflammation targets and therapies." Tina T.I, Associate Scientist, Biogen Idec

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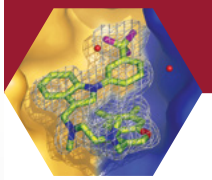

April 19-20, 2016 *9th Annual*

Protein-Protein Interactions

Targeting PPIs for Therapeutic Interventions

TUESDAY, APRIL 19

7:00 am Registration and Morning Coffee

MODULATING PROTEIN-PROTEIN INTERACTIONS IN THE UBIQUITIN PATHWAY

8:00 Chairperson's Opening Remarks
Kevin Lumb, Ph.D., Scientific Director, Discovery Sciences, Janssen R&D

8:10 Conformation-Selective Inhibitors of the AAA ATPase p97
Stacie Bulfer, Ph.D., Post-Doctoral Scholar, Michelle Arkin Laboratory, Pharmaceutical Chemistry, University of California, San Francisco
The AAA ATPase p97 interacts with many adaptor proteins to function in a diverse set of cellular processes that regulate protein homeostasis. Because of p97's role in protein homeostasis, specifically ERAD and autophagy, it has emerged as a drug discovery target for both cancer and neurodegeneration. This talk will describe the discovery and development of an allosteric, conformation-selective inhibitor of p97.

8:40 The Discovery of CB-5083: A First-In-Class Inhibitor of p97 for the Treatment of Cancer
Han-Jie Zhou, Ph.D., Senior Director of Chemistry, Cleave BioSciences
This talk will describe techniques used to discover CB-5083, a potent and selective p97 inhibitor with good pharmaceutical properties currently in Phase I clinical trials against solid tumors and hematological malignancies. The inhibition of the D2 ATPase activity of p97 prevents effective protein-protein interactions which play an important role in protein homeostasis mechanisms. A variety of biochemical, cellular and *in vivo* data supporting CB-5083's selection as a development candidate will be presented.

9:10 Applying the Compound-to-Target™ Platform to PPI Research
Sponsored by ASINEX
Ramon Jimenez-Moreno, Ph.D., Head, Biology, ASINEX Corporation
Making the step from conceptual design to drug discovery candidate is one of the most challenging tasks in drug discovery, especially when one addresses "difficult" or "challenging" targets. At Asinex, we have developed the Compound-to-Target™ platform to efficiently allocate the use of early drug discovery resources in developing tool compounds, hits, leads, and candidates. In this talk, we will relate efficiencies of this platform and show an example of this via our PPI research.

9:40 Coffee Break

10:05 A New Paradigm in Drug Action: Differentiated Gain of Function amongst IMiD® Analogues Binding the E3 Ubiquitin Ligase, CRL4CRBN
Philip Chamberlain, Ph.D., Principal Scientist, Biochemistry and Structural Biology, Celgene
Cereblon is a substrate receptor for the CRL4 ubiquitin ligase. Drugs such as lenalidomide and pomalidomide bind cereblon and trigger the recruitment of substrate proteins for ubiquitylation and degradation. In this presentation we will describe mechanistic and structural studies aimed at discovery of next-generation cereblon modulators.

10:35 Discovery and Characterization of Small Molecule Fragments that Bind and Inhibit the Ubiquitin Specific Protease 7 (USP7)
Paola Di Lello, Ph.D., Scientist, Department of Structural Biology, Genentech
USP7 has recently emerged as an attractive oncology target because its inhibition stabilizes p53, thus promoting p53-dependent apoptosis in cancer cells. Using a multidisciplinary, fragment-based drug discovery approach we found small molecule ligands that, although binding USP7 in a region distinct from the catalytic site (the palm region), inhibit USP7 enzymatic activity. These compounds appear to inhibit USP7 by a novel mechanism of action based on the interference of the interaction between enzyme and substrate.

11:05 Structure-Based Targeting of De-Ubiquitinases (DUBs)
Chitta Das, Ph.D., Associate Professor, Biochemistry, Purdue University

11:35 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

12:05 pm Session Break

PPI INHIBITORS IN DEVELOPMENT

1:15 Chairperson's Remarks
Laura Silvian, Ph.D., Principal Scientist, Cell and Protein Sciences, Biogen

» 1:20 FEATURED PRESENTATION: From Fragment to *in vivo* Activity for a Challenging PPI Target: Discovery of Potent Inhibitors of Keap1-Nrf2 Interaction

Tom Davies, Ph.D., Associate Director, Molecular Sciences, Astex Pharmaceuticals
Keap1 is the key regulator of the Nrf2-mediated cytoprotective response, and a target for diseases involving excessive oxidative stress. Using a fragment-based approach we have developed a small-molecule antagonist KI-696 which combines tight and selective binding to the Keap1 Kelch domain with favourable physicochemical properties. KI-696 potently activates Nrf2 in cells and shows promising activity in *in vivo* models, thereby providing a high quality chemical probe to explore the therapeutic potential of disrupting the Kelch-Nrf2 interaction.

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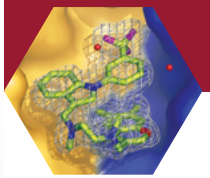

April 19-20, 2016 *9th Annual*

Protein-Protein Interactions

Targeting PPIs for Therapeutic Interventions

1:50 Optimization of Novel Bcl-2 Inhibitors
George Doherty, Ph.D., Principal Research Scientist, Oncology Discovery, Abbvie

2:20 Efficient Small Molecule Inhibitors of the HDM2-p53 Protein-Protein Interaction
Michael H. Reutershan, Senior Scientist, Medicinal Chemistry, Merck Research Laboratories.
This talk will describe efforts to design efficient, low molecular weight inhibitors of the HDM2-p53 protein-protein interaction with good physical properties and PK profiles. In particular, the optimization of a novel lead with modest HDM2 affinity into a highly efficient series of compounds without significantly increasing molecular weight will be described. Our strategy of utilizing conformational control and biostructural information to guide design while focusing on physical properties will be highlighted

2:50 Inhibitors of MAP Kinases Targeting a Novel Allosteric Site
Juan Jesus Perez, Ph.D., Professor, Department of Chemical Engineering, Technical University of Catalonia and Director, Molecular Modeling, Allinky Biopharma
Analysis of the crystallographic structure of the p38 MAP kinase-MK2 complex made us hypothesize that protein-protein interactions force p38 to be lock in its inactive conformation. To explore this hypothesis we considered a combined approach using modeling and medicinal chemistry to develop successfully small molecule inhibitors of this site.

3:20 Sponsored Presentation *(Opportunity Available)*

3:35 Refreshment Break in the Exhibit Hall with Poster Viewing

» 4:30 PLENARY KEYNOTE PRESENTATION

A Chemist's Foray into Translational Research
Peter G. Schultz, Ph.D., Professor, Department of Chemistry, The Scripps Research Institute and Director, California Institute for Biomedical Research
(Please see page 2 for details.)

5:30 Welcome Reception in the Exhibit Hall with Poster Viewing

6:30 Close of Day

WEDNESDAY, APRIL 20

7:30 am Continental Breakfast Breakout Discussions
In this session, attendees choose a specific roundtable discussion to join. Each group has a moderator to ensure focused conversations around key issues within the topic. The small group format allows participants to informally meet potential collaborators, share examples from their work and discuss ideas with peers. Check our website in February to see the full listing of breakout topics and moderators.

IDENTIFYING AND OPTIMIZING MODULATORS OF PROTEIN-PROTEIN INTERACTION SITES

8:30 Chairperson's Remarks
Paola Di Lello, Ph.D., Scientist, Department of Structural Biology, Genentech

8:35 Triage of HTS Hits for Protein-Protein Interactions
Kevin Lumb, Ph.D., Scientific Director, Discovery Sciences, Janssen R&D
The false positive rate for HTS can be high and strategies are required to identify bona fide hits from assay or compound artifacts. This can be especially true for protein-protein interaction screens with an obligate emphasis on through-space methods that report on disruption of the protein-protein interaction rather than substrate/product detection methods. The application of biophysical approaches to triage HTS hits will be described.

9:05 How to Facilitate the Identification of Protein-Protein Interactions Inhibitors
Oliver Sperandio, Ph.D., Senior Research Associate, Inserm
Using a chemoinformatics procedure we show that comparable classes of PPI targets can be formed using either the similarity of their ligands or the shared properties of their binding cavities. Such identified classes of targets can lead to the design of PPI-class specific chemical libraries and therefore facilitate the development of PPI modulators to the stage of drug candidates. We moreover show how these techniques can be used to reposition existing drugs to new therapeutic areas.

9:35 Coffee Break in the Exhibit Hall with Poster Viewing

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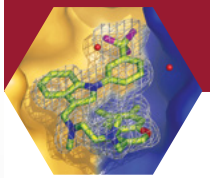

April 19-20, 2016 *9th Annual*

Protein-Protein Interactions

Targeting PPIs for Therapeutic Interventions

10:30 Targeting Ras-GTPase Oncogenic Interactions and Other PPIs with Cyclic Peptides

Dehua Pei, Ph.D., Professor, Department of Chemistry and Biochemistry, The Ohio State University

Protein-protein interactions (PPIs) are challenging targets for small-molecule drug discovery. Cyclic peptides can serve as effective PPI inhibitors *in vitro*, but they are generally impermeable to the cell membrane. We have discovered a novel class of exceptionally active cyclic cell-penetrating peptides (CPPs). Incorporation of these CPPs into cyclic peptides resulted in potent, selective, proteolytically stable, and cell-permeable inhibitors against a variety of intracellular proteins including calcineurin, CFTR-associated ligand, K-Ras, and PTP1B.

11:00 Chemokines and their Receptors: Structural Basis of a Key PPI in Immunity, Inflammation and Cancer

Irina Kufareva, Ph.D., Project Scientist, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego

Chemokines are a family of 7-12 kDa secreted proteins that control cell migration in the context of development, immunity, inflammation, and cancer, all by virtue of their interaction with 7TM cell surface receptors. Inhibitors of receptor-chemokine interactions attract immense attention in several therapeutic areas. By a combination of molecular modeling, biophysical and functional experiments, and X-ray crystallography we elucidate the structural determinants of these interactions, with the goal of rationalizing the discovery of therapeutics targeting the chemokine receptor axis.

11:30 Protein-Protein Interactions at the Synapse: Development of a Potent PDZ-Domain Specific Inhibitor Using Structure-Based Drug Design

Laura Silvian, Ph.D., Senior Scientist, Cell and Protein Sciences, Biogen

In this study we describe development of a potent, non-peptide based inhibitor of the PICK1:AMPA receptor interaction and the efforts to screen for hits and structurally characterize its binding to the PICK1 PDZ domain in order to improve potency and selectivity. We describe here the multi-step method we used to produce a crystal structure of a ligand-bound PDZ domain, which is one of the first of its kind. We will present more generalized rules that we are learning about this type of protein-protein interaction to support development of new PDZ-domain inhibitors.

12:00 pm Close of Track

"The Drug Discovery Chemistry conference offers a compact, dynamic event over three days that allows the scientific community an excellent opportunity to stay aware of current trends." Kenneth D., Director, FLAMMA

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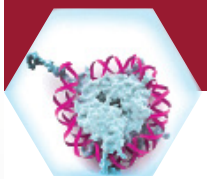

April 19-20, 2016 *3rd Annual*

Epigenetic Inhibitor Discovery

Targeting Histone Methyltransferases, Demethylases and Bromodomains

TUESDAY, APRIL 19

7:00 am Registration and Morning Coffee

DESIGN AND DEVELOPMENT OF NOVEL BROMODOMAIN INHIBITORS

8:00 Chairperson's Opening Remarks

8:10 New Synthetic Routes to Triazolo-Benzodiazepine Analogues: Expanding the Scope of the Bump-and-Hole Approach for Selective Bromo and Extra-Terminal (BET) Bromodomain Inhibition

Alessio Ciulli, Ph.D., Associate Professor & Principal Investigator, Chemical & Structural Biology, College of Life Sciences, University of Dundee

We describe new synthetic routes developed toward a range of substituted analogues of bromo and extra-terminal (BET) bromodomain inhibitors I-BET762/JQ1 based on the triazolo-benzodiazepine scaffold. These new routes allow for the derivatization of the methoxyphenyl and chlorophenyl rings, in addition to the diazepine ternary center and the side chain methylene moiety. Substitution at the level of the side chain methylene afforded compounds targeting specifically and potently engineered BET bromodomains designed as part of a bump and hole approach.

» 8:40 FEATURED PRESENTATION: The Design and Development of Bromodomain Ligands

Stuart Conway, Ph.D., Professor, Department of Chemistry, University of Oxford

Bromodomains are protein modules that bind to *N*-ε-acetyl-L-lysine (acetyl lysine) and facilitate the assembly of multiprotein scaffolds by mediating protein–protein interactions. It is only comparatively recently that bromodomains have been viewed as therapeutically important targets, but subsequent progress in the development of drug-like bromodomain ligands has been rapid. This presentation will discuss advances in the development of BET bromodomain ligands and progress in the identification of non-BET bromodomain ligands.

9:10 Novel Bromodomain & Extra Terminal Domain (BET) Family Bromodomain Assays Utilizing AlphaLISA Technology

Sponsored by PerkinElmer For the Better

Jen Carlstrom, PhD Application Scientist, Global Discovery Applications Group, PerkinElmer, Inc Global Discovery Applications Group PerkinElmer, Inc.

We have developed novel biochemical bromodomain AlphaLISA assays suitable for screening compounds against BRD4 using Histone 4 peptides of differing acetylation states. Assay specificity was confirmed by IC-50 determination of commercially available compounds. In collaboration with EpiCypher, PerkinElmer now offers kits to study modulators of bromodomain activity *in vitro*.

9:40 Coffee Break

10:05 *In silico* Design of Dual PI-3 Kinase/BET Bromodomain Inhibitors; Structural Details for Binding BD1

Adam Burgoyne, M.D., Ph.D., Chief Fellow, Division of Hematology/Oncology, Department of Medicine, University of California San Diego

We will present *in silico* drug discovery of a lead compound which inhibits PI-3 kinase isoforms and BRD4. Specificity and potency are to be presented as well as biological data on the inhibition of tumor growth, metastasis, M1-M2 transition and the activation of the immune checkpoint response to activate immunity.

10:35 Design and Development of Novel BET Bromodomain Inhibitors

Eric Campeau, Ph.D., PMP, Director of Biology, Zenith Epigenetics

Characterization of ZEN-3694, a novel pan-BET bromodomain inhibitor, and Zenith Epigenetics clinical candidate will be presented, including preclinical activity in relevant models. In addition, examples of next generation BET inhibitors, including compounds that are selective for either the BD1 or BD2 bromodomains of the BET proteins, and irreversible inhibitors of the BET proteins, will be discussed.

11:05 Structure-Guided Discovery of Potent and Selective Bromodomain Inhibitors and Their Application to Phenotype Discovery

Alexandre Côté, Ph.D., Senior Scientist, Constellation Pharmaceuticals

We describe the construction of a broad platform designed to interrogate the bromodomain family of acetyl lysine binding proteins. The platform produced multiple potent, selective and cell active bromodomain inhibitors that were then used to probe the biology of these epigenetic targets. Examples taken from our work with PCAF/GCN5 and CBP/EP300 bromodomain inhibitors will be described.

11:35 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

12:05 pm Session Break

DISCOVERY OF NOVEL HISTONE DEMETHYLASE INHIBITORS

1:15 Chairperson's Remarks

Elisabeth Martinez, Ph.D., Assistant Professor, Pharmacology, University of Texas Southwestern Medical Center

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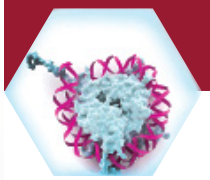

April 19-20, 2016 *3rd Annual*

Epigenetic Inhibitor Discovery

Targeting Histone Methyltransferases, Demethylases and Bromodomains

1:20 Novel Dual Inhibitors of LSD1-HDAC for Treatment of Multiple Myeloma and Other Cancers

Dhanalakshmi Sivanandhan, Ph.D., Principal Scientist & Assistant Director, Jubilant Biosys

We have developed a set of molecules having dual activity on LSD1 and HDAC. Multiple compounds with dual activity show an *in vitro* potency of <0.05 µM against LSD1 with more than 1000 fold selectivity against MAOs. On HDAC, these dual inhibitors showed different isoform selectivity and molecules with LSD1/HDAC1, LSD1/HDAC6/8 and LSD1/pan HDAC activities have been identified. JBI-097, one of the dual molecules with LSD1/HDAC/6/8 selectivity showed an IC50 of µM on LSD1 and an IC50 of 0.04 and µM on HDAC6 and HDAC8, respectively with about 100 fold selectivity over other HDAC isoforms.

1:50 Small Molecule Epigenetic Modulators for the Treatment of Cardiovascular Disorders

Patrick M. Woster, Ph.D., Endowed Chair, Drug Discovery; Professor, Pharmaceutical and Biomedical Sciences, College of Pharmacy, Medical University of South Carolina

We have identified a new series of small molecules that act as potent and selective LSD1 inhibitors. Because of their relatively low toxicity, we have explored the use of these molecules in diseases other than cancer, where cytotoxicity is not a desirable endpoint. In this presentation, we will describe the optimization of this new series of LSD1 inhibitors, and present evidence that LSD1 inhibitor-mediated correction of aberrant gene silencing can have therapeutic potential in cardiovascular disease.

2:20 Discovery of Histone Lysine Demethylase Inhibitors

Takayoshi Suzuki, Ph.D., Professor, Graduate School of Medical Science, Kyoto Prefectural University of Medicine

We have identified compound 6j, which selectively inhibits JARID1A over three other JHDM family members. Compound 7j, a prodrug form of compound 6j, induced a selective increase in the level of trimethylation of histone H3 lysine 4, a substrate of JARID1A. Furthermore, compound 7j synergistically enhanced A549 human lung cancer cell growth inhibition induced by vorinostat, a histone deacetylase inhibitor. These findings support the idea that JARID1A inhibitors have potential as anticancer agents.

2:50 KDM4/JMJD2 Histone Demethylase Inhibitors Block Prostate Tumor Growth by Suppressing the Expression of AR and BMYB-Regulated Genes

Elisabeth Martinez, Ph.D., Assistant Professor, Pharmacology, University of Texas Southwestern Medical Center

We report the anti-tumor growth effect and molecular mechanisms of three novel KDM4 inhibitors (A1, I9, and B3). These inhibitors repressed the transcription of both AR and BMYB-regulated genes. Compound B3 is highly selective for a variety of cancer cell lines including PC3 cells that lack AR. B3 inhibited the *in vivo* growth of tumors derived from PC3 cells and *ex vivo* human PCa explants. We identified a novel mechanism by which KDM4B activates the transcription of Polo-like kinase 1 (PLK1). B3 blocked the binding of KDM4B to the PLK1 promoter.

3:20 Sponsored Presentation *(Opportunity Available)*

3:35 Refreshment Break in the Exhibit Hall with Poster Viewing

» 4:30 PLENARY KEYNOTE PRESENTATION

A Chemist's Foray into Translational Research

Peter G. Schultz, Ph.D., Professor, Department of Chemistry, The Scripps Research Institute and Director, California Institute for Biomedical Research

(Please see page 2 for details.)

5:30 Welcome Reception in the Exhibit Hall with Poster Viewing

6:30 Close of Day

WEDNESDAY, APRIL 20

7:30 am Continental Breakfast Breakout Discussions

In this session, attendees choose a specific roundtable discussion to join. Each group has a moderator to ensure focused conversations around key issues within the topic. The small group format allows participants to informally meet potential collaborators, share examples from their work and discuss ideas with peers. Check our website in February to see the full listing of breakout topics and moderators.

TARGETING HISTONE AND DNA METHYLATION

8:30 Chairperson's Remarks

Matthew Fuchter, Ph.D., Reader, Chemistry, Department of Chemistry, Imperial College London

» 8:35 FEATURED PRESENTATION: Profiling the 'Methylome' Targets of the Histone Lysine Methyltransferases: DOT1L

Matthew Fuchter, Ph.D., Reader, Chemistry, Department of Chemistry, Imperial College London

Indeed to date, no suitable technologies exist for defining the specific contribution of a given HKMT to the protein 'methylome'. In currently unpublished work, we have gained proof-of-concept data towards the development a unique proteomic technology, via a traceable HKMT-cofactor system, that will allow cellular methylome profiling. We have initially applied our approach to DOT1L and in this talk I will present the underlying science of the method, the technological validation obtained so far, and the early insight we have gained on DOT1L biochemistry/biology.

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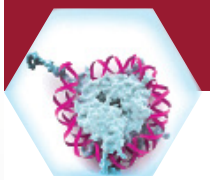

Epigenetic Inhibitor Discovery

Targeting Histone Methyltransferases, Demethylases and Bromodomains

9:05 Identification of a Novel Potent Selective SMYD3 Inhibitor with Oral Bioavailability

Ann Boriack-Sjodin, Ph.D., Senior Director, Protein and Structural Sciences, Lead Discovery, Epizyme, Inc.

In this presentation we describe the discovery and optimization of a novel series of oxindole sulfonamides and sulfamides with SMYD3 inhibitory activity. One of these compounds, EPZ030456, has a SMYD3 biochemical IC50 of 4 nM and is active in cells with an IC50 of 48 nM in a trimethyl MAP3K2 (MEKK2) in-cell western (ICW) assay. The crystal structure of this compound was solved with SMYD3 and the nucleotide substrate, S-adenosylmethionine and shows the oxindole portion of the molecule extends into the SMYD3 lysine binding channel. EPZ030456 shows less than 30% inhibition at a 10 uM screening concentration against 17 histone methyltransferase targets tested, including SMYD2. Further optimization within the series resulted in EPZ031686 which has similar potency to EPZ030456 with a biochemical IC50 of 3 nM and an ICW IC50 of 36 nM and in addition exhibits good bioavailability following oral dosing in mice. Hence, EPZ031686 is a suitable tool to study the role of SMYD3 in cancer and other therapeutic areas, using both *in vitro* and *in vivo* models.

9:35 Coffee Break in the Exhibit Hall with Poster Viewing

10:30 Discovery of A-893, a New Cell-Active Benzoxazinone Inhibitor of Lysine Methyltransferase SMYD2

William Pappano, Ph.D., Senior Scientist, Oncology Discovery, AbbVie, Inc.

A lack of useful small molecule tools has precluded thorough interrogation of the biological function of SMYD2, a lysine methyltransferase with known tumor-suppressor substrates. Systematic exploration of the structure-activity relationships of a previously known benzoxazinone compound led to the synthesis of A-893, a potent and selective SMYD2 inhibitor (IC50: 2.8 nM). A cocrystal structure reveals the origin of enhanced potency, and effective suppression of p53K370 methylation is observed in a lung carcinoma (A549) cell line.

11:00 A Rational Approach for the Discovery of Inhibitors of NSD2 for the Treatment of Cancer

Christian A. G. N. Montalbetti, Ph.D., Head, Chemistry, Inventiva®

We screened 240,000 compounds coming from our proprietary library. This strategy allowed us to identify about 200 compounds. To focus on the most interesting ones, orthogonal counterscreens based on [3]H SAM incorporation and biophysical binding are being completed. To our knowledge, no potent and selective NSD2 inhibitor has been identified to date despite several screening effort performed by other groups. Our library has already produced new chemical starting points for other KMTs, and we believe that our hits could be promising starting points to generate NSD2 inhibitors.

11:30 Chemical Tools to Modulate Gene Expression by Targeting DNA Methylation

Paola B. Arimondo, Ph.D., Director, Research, ETaC - Epigenetic Targeting of Cancer, CNRS

A challenge to develop new anticancer strategies consists in designing chemical molecules able to modulate gene expression. To this aim we have designed inhibitors of DNA methyltransferases to reactive tumor suppressor genes. In order to identify novel inhibitors of DNA methylation, we applied three chemical strategies: High-Throughput Screening of chemical libraries, rational drug design based on molecular modeling and the pharmacomodulation of known inhibitors. The discovery and the biological activity of the compounds will be illustrated as the study of their mechanism of action.

12:00 pm Close of Track

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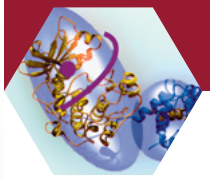

April 20-21, 2016 *7th Annual*

Kinase Inhibitor Chemistry

Shaping Current and Future Development of Kinase Inhibitors

WEDNESDAY, APRIL 20

12:30 pm Registration

OPTIMIZING NEXT-GENERATION KINASE INHIBITORS

1:30 Chairperson's Remarks
Gerhard Mueller, Ph.D., Senior Vice President, Medicinal Chemistry, MercaChem BV

1:40 Novel Kinase Inhibitor Design Paradigms: The Hydrophobic Spine and the Discovery of Slowness
Gerhard Mueller, Ph.D., Senior Vice President, Medicinal Chemistry, MercaChem BV
A paradigm shift has occurred over the last decade in medicinal chemistry in that more emphasis is laid on the improvement of ADME-related and off-target properties, thus avoiding mere IC50-hunting campaigns. To improve the correlation between biochemical and cellular or in-vivo efficacy, it is advantageous to optimize the residence time of compound-target complexes early in the drug discovery process. In this presentation the prospective engineering of binding kinetic signatures into inhibitors that exhibit slow koff by applying "deep-pocket-directed" scaffolds is exemplified.

2:10 CASE STUDY: Structural Basis for High Isoform Selectivity in a Class of Thiazolopiperidine Inhibitors of Phosphoinositide 3-Kinase γ
Philip Collier, Ph.D., Senior Research Scientist, Medicinal Chemistry, Vertex Pharmaceuticals, Inc.
The evolution of a reported phenylthiazole pan-PI3K inhibitor into a family of potent and selective benzothiazole and second-generation thiazolopiperidine inhibitors is described. Selectivity is achieved by exploiting natural sequence differences among PI3K isoforms in a previously unreported hydrophobic binding cleft adjacent to the ATP binding site of PI3Kγ.

2:40 Focused Mapping for Characterizing Binding Sites and Setting Up Ligand and Structure-Based Methods
Istvan Enyedy, Ph.D., Senior Scientist, Chemical and Molecular Therapeutics, Biogen
Computational solvent mapping was originally developed for identifying "hot spots" on protein surfaces. Our goal was to use this information in order to characterize the binding site and obtain information about features a ligand should have in order to optimally bind to the target. To achieve our goal we are using a set of 19 fragments, and evaluated focused mapping to generate "fake" ligands that capture all interactions a ligand can form with the binding site. Results obtained using ROCS, FRED, HYBRID, and POSIT will be presented.

3:10 Organizing 3D Project Data for Structure-Based Drug Design
Sponsored by CHEMICAL COMPUTING GROUP
Essam Metwally, Ph.D., Senior Scientist, Chemical Computing Group
It is often desirable to organize disparate crystallographic project data into a common homogeneous format, ready to use for modelling. We present a web-based application that permits users to specify numerous options controlling superposition and alignment of structures in a family or project, ligand specification, and whether electron densities or other grids are to be included. The final result is a project database containing superposed structures all in the same frame of reference. From here, structures can be dynamical regrouped, for example by scaffold class, for easy management, and can be easily browsed and used as a starting point for further research. The system is able to handle multi-subunit complexes, including structures which may be missing subunits, by using a novel algorithm to determine which subunits of each complex correspond to each other.

3:40 Refreshment Break in the Exhibit Hall with Poster Viewing

4:30 Mitochondrial Toxicity of FDA Approved Tyrosine Kinase Inhibitors: Towards Safer New Drugs?
Qiang Shi, Ph.D., Principal Investigator, National Center for Toxicological Research (NCTR), FDA
Six FDA approved tyrosine kinase inhibitors (TKIs) have a Black Box Warning for hepatotoxicity in the product labelling. The mechanism is unknown. We will present data to demonstrate if mitochondrial toxicity can help predict TKI hepatotoxicity. Hepatotoxicity is the most important safety issue that restricts the clinical use of tyrosine kinase inhibitors (TKIs). The development of some TKIs were discontinued due to hepatotoxicity. Our data will provide mechanistic insights into TKI hepatotoxicity and shed light on how to predict and prevent such toxicity in the drug development process.

5:00 An Integrated Approach to the Discovery, Development, and Clinical Use of Novel Kinase Inhibitors for the Treatment of Cancer
Shahrooz Rabizadeh, Ph.D., CSO, Research and Development, NantOmics, LLC; NantBioScience, Inc.
We are taking a multi-pronged approach to the discovery of novel kinase inhibitors by employing a suite of technologies: genomics to discover novel and patient-specific targets, fragment-based chemistry, high-throughput discovery, and molecular modeling to define novel pockets in kinases and refine hits for more specific targeting. Our kinase inhibitors include a compound targeting c-Met that is in phase 2 clinical trial testing; two multi-kinase inhibitors nearing IND submission; and multiple small molecule compounds that specifically target Trk and FGFR.

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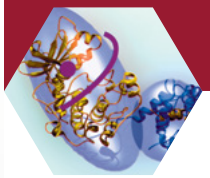

April 20-21, 2016 *7th Annual*

Kinase Inhibitor Chemistry

Shaping Current and Future Development of Kinase Inhibitors

5:30 Breakout Discussions

In this session, attendees choose a specific roundtable discussion to join. Each group has a moderator to ensure focused conversations around key issues within the topic. The small group format allows participants to informally meet potential collaborators, share examples from their work and discuss ideas with peers. Check our website in February to see the full listing of breakout topics and moderators.

6:15 Close of Day

6:30 Dinner Short Courses*

**Separate registration required; please see page 4 for details*

THURSDAY, APRIL 21

7:45 DNA Encoded Libraries and the Economics of Early Stage Drug Discovery: Managing the Economics of Serendipity

Sponsored by HITGEN 先导药物

Barry A. Morgan, Ph.D., Visiting Professor, Institute for Molecular Medicine, University of Texas Health Sciences

A review of FDA approved drugs, and the increased cost of drug discovery over the past few decades highlights the unsustainability of the current model for bringing new medicines to clinical practice. We will review the factors involved in this analysis, and present a case for DNA encoded library technology bringing disruptive change to early stage drug discovery.

» 8:30 PLENARY KEYNOTE PRESENTATION

Cell-Penetrating Miniproteins

Gregory L. Verdine, Ph.D., Professor, Departments of Stem Cell and Regenerative Biology, Chemistry and Chemical Biology, and Molecular and Cellular Biology, Harvard University

(Please see page 2 for details.)

9:30 Coffee Break in the Exhibit Hall with Poster Viewing

ADVANCES IN COVALENT INHIBITOR DEVELOPMENT

10:10 Chairperson's Remarks

» 10:15 FEATURED PRESENTATION: Tailoring Residence Time Utilizing Reversible Covalent Cysteine Targeting

Michael Bradshaw, Ph.D., Senior Scientist, Principia Biopharma

Using an inverted orientation of the cysteine-reactive cyanoacrylamide electrophile, we identified potent and selective BTK inhibitors that demonstrated biochemical residence times spanning from minutes to 7 d. An inverted cyanoacrylamide with prolonged residence time *in vivo* remained bound to BTK for more than 18 h after clearance from the circulation. The inverted cyanoacrylamide strategy was further used to discover fibroblast growth factor receptor (FGFR) kinase inhibitors with residence times of several days, demonstrating the generalizability of the approach.

10:45 Oxopyrido[2,3-d]pyrimidinyl Derivatives as Irreversible Epidermal Growth Factor Receptor (EGFR) Inhibitors with Improved Selectivity for the L858R/T790M Mutant Over Wild-Type

Ryan Wurz, Ph.D., Senior Scientist, Medicinal Chemistry, Amgen, Inc.

One of the leading causes of acquired resistance to the first generation tyrosine kinase inhibitors in non-small cell lung cancer (NSCLC) is the threonine790–methionine790 (T790M) point mutation of EGFR. The discovery of a series of irreversible EGFR inhibitors selective for the T790M mutant will be described. This led to the discovery of compound 1 which showed promising antitumor activity in a H1975 (EGFR T790M bearing cell line) xenograft model upon p.o. dosing. Formulation in PLGA microspheres and subcutaneous administration resulted in improved efficacy.

11:15 Discovery of Kinase Inhibitor Probes Through Broad Selectivity Profiling

Sponsored by DiscoverX

Jeremy Hunt, Director, Screening KINOMEscan, DiscoverX Corporation

Highly selective chemical probes are needed to explore underlying biological function of protein kinases. The SGC recently partnered with DiscoverX to annotate over 600 kinase inhibitors through broad selectivity profiling. Presented here are the resulting data which should facilitate target validation and new drug discovery efforts of understudied kinases.

11:30 Tricyclic Covalent Inhibitors Selectively Target Jak3 through an Active Site Thiol

Eric Goedken, Ph.D., Principal Research Scientist, AbbVie Bioresearch Center

One of the leading causes of acquired resistance to the first generation tyrosine kinase inhibitors in non-small cell lung cancer (NSCLC) is the threonine790–methionine790 (T790M) point mutation of EGFR. The discovery of a series of irreversible EGFR inhibitors selective for the T790M mutant will be described. This led to the discovery of compound 1 which showed promising antitumor activity in a H1975 (EGFR T790M bearing cell line) xenograft model upon p.o. dosing. Formulation in PLGA microspheres and subcutaneous administration resulted in improved efficacy.

12:30 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:30 Ice Cream Refreshment Break in the Exhibit Hall with Poster Awards

DESIGN AND DEVELOPMENT OF NOVEL ALLOSTERIC MODULATORS

2:15 Chairperson's Remarks

Alexandr P. Kornev, Ph.D., Project Scientist, Department of Pharmacology, University of California, San Diego

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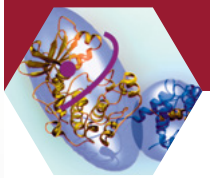

April 20-21, 2016 *7th Annual*

Kinase Inhibitor Chemistry

Shaping Current and Future Development of Kinase Inhibitors

2:20 Dynamics-Based Allostery in Protein Kinases

Alexandr P. Kornev, Ph.D., Project Scientist, Department of Pharmacology, University of California, San Diego

Active kinases reveal a dynamic pattern with residues clustering into semirigid communities that move in μs-ms timescale. Previously detected hydrophobic spines serve as connectors between communities. Integration of the communities depends on the assembly of the hydrophobic spine and phosphorylation of the activation loop. Single mutations can significantly disrupt the dynamic infrastructure and thereby interfere with long-distance allosteric signaling that propagates throughout the whole molecule.

2:50 Discovery of a Potent Allosteric Kinase Modulator by Combining Computational and Synthetic Methods

Alexander Dömling, Ph.D., Professor, Drug Design, University of Groningen

The protein kinase PDK1, which lies at the center of the growth-factor signaling pathway, possesses an allosteric regulatory site previously validated both *in vitro* and in cells. ANCHOR.QUERY software was used to discover a potent allosteric PDK1 kinase modulator. Using a recently published PDK1 compound as a template, several new scaffolds that bind to the allosteric target site were generated and one example was validated. The inhibitor can be synthesized in one step by multicomponent reaction (MCR) chemistry when using the ANCHOR.QUERY approach.

3:20 Refreshment Break

3:40 Small-Molecule Allosteric Modulators of the Protein Kinase PDK1 from Structure-Based Docking

*Fan Hao, Ph.D., Principal Investigator, Bioinformatics Institute, A*STAR*

We used virtual screening against an ensemble of both crystal structures and comparative models to identify ligands for an allosteric peptide-binding site on the protein kinase PDK1 (the PIF pocket). We optimized these ligands through an analog-by-catalog search that yielded compound 4, which binds to PDK1 with 8 μM affinity. We confirmed the docking poses by determining a crystal structure of PDK1 in complex with 4. This approach may enable the discovery of allosteric modulators for other kinases.

4:10 Optimization of a Dibenzodiazepine Hit to a Potent and Selective Allosteric PAK1 Inhibitor

Andreas Marzinzik, Ph.D., Director, Lead Generation Chemistry, Novartis Institutes for BioMedical Research

The discovery of inhibitors targeting novel allosteric kinase sites is very challenging. Such compounds, however, once identified could offer exquisite levels of selectivity across the kinome. Herein we report our structure-based optimization strategy of a dibenzodiazepine hit 1, discovered in a fragment-based screen, yielding highly potent and selective inhibitors of PAK1 such as 2 and 3. Compound 2 was cocrystallized with PAK1 to confirm binding to an allosteric site and to reveal novel key interactions.

4:40 CASE STUDY: Type II Kinase Inhibitors of IRE1 Allosterically Attenuate RNAse Activity to Reduce Apoptosis under Endoplasmic Reticulum Stress

Feroz Papa, M.D., Ph.D., Professor, Department of Medicine, Division of Endocrinology, University of California, San Francisco

Under high/chronic ER stress, IRE1α surpasses an oligomerization threshold that expands RNase substrate repertoire to many ER-localized mRNAs, leading to apoptosis. To modulate these effects, we developed ATP-competitive IRE1α Kinase-Inhibiting RNase Attenuators-KIRAs-that allosterically inhibit IRE1α's RNase by breaking breaking oligomers. One optimized KIRA, KIRA6, inhibits IRE1α *in vivo* and promotes cell survival under ER stress. Intravitreally, KIRA6 preserves photoreceptor functional viability in rat models of ER stress-induced retinal degeneration.

5:10 Close of Conference

"Up-to-date discussion on late breaking strategies for novel kinase inhibitor design." Ann A., Senior Scientist, Pfizer

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April 20-21, 2016 *4th Annual*

Macrocyclics & Constrained Peptides

Bigger, Better, But hopefully still Oral, Small Molecules

WEDNESDAY, APRIL 20

12:30 pm Registration

DESIGN CONSIDERATIONS AND CHALLENGES FOR MACROCYCLICS

1:30 Chairperson's Remarks

Scott Lokey, Ph.D., Professor, Chemistry and Biochemistry, University of California, Santa Cruz

» 1:40 FEATURED PRESENTATION: How to Design Non-Peptidic Cell Permeable Macrocycles

Jan Kihlberg, Ph.D., Professor, Organic Chemistry, Uppsala University

Macrocycles provide unique opportunities to modulate difficult targets like protein-protein-interactions. Analysis of macrocyclic drugs and clinical candidates and experimental profiling of >200 *de novo*-designed macrocycles revealed how functional groups and substituents, stereochemistry and dynamic, intramolecular interactions in the 3D conformations are linked to physicochemical properties and permeability. Combined use of quantitative structure-permeability modelling and conformational analysis now provides a rational approach to design of cell-permeable, non-peptidic macrocycles with potential for oral administration.

2:10 Passive Membrane Permeability in Cyclic Peptides: New Rules for a New Chemical Space

Scott Lokey, Ph.D., Professor, Chemistry and Biochemistry, University of California, Santa Cruz

The prospect that macrocyclic peptides that lie well outside the Rule of 5 can have drug-like, passive cell permeability has stimulated much effort toward understanding the physical basis for the behavior of such outliers. I will discuss our latest results from a series of systematic studies using a variety of synthetic, biophysical, and analytical tools, designed to probe the specific structural and physicochemical constraints that govern ADME behavior in macrocycles in the MW~1000 range.

2:40 Computational and Physical Properties of Orally Bioavailable Cyclic Peptides

Alan M. Mathiowetz, Ph.D., Director, Pfizer Worldwide Medicinal Chemistry – Cardiovascular and Metabolic Diseases

An increasing number of orally bioavailable cyclic peptides have been discovered in recent years, providing us with an opportunity to identify the design principles for achieving improved permeability in this traditionally challenging physical property space. A variety of computational parameters and measured physical properties will be discussed, describing their relationship to permeability and other ADME properties – both across a broad dataset of compounds and for specific published orally bioavailable peptides.

3:10 Technologies Enabling Macrocycle Design

Sponsored by SCHRÖDINGER.

Dan Sindhikara, Ph.D., Senior Scientist, Schrödinger

Macrocycles can offer attractive properties such as defiance of Ro5 guidelines while posing new challenges due to their unique topology. Combining state-of-the-art modelling software with bleeding-edge macrocycle-specific technology, we are paving the way to rational macrocycle design. Our tools focus on our new high-speed, accurate macrocycle sampling algorithm able to rigorously sample macrocycles within seconds to minutes. Leveraging the macrocycle sampling protocol, we can now quickly do physics-based passive-permeability predictions, docking, and binding free energy calculations. Further we are developing technology to quickly generate virtual macrocycle libraries for screening containing millions of compounds or more.

3:40 Refreshment Break in the Exhibit Hall with Poster Viewing

4:30 Computer-Aided Macrocycle Design

Matthew Jacobson, Ph.D., Professor, Pharmaceutical Chemistry, University of California, San Francisco

I will discuss the central challenge in computational modeling of macrocycles—predicting the three-dimensional structure of the backbone—with applications to permeability prediction; structure-based or ligand-based design; and the creation of virtual libraries. Examples will include cyclic peptides, polyketides, and other classes of natural product and synthetic macrocycles.

5:00 From Haystack to Needle: Using Encoded Libraries at GSK

Christopher Phelps, Ph.D., Manager, Drug Design & Selection Boston, RD Platform Technology & Science, GSK

In 2005 scientists at Praecis Pharmaceuticals first realized the power of DNA encoded libraries with successful selections of triazine scaffolds against p38 kinase. A year later, the same team screened four targets from GSK, and the outcome of that collaboration was the acquisition of Praecis and the first integration of encoded library technology (ELT) into the hit ID engine of a major pharmaceutical company. This presentation will review some milestones of that journey and the technical advances in library chemistry, selection methods, and informatics that were enabled within GSK.

5:30 Breakout Discussions

In this session, attendees choose a specific roundtable discussion to join. Each group has a moderator to ensure focused conversations around key issues within the topic. The small group format allows participants to informally meet potential collaborators, share examples from their work and discuss ideas with peers. Check our website in February to see the full listing of breakout topics and moderators.

6:15 Close of Day

6:30 Dinner Short Courses*

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THURSDAY, APRIL 21

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Barry A. Morgan, Ph.D., Visiting Professor, Institute for Molecular Medicine, University of Texas Health Sciences

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» 8:30 PLENARY KEYNOTE PRESENTATION

Cell-Penetrating Miniproteins

Gregory L. Verdine, Ph.D., Professor, Departments of Stem Cell and Regenerative Biology, Chemistry and Chemical Biology, and Molecular and Cellular Biology, Harvard University

(Please see page 2 for details.)

9:30 Coffee Break in the Exhibit Hall with Poster Viewing

MACROCYCLIC SYNTHESIS AND SCREENING

10:10 Chairperson's Remarks

Dehua Pei, Ph.D., Professor, Department of Chemistry and Biochemistry, The Ohio State University

10:15 Synthesis and Screening of Vast Libraries of DNA-Encoded Macrocycles

Thomas Kodadek, Ph.D., Professor, Chemistry and Cancer Biology, The Scripps Research Institute, Scripps Florida

Macrocycles that mimic some of the favorable properties of natural products are of great interest as chemical probes and drug leads. As a potentially rich source of such compounds, we have created vast DNA-encoded combinatorial libraries of structurally complex macrocycles displayed on 10 µm beads. These libraries can be screened by incubation with fluorescently labeled target proteins and unlabeled competitor proteins and hits can be isolated using a flow cytometer. This system constitutes a powerful tool for the discovery of bioactive macrocycles as well as a method for assessing the relative merits of macrocycles and linear molecules as protein ligands.

10:45 Step-Wise Selection of Peptide Binders Using High-Density Peptide Arrays

Jigar Patel, Ph.D., Director, Technology Innovation, Roche NimbleGen Inc.

We will describe a step-wise selection method using L and D amino acids synthesized on High Density Peptide arrays using Streptavidin as a case example. We have identified various binding peptides, and have determined their co-crystal structures. All studied peptides were found to bind to the same biotin-binding pocket of streptavidin and pre-incubation of streptavidin with biotin completely abolishes any of the peptide binding. Discovery of multiple peptides in both linear and cyclic forms with different sequences bound to the biotin site suggests that these peptides can demonstrate a significant plasticity in creating specific contacts with the same target.

11:15 Moving Macrocyclic Research Forward: New Rules and Drug Discovery Application

Sponsored by ASINEX

Roman Kombarov, Ph.D., Head, Business Development, ASINEX Corporation

Over the past 6 years, we have synthesized over 30,000 macrocyclic compounds and optimized synthetic techniques with special focus on reaction types used for scaffold synthesis. This talk will relate lessons learned and stress two main directions in our macrocyclic research: the first is to refine a set of rules for cellular permeability and the second involves drug discovery application of macrocyclic chemistry with a special focus on the areas of oncology and anti-bacterial research.

11:45 Joining Chemistry and Biology to Make Macrocycles

James H. Naismith, Ph.D., Professor, Chemical Biology, St. Andrews University

I will report our progress on combining enzymes, some of which have re-engineered, from the patellamide and patellamide-like pathways with organic chemical synthesis. Our objective is access novel peptide/non-peptide hybrid macrocyclic compounds that would otherwise be very challenging to make. These compounds are being designed as novel inhibitor starting points as they can encode particular epitopes in a conformationally tuneable scaffold. I will also report work on combining solid phase synthesis with the enzymes.

12:15 Conformational Sampling of Macrocycles: Recent Progress

Sponsored by OpenEye Scientific

Paul Hawkins, Ph.D., Head, Scientific Solutions, OpenEye Scientific Software

Macrocyclic molecules have been shown to be orally bioavailable ligands for targets such as GPCRs and protein-protein interfaces. Greater exploitation of macrocycles in drug discovery has been stymied by a lack of computational methods to investigate their properties, including their conformational space. Here we present some recent work on conformational sampling of macrocycles that attempts to balance sampling near conformations likely to be relevant to biological activity with the time required for the calculation.

12:45 Sponsored Presentation *(Opportunity Available)*

1:30 Ice Cream Refreshment Break in the Exhibit Hall with Poster Awards

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CASE STUDIES: COMPOUNDS IN EARLY DEVELOPMENT

2:15 Chairperson's Remarks
Eric Marsault, Ph.D., Professor, Medicinal Chemistry and Pharmacology, University of Sherbrooke

2:20 Lorlatinib (PF-06463922), a Macrocyclic ALK/ROS1 Inhibitor for the Treatment of Resistance Mutations and Brain Metastasis
Ted W. Johnson, Ph.D., Senior Principal Scientist, Oncology Chemistry, Pfizer San Diego
PF-06463922, a novel macrocyclic inhibitor of ALK/ROS1 currently in Phase I/II clinical trials, demonstrated low nanomolar inhibitory activity against a panel of ALK kinase domain mutations with overlapping CNS activity to treat brain metastasis. Structure-based drug design, CNS drug design and efficacy data will be presented.

2:50 Cyclohexylgriselimycin: A Synthetic and New Anti-Tuberculosis Drug Candidate
Evelyne Fontaine, Ph.D., Laboratory Head, Infectious Diseases, Medicinal Chemistry, Sanofi
We present a case study in peptide chemistry: from a poorly drug-like parent compound, the natural cyclodepsipeptide Griselimycin discovered 50 years ago, we'll report how we solved the metabolic lability, improved the oral PK and balanced the antibacterial potency with lipophylicity and solubility. Total synthesis including SPPS and macrocyclisation was used to prepare more than 230 cyclodepsipeptides, and also 200G of cyclohexylgriselimycin. NMR 3D structure of Cyclohexylgriselimycin, RX-structure in complex with DnaN and MOA elucidation will be presented.

3:20 Refreshment Break

3:40 Macrocycle Design for PD1-PD1L and p53-MDM2
Alexander Dömling, Ph.D., Professor, Drug Design, University of Groningen
Protein protein interactions are a key target area for macrocycles due to their often difficult druggability by classical approaches such as small molecules. MDM2-p53 for examples comprise a well-structured interface with 700A2 buried interface while PD1-PD1L is very flat and featureless comprising 2000A2 buried interface. Here we report the design and synthesis of PD1-PD1L and p53-MDM2 directed macrocycles including their protein complexes. PD1-PD1L is a game changing target in immuno-oncology.

4:10 Orally Stable GI restricted Peptides for Inflammatory Bowel Diseases
Gregory Bourne, Ph.D., Senior Research Fellow, Chemistry, Protagonist Therapeutics
Inflammatory bowel disease (IBD) offers clinically validated targets for gut restricted drug development. Protagonist has applied its technology platform and expertise in peptide and medicinal chemistry to develop novel, potent, target specific and orally stable gut restricted peptides for $\alpha 4\beta 7$ integrin and IL23-receptor. These peptides have minimal /no systemic exposure, yet are active in preclinical IBD models. We will discuss strategies in developing these orally stable peptide antagonists for GI restricted diseases.

4:40 Macrocyclic Drug Candidates for Lung Diseases and Novel Antibiotics
Daniel Obrecht, Ph.D., CSO, Pharmaceutical Research, Polyphor Ltd.
We have established two complementary, fully proprietary macrocycle technologies that yield synthetically accessible compounds that are amenable to a rapid and efficient optimization process, and have a proven potential to provide innovative drug candidates for complex target classes. I present two case studies: POL6014 in Phase I development for cystic fibrosis and other rare lung diseases, is a highly potent and selective macrocyclic inhibitor of human neutrophil elastase (HNE) and POL7080, a novel breakthrough antibiotic against Gram-negative bacteria.

5:10 Close of Conference

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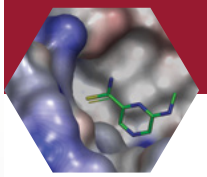

April 20-21, 2016 *11th Annual*

Fragment-Based Drug Discovery

From Hits to Leads and Lessons Learned

WEDNESDAY, APRIL 20

12:30 pm Registration

FRAGMENT CASE STUDIES

1:30 Chairperson's Remarks
Daniel A. Erlanson, Ph.D., Co-Founder, Carmot Therapeutics, Inc.

1:40 Fragment-Screening Antibacterial Targets Using Surface Plasmon Resonance Methods
Adam Renslo, Ph.D., Associate Professor, Department of Pharmaceutical Chemistry, University of California San Francisco

The emergence of expanded-spectrum beta-lactamases (ESBLs) and carbapenemases in Gm-negative pathogens threatens the future effectiveness of important classes of antibiotics. Our group has been applying fragment screening and structure-guided medicinal chemistry to identify novel, non-covalent inhibitors of clinically relevant beta-lactamases. In this talk we will describe computational and SPR methods for fragment screening of ESBLs and carbapenemases.

2:10 Fragment-Based Discovery of Novel MAP4K4 Inhibitors: Tales of Two Fragments
Huifen Chen, Ph.D., Senior Scientist, Discovery Chemistry, Genentech

MAP4K4 is a serine/threonine protein kinase implicated in the regulation of many key biological processes including cell migration, adhesion, invasion and neuronal degeneration. To study its function in various disease contexts, we embarked on an endeavor to identify potent and selective MAP4K4 inhibitors using fragment-based drug discovery approach. Herein I will present the identification and optimization of two fragments and the distinct profiles of two classes of highly potent MAP4K4 inhibitors. One of the classes demonstrated excellent potency and selectivity, and was further optimized to yield a novel biological tool compound (GNE-495) with efficacy in retinal angiogenesis model.

2:40 Overcoming Platform Biases in Fragment Screening
Mary Harner, Ph.D., Research Investigator, Mechanistic Biochemistry, Bristol-Myers Squibb

Fragment screening is now widely accepted as a complementary screening paradigm to HTS for identifying novel chemical moieties leading to target modulation. The chemical simplicity of fragments typically results in the initial positives of a screen having low potency; activities are often near mM concentrations. To detect these weaker compounds, biophysical assays have become the norm, with the 2 most widely used techniques being SPR and NMR. A comparison of various methods for fragment identification reveals that orthogonal methods for fragment detection frequently yield surprisingly low overlap of resultant hit lists. This presentation will describe our efforts to understand this apparent disconnect between assays, and suggest ways to focus subsequent resources on the most promising compounds.

3:10 Sense and Sensitivity: Screening and Characterisation of Fragment Binders Against WT GPCR Drug Targets using Highly Sensitive Biacore S200

Sponsored by

Paul Belcher, Ph.D., Functional Leader, Biacore™ GE Healthcare

G protein coupled receptors (GPCRs) are the targets of 30-40% of all approved drugs. However many approaches successfully applied to drug discovery for soluble protein targets have made a limited impact on GPCR's due to challenges in obtaining pure, active, membrane free receptors for structural and biophysical investigation. In recent years biophysical techniques in combination with improvements in protein engineering and handling have advanced to face the challenges of studying membrane bound GPCR's with SPR in particular becoming increasingly utilized in the study of GPCR's as the sensitivity of the detections systems has improved. Here we present the results from a collaboration with the Hopkins-Navratilova lab at the University of Dundee highlighting the importance of instrument sensitivity characterizing GPCR's with the Biacore™ S200.

3:40 Refreshment Break in the Exhibit Hall with Poster Viewing

4:30 Rapid Elaboration of Fragments into Leads (REFIL)
Martin Scanlon, Ph.D., Associate Professor, Medicinal Chemistry, Monash Institute for Pharmaceutical Sciences

Fragments that emerge from primary screens often have low affinities with KD values in the high μM to mM ranges. Therefore a significant challenge for FBLD is to develop these initial fragments into more potent ligands. In this presentation I will describe a strategy that we have implemented to enable weakly-binding fragment hits to be elaborated into more potent ligands.

5:00 Fragment-Based Discovery of Chemical Probes for BRD9
Jark Böttcher, Ph.D., Distinguished Scientist, Medicinal Chemistry, Boehringer Ingelheim RCV GmbH & Co KG

Three parallel biophysical methods were used to screen our proprietary fragment library against the BRD9 bromodomain (differential scanning fluorimetry (DSF), surface plasmon resonance (SPR) and microscale thermophoresis (MST). Structure guided chemical optimization of the initial hits resulted in the chemical probes, that should prove useful in further probing BRD9 bromodomain biology in both *in vitro* and *in vivo* settings.

5:30 Breakout Discussions

In this session, attendees choose a specific roundtable discussion to join. Each group has a moderator to ensure focused conversations around key issues within the topic. The small group format allows participants to informally meet potential collaborators, share examples from their work and discuss ideas with peers. Check our website in February to see the full listing of breakout topics and moderators.

6:15 Close of Day

6:30 Dinner Short Courses*

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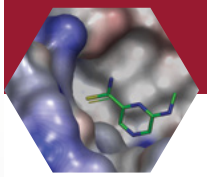

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» 8:30 PLENARY KEYNOTE PRESENTATION

Cell-Penetrating Miniproteins

Gregory L. Verdine, Ph.D., Professor, Departments of Stem Cell and Regenerative Biology, Chemistry and Chemical Biology, and Molecular and Cellular Biology, Harvard University

(Please see page 2 for details.)

9:30 Coffee Break in the Exhibit Hall with Poster Viewing

BEST PRACTICES FOR FRAGMENT-BASED DRUG DESIGN AND SCREENING

10:10 Chairperson's Remarks

Derek Cole, Ph.D., Director, Chemistry, Takeda

» 10:15 FEATURED PRESENTATION: Peptidyl Prolyl Isomerase and Fragment Strategies: The Route from Millimolar to Nanomolar

Matthias Frech, Ph.D., Director, Molecular Interactions & Biophysics, EMD Serono

The substrate binding site of peptidyl prolyl isomerases is in a difficult location for identifying inhibitory molecules against. Besides high throughput screening and computational methods, we set up a fragment approach to identify additional hit matter. Low affinity fragments were identified as starting points. We used different optimization strategies so the initial hit matter could be improved to chemical scaffolds with high affinity and activity.

10:45 FBDD Infrastructure at Takeda

Xiaolun Wang, Ph.D., Senior Scientist, Medicinal Chemistry, Takeda San Diego

Fragment Based Drug Discovery (FBDD) has established itself as a viable and productive approach to lead generation and the optimization of novel small molecule drugs. This presentation will describe how Takeda built its FBDD capabilities including the design and characterization of chemically diverse fragment libraries, the implement of different biophysical screening technologies, and the demonstration of our FBDD effort with a case study.

11:15 Combining Biophysical Methods to Improve the Robustness of FBLD

Ben Davis, Ph.D., Research Fellow, Biology, Vernalis Research

A wide range of techniques is used to detect and characterise the low affinity interactions which typify FBLD. Each of these techniques has distinctive sensitivities and requirements, and this can lead to variations in the output from different assays. However, careful examination and combination of these results can improve the robustness and quality of an FBLD campaign. I will discuss a variety of recent examples of fragment screening and validation to illustrate this approach.

11:45 pm EXPERT PANEL DISCUSSION: Practical Aspects of Fragment Based Drug Discovery

Moderator: Derek Cole, Ph.D., Director, Chemistry, Takeda

Topics will cover:

- Designing and building fragment libraries
- Screening techniques. Success rates
- Strategies for hit selection
- Fragment optimization

12:30 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:30 Ice Cream Refreshment Break in the Exhibit Hall with Poster Awards

NEW APPROACHES

2:15 Chairperson's Remarks

Matthew Marx, Ph.D., Senior Director, Head of Drug Discovery, Mirati Therapeutics

2:20 Protein-Observed Fluorine NMR for Fragment Screening

William Pomerantz, Ph.D., Assistant Professor, Department of Chemistry, University of Minnesota

To facilitate early lead discovery, we describe a rapid, protein-based 19F NMR method for fragment screening. We report on testing the sensitivity, accuracy, and speed of this method from a small molecule screen with the protein interaction domain of CBP, KIX. We have extended our method to screening against bromodomains Brd4, BrdT and BPTF. The speed, ease of interpretation,and low concentration of protein needed for binding experiments affords a new method to discover leads in fragment screens.

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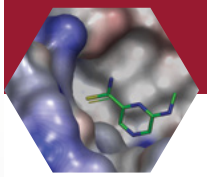

April 20-21, 2016 *11th Annual*

Fragment-Based Drug Discovery

From Hits to Leads and Lessons Learned

2:50 A Fully Automated Pipeline for Fragment-Based Screening through Macromolecular Crystallography

Jose A. Marquez, Ph.D., Team Leader, Head of Crystallization Facility, Grenoble Outstation, European Molecular Biology Laboratory (EMBL) Grenoble Outstation

Macromolecular crystallography is a powerful tool in drug design and in particular in the context of fragment-based approaches. However, manual crystal handling makes it a manpower intensive application limiting the size of the libraries that can be analyzed as compared to other biophysical approaches. We present the fully automated system we have developed for crystal soaking, mounting and cryocooling (CrystalDirect), which is currently in operation at the High Throughput Crystallization laboratory of the EMBL Grenoble outstation.

3:20 Refreshment Break

3:40 A New Approach for Quality-Control Screening of Fragment Libraries

Yutao Jiang, MS, Senior Research Associate, Medicinal Chemistry, Genentech

We introduce a novel high throughput LCMS/UV/CAD/CLND system by increasing both the quantitation accuracy and the range of compounds amenable to testing, in particular, low molecular weight "fragment" compounds. Our results show that the addition of CAD and CLND to LCMS/UV is more reliable for concentration determination for a wider range of compounds than either detector alone without significantly increasing run time per sample.

4:10 X-Ray and Activity Fragment Screening across Subfamilies of Lysine Demethylases and Ribosomal Hydroxylases for Active-Site Characterization

Radek Nowak, Ph.D., Research Associate, Structural Genomics Consortium, University of Oxford

We combined X-ray based fragment screening with inhibitor data for several subfamilies of human oxoglutarate dependent oxygenases to prioritize fragments for further lead development. We developed an X-ray fragment screening platform with JARID1B and JMJD2D and obtained crystal structures for selected fragments showing diverse active site metal binding modes. The fragments occupied different parts of the active site pockets including putative allosteric sites, non-metal binding active sites and metal chelator sites. These starting points can be used to rationalize ligand binding hotspots for various subfamilies for further development of selective chemical tools for this epigenetic enzyme family.

4:40 Fragment-Based Drug Discovery with Dual-Display DNA-Encoded Chemical Libraries

Joerg Scheuermann, Ph.D., Senior Scientist, Chemistry and Applied Biosciences, ETH Zurich

We describe our development of DNA-encoded chemical libraries (DECLs), which are increasingly considered for hit identification. While single-pharmacophore DECLs typically display drug-like compounds on one DNA strand, dual-pharmacophore feature the simultaneous display of fragments on both DNA strands, which allows for the identification of synergistically binding pairs of fragments. We will report on the use of both types of DECLs for the identification of hits against "difficult" protein targets.

5:10 Close of Conference

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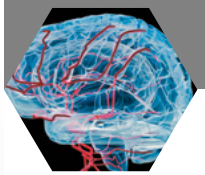

Friday
April 22, 2016

Inaugural Symposium

Brain Penetrant Inhibitors

8:00 am Registration and Morning Coffee

UNDERSTANDING THE BBB AND ITS EFFECTS ON SMALL MOLECULES

8:30 Chairperson's Opening Remarks
Snahel Patel, Scientific Manager, Discovery Chemistry, Genentech, Inc.

» 8:40 FEATURED PRESENTATION: Small Molecule Permeability across an Intact BBB: Necessary for Effective Treatment of Brain Tumors?
William F. Elmquist, Pharm.D., Ph.D., Professor and Head, Department of Pharmaceutics; Director, Brain Barriers Research Center, University of Minnesota
This talk will focus on the issues surrounding effective drug delivery to the invasive cells in brain tumors, both primary and metastatic. Many of the newer, molecularly-targeted anti-cancer agents have impressive inhibitory action against various signaling pathways that drive tumor growth. However, they have been ineffective in treating brain tumors. Molecularly-targeted signal transduction inhibitors are often substrates for active efflux transporters at the BBB, and this delivery-limiting mechanism must be overcome before these inhibitors can be adequately tested in clinical trials.

9:25 Predicting P-Glycoprotein Substrates Using Kriging
Istvan Enyedy, Ph.D., Senior Scientist, Drug Discovery, Biogen
P-glycoprotein is one of most important transporters involved in stopping compounds from penetrating the blood-brain barrier. Thus, predicting P-glycoprotein mediated efflux is important in the development of therapeutic agents targeting the central nervous system. Data obtained from testing more than 800 in house compounds in MDR1-MDCK permeability assay was used to build a prediction model using Kriging. The performance of full and local Kriging models and the nearest neighbor approach will be presented.

9:55 Coffee Break in the Exhibit Hall with Poster Viewing

DISCOVERY AND DEVELOPMENT OF BRAIN PENETRANT INHIBITORS FOR CANCER

10:35 NKTR-102 Efficacy Versus Irinotecan in a Mouse Model of Brain Metastases of Breast Cancer
Paul Lockman, Ph.D., Professor and Douglas D. Glover Endowed Chair, Department of Basic Pharmaceutical Sciences, School of Pharmacy, West Virginia University Health Sciences Center
Brain metastases are an increasing problem in women with invasive breast cancer. Strategies designed to treat brain metastases of breast cancer, particularly chemotherapeutics such as irinotecan, demonstrate limited efficacy. Conventional irinotecan distributes poorly to brain metastases; therefore, NKTR-102, a PEGylated irinotecan conjugate should enhance irinotecan and its active metabolite SN38 exposure in brain metastases leading to brain tumor cytotoxicity.

11:05 PF-06463922, an ALK/ROS1 Inhibitor, Overcomes Resistance to First and Second Generation ALK Inhibitors in Preclinical Models
Ted W. Johnson, Ph.D., Research Fellow, Medicinal Chemistry, Pfizer Oncology
PF-06463922, a novel macrocyclic inhibitor of ALK/ROS1, demonstrated low nanomolar inhibitory activity against a panel of ALK kinase domain mutants representing all of the patient crizotinib resistant mutations reported to date. Successful optimization of molecular weight and lipophilic efficiency leveraging structure-based drug design techniques led to ligands with overlapping broad spectrum potency, low transporter efflux, and brain penetration. PF-06463922 is currently in Phase 1/2 clinical trials.

11:35 Discovery and Evaluation of Clinical Candidate AZD3759, a Potent, Oral Active, Central Nervous System-Penetrant, Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor
Xiaolin Zhang, Ph.D., Vice President and Head, Innovation Center China, AstraZeneca
Recent reports suggest that an increasing number of patients with lung cancer, especially those with activating mutations of the epidermal growth factor receptor (EGFR), also present with brain metastases and leptomeningeal metastases. These patients have poor prognosis as there are no approved drugs for these indications. Available agents have poor efficacy for these patients even at well above their standard dose. Herein, we report the discovery of (4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl (2R)-2,4-dimethylpiperazine-1-carboxylate 1m (AZD3759), an investigational drug currently in Phase 1 clinical trial, which has excellent central nervous system penetration and which induces profound regression of brain metastases in a mouse model.

12:05 pm Sponsored Presentation *(Opportunity Available)*

12:20 Enjoy Lunch on Your Own

DISCOVERY AND DEVELOPMENT OF BRAIN PENETRANT INHIBITORS FOR NEURODEGENERATIVE DISORDERS

1:35 Chairperson's Remarks
William M. Pardridge, M.D., Founder and CSO, ArmaGen

1:40 Blood-Brain Barrier Endogenous Transporters as Therapeutic Targets: New Model for Small Molecule CNS Drug Discovery
William M. Pardridge, M.D., Founder and CSO, ArmaGen
The blood-brain barrier (BBB) limits the uptake of most drugs by brain, and the traditional approach to the BBB problem is the use of medicinal chemistry to increase drug lipid solubility, and increase lipid-mediated transport across the BBB. This presentation advocates a new model to CNS drug discovery of BBB-penetrating small molecules, whereby drug candidates are screened for carrier-mediated transport (CMT) across the BBB.

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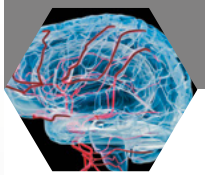

Friday
April 22, 2016

Inaugural Symposium

Brain Penetrant Inhibitors

2:10 Rational Design of Exquisitely Selective Inhibitors of the GSK3 Kinase Isoforms for the Treatment of Psychiatric and Neurological Disorders

Florence Wagner, Ph.D., Senior Group Leader, Medicinal Chemistry, Stanley Center for Psychiatric Research, The Broad Institute

We report the discovery of the first isoform selective inhibitors of GSK3β or GSK3β. Exploiting a single amino acid difference within the ATP binding domain, we have developed novel, potent, brain penetrant inhibitors with unprecedented kinome selectivity. These isoform selective inhibitors of GSK3β or GSK3β successfully decouple effects on β-catenin, and therefore mitigates oncogenic concerns. These compounds will help to delineate the biological function of each isoforms and for their potential use in a variety of disorders including psychiatric and neurological disorders.

2:40 Lead Optimization of Pyrazole Inhibitors of Dual Leucine Zipper Kinase (DLK, MAP3K12)

Snahel Patel, Senior Scientific Manager, Discovery Chemistry, Genentech, Inc.

Neurodegenerative diseases such as Alzheimer's and Parkinson's represent significant unmet medical needs with no therapies able to slow the course of disease. Dual Leucine Zipper Kinase (DLK) is a neuronal specific upstream regulator of the JNK pathway that was recently identified as a central regulator of degeneration in multiple contexts. We have progressed lead optimization of a pyrazole scaffold towards a desirable profile for a small molecule therapeutic and demonstrating activity in neurodegeneration models.

3:10 Refreshment Break in the Exhibit Hall with Poster Viewing

3:40 Discovery, Synthesis, and Characterization of an Orally Bioavailable, Brain Penetrant Inhibitor of Mixed Lineage Kinase 3

Val S. Goodfellow, Ph.D., CEO, Califia Bio, Inc.

Previously, inhibitors of mixed lineage kinase 3 (MLK3) showed great promise for treatment of Parkinson's disease in pre-clinical models, but interest in this area halted when a non-selective inhibitor (CEP-1347) failed in Phase II clinical trials. We have investigated the poor target specificity and poor ability of CEP-1347 to penetrate the blood-brain barrier and have developed new compounds with much higher selectivity for MLK3 and much improved ability to achieve high concentrations in the brain.

4:10 Discovery and Preclinical Profiling of LRRK2 Kinase Inhibitors for the Treatment of Parkinson's Disease

Paul Galatsis, Ph.D., Senior Principal Scientist, Worldwide Medicinal Chemistry, Pfizer

We will communicate our strategy for designing brain penetrant kinase inhibitors and share medicinal chemistry insights into targeting the key cause of familial Parkinson's disease, LRRK2. We will provide examples of compounds that have *in vivo* activity at less than 1 mg/kg oral dosing.

4:40 Close of Symposium

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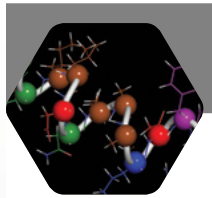

Friday
April 22, 2016

Inaugural Symposium

Biophysical Approaches for Drug Discovery

8:00 am Registration and Morning Coffee

BIOSENSOR-BASED APPROACHES

8:30 Chairperson's Opening Remarks
Chris Smith, Ph.D., Director, Medicinal Chemistry, COI Pharmaceuticals

» **8:40 FEATURED PRESENTATION: Application of Label-free Biosensors in Drug Discovery: The Past, Present and Future**
John Quinn, Ph.D., Director, Structural and Biophysical Chemistry, Genentech
Label-free biosensing enables a diverse range of information rich functional assays informing the entire drug discovery-development process. A low barrier to ownership and seemingly intuitive operation have contributed to the success of the technology. However label-free biosensing is not a "turn-key" technology as practitioners must optimize methodologies and data analysis protocols for each affinity system of interest. What are the components of a successful label-free biosensing group? What are the current capabilities and limits? What does the future hold? To address these questions we provide a brief historical overview of the technology and then review high impact applications with emphasis on practical strengths and limitations. We conclude with perspectives on the future direction of the technology.

9:25 Commitment to Covalency: Using SPR to Understand and Evaluate the Potency of Highly Optimized Irreversible Inhibitors
Phillip Schwartz, Ph.D., Senior Scientist, Biophysical Chemistry, Takeda California
Kinetic analysis of potent, highly optimized irreversible inhibitors is a complex prospect. This work presents an approach for the understanding and evaluation of optimized irreversible inhibitor potency and identifies the key parameters that should be used to characterize them. The practical considerations that arise from these inhibitors are discussed. Among these are methods to assess potency, SAR optimization strategies and the impact on pharmacokinetics/pharmacodynamics.

9:55 Coffee Break in the Exhibit Hall with Poster Viewing

INTEGRATING BIOPHYSICAL APPROACHES

10:35 Nuclear Magnetic Resonance (NMR) Spectroscopy in Pharma Today: We've Got an App for That
Mary Harner, Ph.D., Research Investigator, Mechanistic Biochemistry, Bristol Myers-Squibb
NMR spectroscopy has been demonstrated as a powerful tool in drug discovery for structure determination and the detection of ligand binding events. The flexibility of NMR can be harnessed to address challenging questions and systems by finding the proper balance of its applications. Approaches will be described to accelerate data acquisition and analysis to enable NMR to remain an essential tool among biophysical technologies.

11:05 Medium to High-Throughput Methods for Biophysical Profiling of Compounds during Drug Discovery
Rumin Zhang, Ph.D., Senior Principal Scientist, in vitro Pharmacology, Merck Research Laboratories
We share our best practices in various biophysical profiling methods including automated stopped flow, global progress curve analysis, biosensors, mass spectrometry and thermal shift assays. These methods cover up to nine orders of kinetic time frame from milliseconds to days. They also cover nine orders of magnitude in thermodynamic potency measurement. The audience should gain both, the breadth and depth of our biophysical profiling methods, as well as valuable best practices employed in our labs.

11:35 Panel Discussion: Finding Hits without HTS
Moderator: Chris Smith, Ph.D., Director, Medicinal Chemistry, COI Pharmaceuticals
An HTS screen continues to dominate as the preferred method of choice to find hits for novel small molecule drug discovery projects by pharma and venture backed biotechs. The panel will lead a discussion to examine alternative approaches to HTS for hit generation. We will discuss Fragment, Encoded and Virtual/Focused Library Screening. Check the website for specific discussion points.

12:05 pm Sponsored Presentation *(Opportunity Available)*

12:20 Enjoy Lunch on Your Own

NEW APPLICATIONS OF BIOPHYSICAL METHODS

1:35 Chairperson's Remarks
Yongchao Su, Ph.D., Senior Scientist, Pharmaceutical Sciences & Clinical Supply, Merck Research Laboratories

1:40 The Structure-Function Relationship of Membrane Proteins using Solid-State NMR Spectroscopy
Yongchao Su, Ph.D., Senior Scientist, Pharmaceutical Sciences & Clinical Supply, Merck Research Laboratories
I describe using solid state NMR (ssNMR) to investigate the atomic-level structures of insoluble and pharmaceutically important bio-macromolecules, and correlate to their biological functions. A few interesting membrane-active proteins, peptides and drug molecules, including cell-penetrating peptides (CPPs), antimicrobial peptides (AMPs), antimicrobial drugs (AMDs), and ion channels (gating helix of K+ channel, transmembrane 1H channel of influenza M2 protein, voltage-dependent anion channel), will be included.

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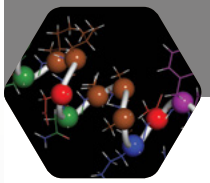

Friday
April 22, 2016

Inaugural Symposium

Biophysical Approaches for Drug Discovery

2:10 GPCR Studies with Nuclear Magnetic Resonance: Challenges and Advances

Matthew Eddy, Ph.D., Postdoctoral Fellow, Ray Stevens Laboratory, The Bridge Institute, University of Southern California

To understand the function of G Protein-Coupled Receptors (GPCRs), deeper insight is needed into the role of conformational dynamics in molecular recognition and activation. Nuclear magnetic resonance (NMR) is uniquely suited to deliver information about dynamics at atomic resolution and over a large range of time scales. However, application of NMR to study GPCRs has so far been very challenging. I will present advances in the field that address some of these challenges and reveal initial insights into mechanisms of GPCR activation.

2:40 Liposome-Protein Binding Assays based on Bio-Layer Interferometry

Jakob Wallner, Ph.D., Research Scientist, Department of Biotechnology, University of Natural Resources and Life Sciences, Vienna

Due to the attractiveness of biosensor based methods, there is a growing need for more efficient, more simple and reliable methods for the intended purpose. Based on Fortebio's BLI platform we are establishing different assays to study protein/liposome interactions in more detail. The selected examples address assay development for the liposome approach, the use of different sensor types and individual protein aspects. Individual assays emphasis the binding kinetics of liposomes with different protein classes such as enzymes, antibodies and hormones.

3:10 Refreshment Break in the Exhibit Hall with Poster Viewing

3:40 A Mass-Spectrometry platform for Discovery and Characterization of Modulators of Histone Post-Translational Modifications

Andrew Andrews, Ph.D., Assistant Professor, Cancer Genetics, Fox Chase Cancer Center

Previously, little was known about the residue specificity of histone modifying enzymes because standard assays either quantitate or determine the location of modification. We have developed a high/medium throughput label-free quantitative mass spectrometry assay that can provide both of these pieces of data, from any source. Furthermore, we demonstrate the ability of small molecules to alter the selectivity of these enzymes, suggesting the ability to pharmacology alter histone modification patterns and disease outcomes.

4:10 Drug Discovery at the Single Molecule Level

Tim Kaminski, Ph.D., Postdoctoral Fellow, Biophysics/Discovery Sciences, AstraZeneca

I present a toolbox we are developing to advance single molecule microscopy from a method primarily used in academia into a versatile tool for drug discovery. We aim to address shortcomings of established biophysical methods such as tight binding limit, working with membrane proteins and higher throughput. Additionally we are able to extract kinetic profiling of inhibition reactions in solution by observing the association and dissociation of thousands of molecules in parallel with a surface-based single molecule platform.

4:40 Close of Symposium

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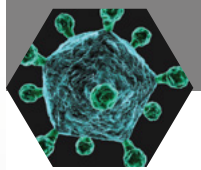

Friday
April 22, 2016

Inaugural Symposium

Antivirals: Small Molecule Inhibitors of Viral Targets

FRIDAY, APRIL 22

8:00 am Registration and Morning Coffee

HEPATITIS B VIRUS (HBV) AND RESPIRATORY SYNCYTIAL VIRUS (RSV)

8:30 Chairperson's Opening Remarks
David Smith, Ph.D., Vice President, Global Research and Development Leader, Hepatitis, Alios BioPharma, Inc., a Janssen Pharmaceutical Company of Johnson & Johnson

» **8:40 FEATURED PRESENTATION: Overview of Hepatitis B Virus Infection and Medical Landscape**
Robert Gish, M.D., President, Robert G. Gish Consultants, LLC
This presentation will cover the hepatitis B life cycle, as a virus and in humans. The epidemiology of infection will also be presented. Promising future treatments and challenges will be highlighted.

9:25 Development of Combination Therapies for HBV
Michael J. Sofia, Ph.D., CSO, Arbutus Biopharma Inc.
Developing a cure for HBV is hindered by the ability of the virus to control and suppress the host immune response to infection and a reservoir of viral cccDNA. A therapeutic regimen that simultaneously controls viral replication, reactivates the host immune response and addresses the viral reservoir by combining drugs with different mechanisms of action has the potential to deliver an HBV cure. This presentation addresses the concept of combination therapy as a strategy for delivering a cure for HBV infection.

9:55 Coffee Break in the Exhibit Hall with Poster Viewing

10:35 Nucleic Acid Polymers: Antiviral Mechanisms and Application in the Treatment of Chronic HBV and HBV / HDV Infection
Andrew Vaillant, Ph.D., CSO, Replicor Inc.
Nucleic acid polymers (NAPs) are a newly emerging antiviral technology for the treatment of chronic HBV infection and HBV / HDV co-infection. NAPs have the unique ability to clear HBsAg from the blood of human patients, a critical step in achieving a functional cure in HBV and HBV / HDV infection. Replicor will present its current mechanistic data underlying the basis for this unique antiviral effect of NAPs as well as updated clinical data showing Replicor's progress in using NAP-based combination therapy in patients with chronic HBV infection and HBV / HDV co-infection towards achieving functional cure for these infections.

11:05 RSV Therapeutics: Drug Design and Clinical Development
Jerome Deval, Ph.D., Scientific Director, Biochemistry, Alios BioPharma
Matthew W. McClure, M.D., Senior Medical Director, Alios BioPharma, Inc., a Janssen Pharmaceutical Company of J&J
Respiratory syncytial virus (RSV) is a seasonal virus that causes serious morbidity and mortality, yet no effective vaccine or treatment exists. The drug development paradigm, including medicinal chemistry and biochemical approaches, that led to the discovery and selection of the RSV therapeutic ALS-008176 will be discussed. The regulatory and clinical challenges in developing a drug targeting RSV, particularly in an infant population, will then be highlighted.

11:35 Discovery of a Potent and Orally Bioavailable Fusion Inhibitor of Respiratory Syncytial Virus
Sandrine Vendeville, Pharm.D., Ph.D., Senior Principal Scientist, Medicinal Chemistry, Janssen Infectious Diseases (Johnson & Johnson), Belgium
Optimization of a benzimidazole-based chemotype led to a new series of potent and orally bioavailable inhibitors of the fusion protein of RSV (Respiratory syncytial virus), a clinically validated target. This talk will be the first disclosure of the medchem optimization strategy, leading to the selection of JNJ-63718678, a picomolar inhibitor, having demonstrated good efficacy and tolerability in a human challenge study upon oral QD dosing. New insights on the mechanism of action and binding of this class of inhibitors will also be presented.

12:05 pm Sponsored Presentation *(Opportunity Available)*

12:20 Enjoy Lunch on Your Own

TARGETING THE HOST

1:35 Chairperson's Remarks
Michael J. Sofia, Ph.D., CSO, Arbutus Biopharma Inc.

1:40 Exploiting Apoptosis to Control Intracellular Infectious Agents: Development of Birinapant
C. Glenn Begley, Ph.D., CSO, TetraLogic Pharmaceuticals
Avoidance of cell death is important in both infectious diseases and cancer, where the Inhibitor of Apoptosis (or IAP) proteins are key. The endogenous inhibitor of IAPs is SMAC, and birinapant is a SMAC-mimetic currently in phase 2 oncology trials. In a mouse model of hepatitis B virus (HBV), birinapant caused loss of HBV-DNA, loss of HBsAg, appearance of anti-HBsAg antibodies, and cooperated with the anti-viral entecavir. Birinapant will now be studied in HBV patients.

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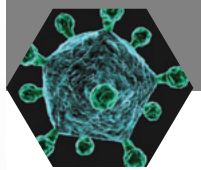

Friday
April 22, 2016

Inaugural Symposium

Antivirals: Small Molecule Inhibitors of Viral Targets

2:10 CPI-431-32, a Novel Cyclophilin Inhibitor for the Treatment of HBV

Robert T. Foster, Pharm.D., Ph.D., CEO, Ciclofilin Pharmaceuticals Inc.

Cyclophilins are host proteins that play critical roles in the life cycles of HBV and other viruses. CPI-431-32 is a synthetic derivative of cyclosporin A that potently inhibits cyclophilins and blocks multiple HBV activities *in vitro*: cellular entry, DNA replication, HBeAg and HBsAg production, and generation of cccDNA. Oral administration of CPI-431-32 to HBV transgenic mice reduces HBV replication. CPI-431-32 also demonstrates anti-fibrotic activity in a NASH model. Investigations are underway to further characterize mechanisms of action.

2:40 CMX157, a Novel, Liver-Targeted, Tenofovir Prodrug, for the Treatment of Chronic HBV Infection

John Sullivan-Bólyai, M.D., CMO, ContraVir Pharmaceuticals Inc.

CMX157 is a novel, liver-targeted, lipid conjugate prodrug of tenofovir (TFV) designed to utilize natural lipid uptake pathways to achieve high hepatocellular levels of the active antiviral. Greater than 60 fold potency vs. TFV, high plasma stability and high first-pass liver extraction are expected to result in low clinical doses, anchoring single pill antiviral combinations, decreasing circulating TFV and off-target TFV toxicities, particularly to bone and kidneys, compared to the currently licensed TFV prodrug.

3:10 Refreshment Break in the Exhibit Hall with Poster Viewing

3:40 Host-Based Serine Protease Inhibitors as an Emerging Treatment against Influenza

Eric Marsault, Ph.D., Professor, Medicinal Chemistry and Pharmacology, University of Sherbrooke

Influenza is a leading cause of hospitalization and death, and occasionally the source of pandemics. Besides vaccination, current treatments target viral proteins and are associated with increasing resistance. Proteolytic cleavage of the virus hemagglutinin by host cell proteases is a pivotal early step of infectivity. We present herein potent and selective inhibitors of type 2 transmembrane serine proteases. Their efficacy and selectivity *in vitro* their ability to reduce virus replication of H1 and H3 subtypes in human epithelial respiratory cells (Calu-3) as well as their efficacy *in vivo* will be presented.

4:10 Broad-Spectrum Antiviral Agent: SB 9200 - a Potent, Novel Nucleotide Compound that Activates and Induces Intracellular Viral Sensors

Radhakrishnan P. Iyer, Ph.D., CSO, Spring Bank Pharmaceuticals

Compounds that activate pathogen recognition receptors (PRRs) such as RIG-I, NOD2, STING etc., are of immense interest for the development of new generation antiviral agents. We have discovered SB 9200 as an oral broad-spectrum antiviral that activates RIG-I and NOD2 thereby causing the induction of expression of intracellular Interferons and ISGs. SB 9200 is being advanced into Phase II clinical trials against HBV, and RSV following successful completion of Phase I clinical trials in HCV-infected patients.

4:40 Close of Symposium

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Applying Pharmacology to New Drug Discovery

The System-independent quantification of molecular drug properties for prediction of therapeutic utility

Over the past 6 six years, the primary cause of new drug candidate failures (50%) has been failure of therapeutic efficacy. Put another way, drug discovery programs do everything right, get the defined candidate molecule, only to have it fail in therapeutic trials. Among the most prevalent reasons proposed for this shortcoming is the lack of translation of *in vitro* and recombinant drug activity to therapeutic *in vivo* whole systems. Drug activity in complete systems can be characterized with the application of pharmacological principles which translate drug behaviors in various organs with molecular scales of affinity and efficacy.

Pharmacological techniques are unique in that they can convert descriptive data (what we see, potency, activity in a given system) to predictive data (molecular scales of activity that can be used to predict activity in all systems including the therapeutic one, i.e. affinity, efficacy). The predicted outcome of this process is a far lower failure rate as molecules are progressed toward clinical testing.

Instructor: *Terry Kenakin presently is a Professor of Pharmacology in the Department of Pharmacology, University of North Carolina School of Medicine. The course is taught from the perspective of industrial drug discovery; Dr. Kenakin has worked in drug industry for 32 years (7 at Burroughs-Wellcome, RTP, NC and 25 at GlaxoSmithKline, RTP. NC). He is Editor-in-Chief of the Journal of Receptors and Signal Transduction and Co-Editor-in-Chief of Current Opinion in Pharmacology and is on numerous journal Editorial Boards. In addition, he has authored over 200 peer reviewed papers and reviews and has written 10 books on Pharmacology.*

Course Material: Summary sheets, exercises with answers, relevant papers are included as well as a pdf of all slides. The course is based on the book A Pharmacology Primer: Techniques for More Effective and Strategic Drug Discovery. 4th Edition, Elsevier/Academic Press, 2014.

Please visit **DrugDiscoveryChemistry.com** for more information

This course will describe pharmacological principles and procedures to quantify affinity, efficacy, biased signaling and allostery to better screen for new drugs and characterize drug candidates in lead optimization assays.

1. **Assay Formats/Experimental Design**
   a. Binding
   b. Functional Assays
   c. Null Method Assays
2. **Agonism**
   a. Agonist Affinity/Efficacy
   b. Black/Leff Operational model
3. **Biased Signaling (Agonism)**
   a. Mechanism of Biased Signaling
   b. Quantifying Biased Agonism
   c. Therapeutic application(s)
4. **Orthosteric Antagonism (I)**
   a. Competitive
   b. Non-Competitive/Irreversible
5. **Orthosteric Antagonism (II)**
   a. Partial Agonism
   b. Inverse Agonism
6. **Allosteric Modulation (I)**
   a. Functional Allosteric Model
   b. Negative Allosteric Modulators (NAMs)
7. **Allosteric Modulation (II)**
   a. Positive Allosteric Modulators (PAMs)
   b. Allosteric Agonism
8. **Drug-Receptor Kinetics**
   a. Measuring Target Coverage
   b. Allosteric Proof-of-Concept
   c. Application of Real-Time Kinetics
9. **Drug Screening**
   a. Design of Screening Assays
   b. Screening for Allosteric Modulators

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Cambridge Healthtech Institute,
250 First Avenue, Suite 300,
Needham, MA 02494
www.healthtech.com

Sponsorship, Exhibit, and Lead Generation Opportunities

CHI offers comprehensive sponsorship packages which include presentation opportunities, exhibit space, branding and networking with specific prospects. Sponsorship allows you to achieve your objectives before, during, and long after the event. Any sponsorship can be customized to meet your company's needs and budget. Signing on early will allow you to maximize exposure to qualified decision-makers.

Podium Presentations – *Available Within the Main Agenda!*

Showcase your solutions to a guaranteed, targeted audience. Package includes a 15- or 30-minute podium presentation within the scientific agenda, exhibit space, on-site branding, access to cooperative marketing efforts by CHI, and more.

Breakfast & Luncheon Podium Presentations

Opportunity includes a 30-minute podium presentation. Boxed lunches are delivered into the main session room, which guarantees audience attendance and participation. A limited number of presentations are available for sponsorship and they will sell out quickly. Sign on early to secure your talk!

Invitation-Only VIP Dinner/Hospitality Suite

Sponsors will select their top prospects from the conference pre-registration list for an evening of networking at the hotel or at a choice local venue. CHI will extend invitations and deliver prospects, helping you to make the most out of this invaluable opportunity. Evening will be customized according to sponsor's objectives i.e.:

- Purely social
- Focus group
- Reception style
- Plated dinner with specific conversation focus

Exhibit

Exhibitors will enjoy facilitated networking opportunities with qualified delegates. Speak face-to-face with prospective clients and showcase your latest product, service, or solution.

One-on-One Meetings

Select your top prospects from the pre-conference registration list. CHI will reach out to your prospects and arrange the meeting for you. A minimum number of meetings will be guaranteed, depending on your marketing objectives and needs. A very limited number of these packages will be sold.

Additional branding and promotional opportunities are available, including:

- Conference Tote Bags
- Literature Distribution (Tote Bag Insert or Chair Drop)
- Badge Lanyards
- Padfolios
- Program Guide Advertisement

Looking for additional ways to drive leads to your sales team?

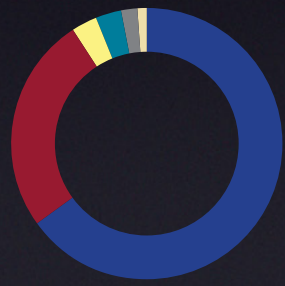
CHI's Lead Generation Programs will help you obtain more targeted, quality leads throughout the year. We will mine our database of 800,000+ life science professionals to your specific needs. We guarantee a minimum of 100 leads per program! Opportunities include:

- Whitepapers
- Web Symposia
- Custom Market Research Surveys
- Podcasts

For sponsorship and exhibit information, please contact:

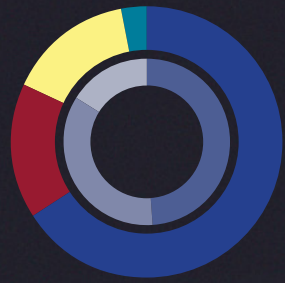
Carolyn Benton
Business Development Manager
781-972-5412 | cbenton@healthtech.com

2015 Attendee Demographics



Company Type

Biotechnical/ Commercial/Pharma	65%
Academic	26%
Government	3%
Services/Societies	3%
Hospital	2%
Other	1%



Geographic Location

USA	66%
Asia	16%
Europe	15%
Other	3%

USA Breakdown

West Coast	49%
East Coast	35%
Midwest	16%

Company Title

Scientist/Technologist	52%
Executive/Director	22%
Professor	14%
Other	7%
Manager	5%

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Current Sponsors & Exhibitors (As of November 30, 2015)

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PolyPeptide Group
Reaction Biology Corporation
Schrödinger
SensiQ Technologies, Inc.
Simulations Plus, Inc.
Synthonix, Inc.
Thermo Fisher Scientific - Maybridge Brand
Wiley

Hotel & Travel Information

Conference Hotel:
Hilton San Diego Resort
1775 East Mission Bay Drive
San Diego, CA 92109
Tel: 619-276-4010

Discounted Room Rate: $204 s/d
Discounted Room Rate Cutoff Date: March 28, 2016

For more hotel and travel information please visit our website at www.drugdiscoverychemistry.com

San Diego Highlights:

- The **Gaslamp Quarter** is Southern California's premier dining, shopping and entertainment district, where you'll find a truly eclectic blend of food, fun and culture all within one of San Diego's most historic areas.
- Just south of Mission Valley and known as the birthplace of California, **Old Town** teems with a lively, authentic atmosphere, boasting museums, historical sites and restaurants.
- At the world-famous **San Diego Zoo**, you'll see some of the world's rarest wildlife including giant pandas and koalas. A visit to the San Diego Wild Animal Park is like a safari to many of the world's most exotic places.
- World-renowned **Balboa Park** is home to fifteen museums, various arts and international culture associations, as well as the San Diego Zoo, making it one of the nation's largest cultural and entertainment complexes.
- **SeaWorld San Diego** entertains, amazes and educates, creating memories that will last a lifetime. See live shows, ride the rides, and get up-close to beluga whales, polar bears, sharks and penguins.

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Pricing and Registration Information

CONFERENCE PRICING

PREMIUM PACKAGE (Includes access to 2 conferences, two short courses, and one symposia or training seminar)	**Commercial**	**Academic, Government, Hospital-affiliated**
Registrations after March 18, 2016, and on-site	$3299	$2199
STANDARD PACKAGE (Includes access to 2 conferences, excludes short courses, symposia and training seminar)		
Registrations after March 18, 2016, and on-site	$2649	$1324
BASIC PACKAGE (Includes access to 1 conference, excludes short courses, symposia and training seminar)		
Advance Registration Discount until March 18, 2016	$1849	$999
Registrations after March 18, 2016, and on-site	$1949	$1099

SHORT COURSES

One short course	$699	$399
Two short courses	$999	$699
Three short courses	$1199	$799
Four short courses	$1299	$899

SYMPOSIA PRICING

One Symposium	$999	$599

TRAINING SEMINAR PRICING

One Training Seminar	$999	$599

Morning Short Courses (April 18)	Concurrent Conferences (April 19-20)	Concurrent Conferences (April 20-21)	Concurrent Symposia/ Training Seminar (April 22)
SC1: Trends in Physical Properties of Drugs SC2: GPCR Structure-Based Drug Discovery SC3: Designing Peptide Therapeutics for Specific PPIs	T1: Inflammation Inhibitors	T4: Kinase Inhibitor Chemistry	S1: Brain Penetrant Inhibitors
Afternoon Short Course (April 18) SC4: Immunology Basics for Chemists SC5: Phenotypic Screening and Chemical Probe Development ~~SC6: Crystallography for Drug Design~~	T2: Protein-Protein Interactions	T5: Macrocyclics and Constrained Peptides	S2: Biophysical Approaches
Dinner Short Courses (April 18) SC7: Molecular Interactions and Drug Design SC8: Inhibitor Design using MOE SBDD Applications	T3: Epigenetic Inhibitor Discovery	T6: Fragment-Based Drug Discovery	S3: Antivirals
		Dinner Short Courses (April 20) SC10: Enabling Macrocyclic Compounds for Drug Discovery SC11: Advancing Tools and Technologies for Fragment-Based Design SC12: Introduction to Targeted Covalent Inhibitors	Training Seminar: Applying Pharmacology to New Drug Discovery

CONFERENCE DISCOUNTS

Poster Submission - Discount ($50 Off): Poster abstracts are due by March 11, 2016. Once your registration has been fully processed, we will send an email containing a unique link allowing you to submit your poster abstract. If you do not receive your link within 5 business days, please contact jring@healthtech.com. *CHI reserves the right to publish your poster title and abstract in various marketing materials and products.

REGISTER 3 - 4th IS FREE: Individuals must register for the same conference or conference combination and submit completed registration form together for discount to apply.

Alumni Discount: Cambridge Healthtech Institute (CHI) appreciates your past participation at Drug Discovery Chemistry. As a result of the great loyalty you have shown us, we are pleased to extend to you the exclusive opportunity to save an additional 20% off the registration rate.

Group Discounts: Discounts are available for multiple attendees from the same organization. For more information on group rates contact
Uma Patel at +1-781-972-5447

If you are unable to attend but would like to purchase the **Drug Discovery Chemistry** CD for $750 (plus shipping), please visit DrugDiscoveryChemistry.com. Massachusetts delivery will include sales tax.

ADDITIONAL REGISTRATION DETAILS

Each registration includes all conference sessions, posters and exhibits, food functions, and access to the conference proceedings link.

Handicapped Equal Access: In accordance with the ADA, Cambridge Healthtech Institute is pleased to arrange special accommodations for attendees with special needs. All requests for such assistance must be submitted in writing to CHI at least 30 days prior to the start of the meeting.

To view our Substitutions/Cancellations Policy, go to healthtech.com/regdetails

Video and or audio recording of any kind is prohibited onsite at all CHI events.

How to Register: **DrugDiscoveryChemistry.com**
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Please use keycode **DCH F** when registering!