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CHI's 13th Annual

Drug Discovery Chemistry

Optimizing Small Molecules for Tomorrow's Therapeutics

April 2-6, 2018 | San Diego, CA | Hilton San Diego Bayfront

Plenary Keynotes

Activity-Based Proteomics: Protein and Ligand Discovery on a Global Scale
Benjamin F. Cravatt, PhD, Professor and Co-Chair, Department of Molecular Medicine, The Scripps Research Institute

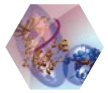
Targeting Ras and MYC for the Treatment of Cancer
Stephen Fesik, PhD, Professor of Biochemistry, Pharmacology, and Chemistry, Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University School of Medicine

CONFERENCE PROGRAMS

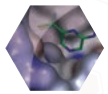
APRIL 3-4


Protein-Protein Interactions

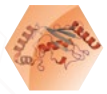

Inflammation & Autoimmune Inhibitors


Kinase Inhibitor Chemistry


GCPR-Targeted Drug Design

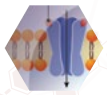

Fragment-Based Drug Discovery

APRIL 4-5

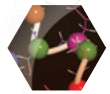

Ubiquitin Proteasome System Inhibitors


Small Molecules for Cancer Immunotherapy


Macrocyclics & Constrained Peptides


Targeting Complex Membrane Proteins

APRIL 6


Biophysical Approaches for Drug Discovery


Lead Optimization for Drug Metabolism & Safety


Blood-Brain Penetrant Inhibitors

Plus Short Courses on April 2 & April 4

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CONFERENCE AT-A-GLANCE

Monday APRIL 2	Tuesday APRIL 3	Wednesday APRIL 4	Thursday APRIL 5	Friday APRIL 6
PRE-CONFERENCE SHORT COURSES*	PROTEIN-PROTEIN INTERACTIONS	DINNER SHORT COURSES*	UBIQUITIN PROTEASOME SYSTEM INHIBITORS	BIOPHYSICAL APPROACHES FOR DRUG DISCOVERY
	INFLAMMATION & AUTOIMMUNE INHIBITORS		SMALL MOLECULES FOR CANCER IMMUNOTHERAPY	LEAD OPTIMIZATION FOR DRUG METABOLISM & SAFETY
	KINASE INHIBITOR CHEMISTRY		MACROCYCLICS & CONSTRAINED PEPTIDES	BLOOD-BRAIN PENETRANT INHIBITORS
	GCPR-TARGETED DRUG DESIGN		TARGETING COMPLEX MEMBRANE PROTEINS	
	FRAGMENT-BASED DRUG DISCOVERY			

*Separate registration is required

TRACK-HOPPING

Attendees at Drug Discovery Chemistry are encouraged to "track-hop" between concurrent sessions: Though you register for a particular conference or symposium, in reality you gain access to all concurrent conferences or symposia. For the best value, register for a Premium Package, and gain access to all 12 conferences/symposia, plus two short courses, over five days of programming that best fits your research needs.

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PLENARY KEYNOTES

April 3, 2018 | 4:40 pm

Activity-Based Proteomics: Protein and Ligand Discovery on a Global Scale

Benjamin F. Cravatt, PhD

Professor and Co-Chair, Department of Molecular Medicine, The Scripps Research Institute

Dr. Cravatt is a Professor and Co-Chair of the Department of Molecular Medicine at The Scripps Research Institute. His research group is interested in understanding the roles that enzymes play in physiological and pathological processes, especially as pertains to the nervous system and cancer. Dr. Cravatt obtained his undergraduate education at Stanford University, receiving a BS in the Biological Sciences and a BA in History. He then received a PhD from The Scripps Research Institute (TSRI) in 1996. Professor Cravatt joined the faculty at TSRI in 1997. Dr. Cravatt is a co-founder and scientific advisor of Activx Biosciences, Abide Therapeutics, and Vividion Therapeutics. His honors include a Searle Scholar Award, the Eli Lilly Award in Biological Chemistry, a Cope Scholar Award, the Protein Society Irving Sigal Young Investigator Award, the Tetrahedron Young Investigator Award in Bioorganic and Medicinal Chemistry, the ASBMB Merck Award, and memberships in the National Academy of Sciences and American Academy of Arts and Sciences.

April 5, 2018 | 8:55 am

Targeting Ras and MYC for the Treatment of Cancer

Stephen Fesik, PhD

Professor of Biochemistry, Pharmacology, and Chemistry, Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University School of Medicine

Dr. Fesik's research focus is on cancer drug discovery using fragment-based approaches and structure-based drug design. Prior to joining Vanderbilt in May 2009, Dr. Fesik was the Divisional Vice President of Cancer Research at Abbott (2000-2009) where he built a pipeline of compounds that are showing promising anti-cancer activities in early stage clinical trials. While at Abbott, he also developed a few new NMR methods, determined the three-dimensional structures of several proteins and protein/ligand complexes, pioneered a method for drug discovery called SAR by NMR, and applied this method to identify and optimize ligands for binding to many protein drug targets. His research has also involved the use of siRNA for target identification and target validation. Dr. Fesik has published more than 240 papers, trained 38 postdoctoral fellows, has been a reviewer for several government funding agencies and has served as a member of the Editorial Boards of many peer-reviewed journals. He is currently a member of Aileron Therapeutics SAB and the Bruker Board of Directors. His three awards from Abbott include Researcher of the Year Team Award (2008). He has also received the NIH Director's Pioneer Award (2010), and honors from numerous academic societies, the most recent being the AACR Award for Outstanding Achievement in Chemistry in Cancer Research (2012).

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Short Courses*

Afternoon Short Courses

MONDAY, APRIL 2, 2:00 - 5:00 PM

SC1: Ligand-Receptor Molecular Interactions and Drug Design
Instructor: Maricel Torrent, PhD, 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 model
- Understanding the relative amounts of potency gain from different interactions
- Case studies illustrate all the design strategies

SC2: Advancing Tools and Technology for Fragment-Based Design
Instructors: Mary Harner, PhD, Research Investigator II, Mechanistic Biochemistry, Bristol-Myers Squibb R&D
Daniel A. Erlanson, PhD, Co-Founder, Carmot Therapeutics, Inc.
- 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

SC3: Drug Metabolism and Its Impact on Decisions in Lead Discovery and Drug Development
Instructor: John C. L. Erve, PhD, DABT, Consultant, Jerve Scientific Consulting, Inc.
- Applying drug metabolism concepts to lead optimization
- Impact of drug structures on important PK parameters
- Common assays for predicting clearance and metabolism-based drug-drug interactions
- Growing application of *in silico* tools in drug metabolism
- Role of bioactivation in drug toxicity

SC4: Diversity-Oriented Platforms for Ligand Discovery
Instructors: Sepideh Afshar, PhD, Principal Research Scientist, Department of Protein Engineering, Eli Lilly and Company
Svetlana Belyanskaya, PhD, Encoded Library Technologies, R&D Platform Technology & Science, GSK Boston
Pros and cons of affinity based screening platforms in drug discovery:
- Phage display
- mRNA display
- DNA-encoded libraries

Dinner Short Courses

MONDAY, APRIL 2, 6:00 - 9:00 PM

SC5: Immunology Basics for Chemists
Instructors: Songqing Na, PhD, Senior Scientist, Biotechnology & Autoimmunity Res-AME, Eli Lilly and Company
Thomas Sundberg, PhD, Senior Research Scientist I, Center for Development of Therapeutics, Broad Institute of MIT and Harvard
- Review of immune system's cellular players
- Review of inflammatory process
- Autoimmune & inflammation-related diseases
- Current treatment landscape and promising drug targets
- Principles in immune-oncology (e.g., checkpoint blockade)

SC6: Introduction to Allosteric Modulators and Biased Ligands of GPCRs
Instructor: Terry Kenakin, PhD, Professor, Department of Pharmacology, University of North Carolina School of Medicine
- Overview of allosteric modulators and pathway biased ligands
- Approaches for screening and validation
- Fitting functional allosteric data to obtain allosteric drug parameters

SC7: Introduction to Targeted Covalent Inhibitors
Instructor: Mark Schnute, PhD, Associate Research Fellow, Biotherapeutics Chemistry & Immunoscience Research, Pfizer Global R&D
- 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

SC8: Introduction to the Ubiquitin Proteasome System
Instructor: Alexander Statsyuk, PhD, Assistant Professor, Department of Pharmacological and Pharmaceutical Sciences, University of Houston
- Mechanisms of E1, E2, E3, and DUB enzymes
- Technologies available and experimental controls
- Discovered inhibitors and emerging biology

Dinner Short Courses

WEDNESDAY, APRIL 4, 6:30 - 9:00 PM

SC9: Impact of Convergence of Immunotherapy and Epigenetics on Drug Discovery
Instructors: Katherine Chiappinelli, PhD, Assistant Professor, Department of Microbiology, Immunology, and Tropical Medicine, The George Washington University Cancer Center
Alejandro Villagra, PhD, Assistant Professor, Department of Biochemistry and Molecular Medicine, School of Medicine and Health Sciences, The George Washington University
Wayne W. Hancock, MD, PhD, Professor of Pathology and Chief of Transplant Immunology, Children's Hospital of Philadelphia and University of Pennsylvania
- Epigenetic pathways that intersect and interact with the immune system
- Effect of epigenetic therapies on the tumor and host immune system
- Exploiting immunoepigenetics to enhance the efficacy of current drug treatments
- Case studies highlighting promises and challenges

Short courses continued on next page...

**Separate registration is required.*

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Short Courses*

SC10: Enabling Macrocyclic Compounds for Drug Discovery: Opportunities, Challenges and Strategies
Instructors: Eric Marsault, PhD, Professor, Medicinal Chemistry and Pharmacology, University of Sherbrooke
Mark Peterson, PhD, COO, Cyclenium Pharma, Inc.

- 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: Trends in Physical Properties of Drugs
Instructors: Terry Stouch, PhD, President, R&D, Science for Solutions, LLC
Robert Fraczkiewicz, PhD, Team Leader, Simulations Plus, Inc.
Max Totrov, PhD, Principal Scientist, MolSoft, LLC

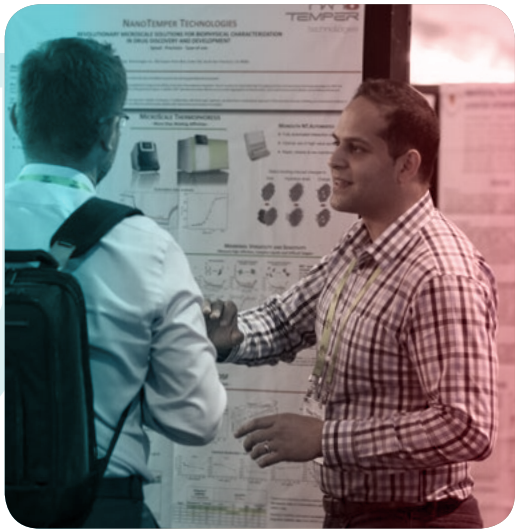
- Properties important for enhanced efficacy, delivery, and formulation
- pKa, tautomerism, crystallization, others
- Computational prediction: What works - what doesn't
- Experimental best practices

SC12: Covalent Fragments: Applications in Target-Based and Phenotypic Screens
Instructor: Alexander Statsyuk, PhD, Assistant Professor, Department of Pharmacological and Pharmaceutical Sciences, University of Houston

- Design principles of covalent fragment libraries, target-based and phenotypic screens using covalent fragments
- Strategies to grow fragments into drug leads, and case studies
- Coupling covalent fragment growth with selectivity profiling in cells

Student Fellowships Now Available – New for 2018!

Full-time graduate students and PhD candidates presenting a poster are now encouraged to apply for a **Student Fellowship.** Spaces are limited! Please see website for details.



PRESENT A POSTER AND SAVE $50!

Cambridge Healthtech Institute encourages attendees to gain further exposure by presenting their work in the poster sessions. To secure a poster board and inclusion in the conference materials, your abstract must be submitted, approved and your registration paid in full by **February 23, 2018.** Reasons you should present your research poster at this conference:

- Your poster will be seen by our international delegation, representing leaders from top pharmaceutical, biotech, academic and government institutions
- Receive $50 off your registration
- Your poster will be automatically entered into the main conference poster competition
- Your poster abstract will be published in our conference materials

Separate registration is required.

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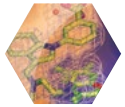
CONFERENCES & SYMPOSIA

CONFERENCES

APRIL 3-4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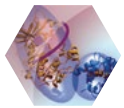
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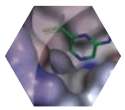
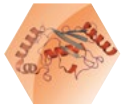
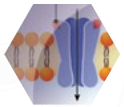

Fragment-Based Drug Discovery

APRIL 4-5


Ubiquitin Proteasome System Inhibitors

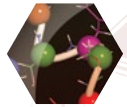

Small Molecules for Cancer Immunotherapy


Macrocyclics & Constrained Peptides


Targeting Complex Membrane Proteins

SYMPOSIA

APRIL 6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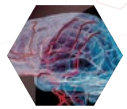
Blood-Brain Penetrant Inhibitors

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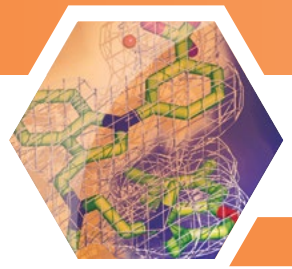

11TH ANNUAL

Protein-Protein Interactions

Targeting PPIs for Therapeutic Interventions

April 3-4, 2018 | Hilton San Diego Bayfront | San Diego, CA

TUESDAY, APRIL 3

7:00 am Registration and Morning Coffee

ONCOLOGY PPI TARGETS

8:00 Welcome Remarks
Anjani Shah, PhD, Conference Director, Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks
Kevin Lumb, PhD, Director, Discovery Sciences, Janssen R&D

8:10 Enabling Fragment and Structure-Based Discovery for Challenging Targets (Bcl-2, Mcl-1)
Roderick E. Hubbard, PhD, Professor, University of York and Director, Vernalis
Working on unprecedented targets is tough. It can take some time to generate suitable protein, develop an assay that can be trusted, identify tool compounds and design optimised molecules in the absence of structural information. I will describe our approaches to establish fragment and structure-based discovery for such targets, using as examples the early work on Bcl-2 and Mcl-1 with Servier that resulted in compounds that are now in Phase I clinical trials.

8:40 Structure-Based Design of Novel Inhibitors of the MCL-1's Protein-Protein Interaction
Xin Huang, PhD, Principal Scientist, Department of Molecular Engineering, Amgen
Mcl-1, a member of the Bcl-2 family, inhibits pro-death components of the intrinsic apoptosis pathway and thus is a key survival factor in multiple myeloma and other malignancies. Although compelling, targeting disruption of Mcl-1's protein–protein interaction to induce tumor cell death was previously thought to be "un-druggable" due to the high affinities of Mcl-1 to the pro-apoptotic Bcl-2 proteins and lack of a small molecule binding pocket. We report here our structure-based drug design of novel inhibitors of the Mcl-1 that led to AMG 176, a potent, selective, and bioavailable Mcl1 inhibitor in clinical development.

9:10 Screening for Conformational Changes using Second Harmonic Generation (SHG)
Sponsored by HARKERBIO
Artem Evdokimov, PhD, CSO, HarkerBIO

9:40 Coffee Break

10:05 Discovery of Potent and Selective Mcl-1 Inhibitors Using Fragment Merging and Structure-Guided Design
James (Chris) Tarr, PhD, Drug Discovery Scientist II, Stephen Fesik Laboratory, Department of Biochemistry, Vanderbilt University
Mcl-1 is a member of the Bcl-2 family of proteins responsible for the regulation of apoptosis and a highly validated target for cancer therapy. Using fragment screening by NMR followed by lead optimization employing structure-based design methods, we have developed selective, picomolar inhibitors of Mcl-1. These compounds act via the intrinsic apoptotic pathway, potently inhibit proliferation in cellular assays, and deliver efficacy in xenograft tumor models. Efforts to develop a suitable clinical candidate are underway.

10:35 Targeting Nuclear Lamins to Inhibit DNA Repair
Xiangshu Xiao, PhD, Associate Professor, Physiology and Pharmacology, Oregon Health & Science University
Targeting DNA repair pathways has been validated as a promising strategy to develop novel cancer therapeutics. However, it has been very challenging to target DNA repair proteins. We have discovered a novel role of lamins in DNA repair and have developed the first-in-class small molecules to target lamins to inhibit DNA repair. We will present our exciting discovery in this space.

11:05 Computational Screening for Small-Molecule Protein-Protein Interaction Inhibitors
Samy Meroueh, PhD, Associate Professor, Department of Biochemistry and Molecular Biology, Indiana University School of Medicine

11:35 Luncheon Presentation: The Rational Design of Small-Molecule Neuropilin-1 Antagonists
Trevor Perrior, PhD, Chief Scientific Officer, Domainex
Neuropilin-1 (NRP1) is a receptor for vascular endothelial growth factor A165 (VEGF-A) and the neuronal guidance molecule semaphorin 3A (SEMA3A), which plays a key role in vascular and neuronal development. Molecules which antagonise the interaction of NRP-1 with its protein ligands may be useful in a number of therapeutic settings, in particular for the treatment of certain types of cancer. In collaboration with Ark Therapeutics and scientists at University College London we have designed the first small-molecule inhibitors of this protein-protein interaction and have shown that they display the expected pharmacological profile

12:20 pm Session Break

TARGETING VIRAL, NEURODEGENERATION AND OTHER PROTEIN COMPLEXES

1:15 Chairperson's Remarks
Roderick E. Hubbard, PhD, Professor, University of York and Director, Vernalis

1:20 HBV Capsid Assembly Inhibitors
Andrew Cole, PhD, Research Fellow, Medicinal Chemistry, Arbutus
The encapsidation of pregenomic RNA by dimeric units of hepatitis B virus core protein is an essential step in the viral life cycle of HBV, facilitating viral genome relaxed circular DNA synthesis, infectious virion production and maintenance of a nuclear covalently closed circular DNA pool. Small molecules that bind at the core protein dimer:dimer interface have been shown to demonstrate antiviral activity *in vitro* and *in vivo*, through interference with the HBV capsid assembly process.

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1:50 FEATURED PRESENTATION: Assessing Mitochondrial Quality Control to Inform Discovery of Small Molecules Targeting the Keap1-NRF2 System

Michelangelo Campanella, PhD, PharmD, Professor and Unit Head, Mitochondrial Cell Biology and Pharmacology Research Group RVC and University College London Consortium for Mitochondrial Research

My talk will report upon Nrf2 inducers as pharmacological tolls in mitochondrial quality control operated by targeted autophagy. It will elaborate on the prominent biological activity in cellular homeostasis of the non-covalent Keap1-Nrf2 protein-protein interaction (PPI) inhibitor PMI, which is structurally distinct from the covalent Keap1 modifiers (e.g. sulforaphane) and amenable to therapeutic exploitation. Contextually, a newly devised method for High Throughput Screening (HTS) for this specific category of Keap1-Nrf2 inhibitors will be presented.

2:20 Thermodynamics-driven Structure-Activity Relationship Studies: Breaking the Enthalpy-Entropy Compensation Saga Results in Novel and Potent IAP and XIAP Antagonists

Maurizio Pellecchia, PhD, Professor of Biomedical Sciences, University of California, Riverside (UCR) School of Medicine

Using NMR and thermodynamic screening approaches with focused positional scanning libraries (fPOS) novel areas on the target surface can be identified that can be further exploited to design more potent and selective ligands. I will report on our recent work targeting the BIR3 domains of IAP family proteins, and will illustrate that enthalpy-entropy compensation in thermodynamics-driven structure activity relationships studies can be used to design both novel pan-active agents and novel XIAP selective compounds.

2:50 Drug Leads Originating from the Public/Private Consortium: European Lead Factory

Dimitrios Tzalis, PhD, CEO, Taros Chemicals; Head of Chemistry, European Lead Factory

Highlights of the European Lead Factory (ELF)
• a public-private partnership that provides researchers in Europe a unique platform for translating innovative biology and chemistry into high-quality starting points for drug discovery
• 200.000 *de novo* synthesized compounds are complimenting 300.000 compounds provided by participating pharmaceutical partners
• So far resulted in >5.000 hit compounds with a defined biological activity from >90 successfully completed HTS and hit evaluation campaigns out of which a significant number of targets are PPIs

3:20 Sponsored Presentation *(Opportunity Available)*

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

4:30 Plenary Session Welcome Remarks from Event Director

Anjani Shah, PhD, Conference Director, Cambridge Healthtech Institute

4:35 Sponsored Plenary Keynote Introduction *(Opportunity Available)*

4:40 PLENARY KEYNOTE: Activity-Based Proteomics: Protein and Ligand Discovery on a Global Scale

Benjamin F. Cravatt, PhD, Professor and Co-Chair, Department of Molecular Medicine, The Scripps Research Institute

To address uncharacterized proteins, we have introduced chemical proteomic technologies that globally profile the functional state of proteins in native biological systems. Among these methods is activity-based protein profiling (ABPP), which utilizes chemical probes to map activity states of large numbers of proteins in parallel. I will discuss the application of ABPP to discover and functionally annotate proteins in mammalian physiology and disease, and the generation and implementation of advanced ABPP platforms for proteome-wide ligand discovery.

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

6:30 End of Day

WEDNESDAY, APRIL 4

7:30 am Continental Breakfast Breakout Discussions

CANCER, EPIGENETICS AND PPIs

8:30 Chairperson's Remarks

Chris Smith, PhD, Director, Medicinal Chemistry, COI Pharmaceuticals

8:35 Design of Allosteric K-Ras Inhibitors Targeting the Switch II Pocket

Juan J. Perez, PhD, Professor, Department of Chemical Engineering, Universitat Politecnica de Catalunya, Barcelona

K-Ras is an oncoprotein involved in numerous cancers. Inhibition of K-Ras has been elusive for many years because it cannot be competitive, due to the high affinity of the protein for GTP. Recently, small molecule inhibitors targeting the G12C K-Ras mutant have been disclosed. These molecules produce their action binding irreversibly into the inducible switch II pocket. In the present communication, we describe a novel series of reversible switch II inhibitors with nanomolar affinity.

9:05 NuRD Epigenetic Complex: An Emerging Target for Cancer Chemo-Sensitization

Elmar Nurmemmedov, PhD, MBA, Assistant Professor, Director of Drug Discovery, Translational Neurosciences and Neurotherapeutics, John Wayne Cancer Institute

NuRD complex plays a major role in the regulation of gene expression, chromatin organization, DNA damage repair, and genomic stability. NuRD complex is also involved in acquired resistance to chemotherapies in a number of cancers, including deadly brain cancers. Targeting RBBP4, an integral component of this complex, sensitizes resistant cancer cells to chemotherapy. We developed an approach that enables inhibition of RBBP4 and leads to selective elimination of resistant cancer cells; this is a new direction in targeting of chemo-resistant cancer cells.

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

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FRAGMENT-BASED APPROACHES TO FIND PPI INHIBITORS

10:30 Fragment-Based Discovery of a Chemical Probe for the NSD3-PWWP-1 Domain
Jark Böttcher, Principal Scientist, Medicinal Chemistry, Boehringer Ingelheim RCV GmbH & Co KG
We describe the fragment-based discovery of molecules binding to the proposed methyl-lysine binding site of the PWWP-1 domain of NSD3. Supported by a virtual screening approach and subsequent structure-based optimization, the initial hits were optimized into a chemical probe with confirmed binding in cellular assays. The probe and the related negative control can be used to explore the functions of the PWWP-1 domain.

11:00 Lead Generation without an X-Ray Crystal Structure: An NMR Method to Probe Protein-Ligand Complexes
Julien Orts, PhD, Professor, Laboratory of Physical Chemistry, Swiss Federal Institute of Technology ETH
My talk is about a NMR method to solve protein-ligand complex structure. I will present two or three examples of this method applied to finding inhibitors against specific PPI targets.

11:30 *In silico* Fragment Screening to Identify Cryptic Pockets and Allosteric Sites for PPI Inhibitor Development
Ben Cossins, PhD, Principal Scientist, UCB Pharma
Drug development is increasingly difficult and expensive. Valuable targets are not always amenable to modulation by small molecules and resources are often directed towards seemingly intractable targets. We have been building and applying molecular dynamics based fragment screening and *de novo* design approaches to try and understand ligandability and functionality for protein-protein interaction targets. We believe this approach can steer us towards hit compounds for tractable PPI targets.

12:00 pm End of Conference

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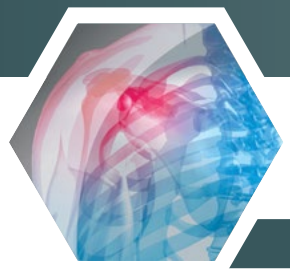

9TH ANNUAL

Inflammation & Autoimmune Inhibitors

Small-Molecule Approaches for Oral-Based Therapeutics

April 3-4, 2018 | Hilton San Diego Bayfront | San Diego, CA

TUESDAY, APRIL 3

7:00 am Registration and Morning Coffee

TARGETING INTRACELLULAR KINASES FOR AUTOIMMUNITY AND INFLAMMATION

8:00 Welcome Remarks
Anjani Shah, PhD, Conference Director, Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks
John Robinson, PhD, Director, Medicinal Chemistry, Array Biopharma

8:10 BTK for Lupus and Other Indications: Lead Optimization of a Covalent Inhibitor
Lesley M. Liu-Bujalski, PhD, Group Leader, Medicinal Chemistry, EMD Serono Research and Development Institute, Inc.
Bruton's tyrosine kinase (Btk) is a promising drug target for the treatment of autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). We set out to identify an orally bioavailable, highly selective BTK inhibitor, that might be suitable for the treatment of chronic diseases. Using a combination of X-ray crystallography, wild-type and mutant BTK functional assays, stability studies, and *in vivo* PK/PD models, lead optimization efforts led to the identification of evobrutinib.

8:40 Discovery and Optimization of Spleen Tyrosine Kinase Inhibitors for Immunological Diseases
Michael Hoemann, PhD, Senior Scientist, Department of Chemistry, AbbVie, Inc.
This talk will focus on the approach to designing and optimizing a series of Spleen Tyrosine Kinase (Syk) inhibitors. We will highlight the methods used to enhance potency, overcome the challenge of off-target kinase selectivity and optimization of PK properties to yield compounds with *in vivo* efficacy in the rat CIA model. In addition, the talk will highlight the use of *in vitro* assays to identify compounds with superior cardiovascular safety profiles.

9:10 Late Breaking Presentation

9:40 Coffee Break

TARGETING INTRACELLULAR KINASES AND GPCRs FOR AUTOIMMUNITY AND INFLAMMATION

10:05 Discovery of Potent and Selective Inhibitors of Receptor-Interacting Protein Kinase 1 (RIPK1) with *in vivo* Activity
Snahel Patel, PhD, Senior Scientific Manager, Discovery Chemistry, Genentech, Inc.
Regulation of cell death signaling is critical for the maintenance of homeostasis and prevention of disease. A caspase-independent regulated form of cell death called necroptosis is rapidly emerging as an important mediator of a number of human pathologies including inflammatory bowel disease and ischemia reperfusion organ injury. Activation of necroptotic signaling through TNF signaling or organ injury leads to the activation of kinases RIPK1 and RIPK3 and culminates in inflammatory cell death. Here we present the interesting development of potent and selective RIPK1 specific inhibitors that demonstrate protection in a mouse systemic inflammatory response syndrome (SIRS) model.

10:35 Modulation of Heterotrimeric G proteins by AMP-Kinase: An actionable target in Inflammatory Bowel Disease
Pradipta Ghosh, MD, Professor, Departments of Medicine and Cell and Molecular Medicine, UC San Diego
The gut barrier is a final frontier where trillions of bacteria face-off the largest immune system of the body; a compromised "leaky" gut barrier is frequently associated with chronic inflammation, which is a key initiator and driver for many autoimmune diseases, such as inflammatory bowel disease (IBD). Using normal and IBD-afflicted human enteroids and enteroid-derived monolayers we have revealed an actionable target (AMPK) within a specialized pathway, the stress-polarity signaling pathway, whose activation appears to mend the leaky gut in IBD.

11:05 Ozanimod (RPC1063), an oral S1P1 and S1P5 modulator, in Relapsing Multiple Sclerosis
Kristen Taylor Meadows, PhD, Principal Scientist, Cell and Molecular Biology, Celgene
Ozanimod, a small molecule S1P1 and S1P5 agonist, demonstrated positive Phase III efficacy with a good safety profile in Relapsing Multiple Sclerosis, an autoimmune disorder targeting myelin within the central nervous system. Ozanimod's primary mechanism of action is to retain lymphocytes in secondary lymphoid tissue. This talk will present data identifying specific peripheral immune populations targeted by ozanimod in preclinical models of MS, and investigate direct effects on resident cells within the central nervous system.

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

12:20 pm Session Break

NEW INFLAMMATION AND AUTOIMMUNITY TARGETS

1:15 Chairperson's Remarks
Lesley M. Liu-Bujalski, PhD, Group Leader, Medicinal Chemistry, EMD Serono Research and Development Institute, Inc.

1:20 Inhibition of the Serine Hydrolase Monoacylglycerol Lipase (MGLL) for the Treatment of Neurological and Neuroinflammatory Disorders
Jacqueline Blankman, PhD, Director of Biology, Abide Therapeutics
ABX-1431 is a first-in-class, small molecule inhibitor of monoacylglycerol lipase (MGLL), a serine hydrolase enzyme that regulates flux of the endocannabinoid 2-arachidonoylglycerol (2-AG). Oral administration of ABX-1431 results in potent and selective MGLL inhibition in preclinical species and man. In an exploratory Phase 1b study in Tourette Syndrome (TS), ABX-1431 administration consistently showed benefit on TS symptoms, supporting MGLL inhibition as a novel CNS mechanism for the treatment of TS and other neurological diseases.

1:50 Late Breaking Presentation

2:20 The Design of Mechanism-Based Amine Oxidase Inhibitors for the Treatment of Inflammation
Jonathan Foot, PhD, Senior Research Scientist, Drug Discovery, Pharmaxis Ltd.
Amine oxidases are a family of enzymes that catalyze the oxidation of a wide variety of endogenous amines such as collagen or dopamine. They play a key role in oxidative stress, inflammation and protein cross-linking, and in the initiation and progression of fibrosis and cancer. Herein we will present strategies and chemical routes to identify selective amine oxidase inhibitors for the treatment of inflammation-driven diseases.

2:50 Targeting Lipid Mediator, Hepoxilin, for Combatting Inflammation and Inflammatory Bowel Disease
Cecil Robert Pace-Asciak, PhD, Professor, Translational Medicine and Pharmacology, Hospital for Sick Children Research Institute
Findings related to inflammation will be presented for a family of small molecules, Hepoxilins (HX), originally isolated in my laboratory, and of structural analogs (PBTs) that antagonize HX actions *in vivo*. Results for lung fibrosis and inflammatory bowel disease and enhanced neutrophil migration will be presented and stimulation of neutrophil extracellular trap formation (NETosis). Other promising biological actions will be discussed. It is hoped that interest in this area will allow clinical development.

3:20 Selected Poster Presentations

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

4:30 Plenary Session Welcome Remarks from Event Director
Anjani Shah, PhD, Conference Director, Cambridge Healthtech Institute

4:35 Sponsored Plenary Keynote Introduction
(Opportunity Available)

4:40 PLENARY KEYNOTE: Activity-Based Proteomics: Protein and Ligand Discovery on a Global Scale
Benjamin F. Cravatt, PhD, Professor and Co-Chair, Department of Molecular Medicine, The Scripps Research Institute
To address uncharacterized proteins, we have introduced chemical proteomic technologies that globally profile the functional state of proteins in native biological systems. Among these methods is activity-based protein profiling (ABPP), which utilizes chemical probes to map activity states of large numbers of proteins in parallel. I will discuss the application of ABPP to discover and functionally annotate proteins in mammalian physiology and disease, and the generation and implementation of advanced ABPP platforms for proteome-wide ligand discovery.

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

6:30 End of Day

WEDNESDAY, APRIL 4

7:30 am Continental Breakfast Breakout Discussions

TARGETING THE IL17 PATHWAY VIA ROR NUCLEAR HORMONE RECEPTORS

8:30 Chairperson's Remarks
Jacqueline Blankman, PhD, Director of Biology, Abide Therapeutics

8:35 FEATURED PRESENTATION: RORC2 Inverse Agonists – Finding Lipophilic Efficiency in a Hydrophobic Pocket
Mark Schnute, PhD, Associate Research Fellow, Medicine Design, Inflammation & Immunology Research, Pfizer
Small molecule, inverse agonists of the nuclear hormone receptor RORC2 are potential therapies for several autoimmune diseases through their ability to inhibit pro-inflammatory cytokine production. This presentation will describe how we have used the key design strategies of optimization of lipophilic efficiency and understanding the interplay of structure, pharmacology and target residence time to advance a high-throughput screening hit into a highly

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potent, selective and orally bioavailable preclinical development candidate.

9:05 Investigation of Thiazole Bis-Amides as RORγt Inverse Agonists
Kelly McClure, Senior Scientist, Immunology Chemistry, Janssen Research & Development
The nuclear transcription factor retinoic acid receptor-related orphan receptor gt (RORgt) drives Th17 cell differentiation and expansion, and cytokine production. Blocking the production of pro-inflammatory cytokines by RORgt modulation has the potential to be an effective treatment for autoimmune diseases. A promising series of thiazole bis-amide RORgt inverse agonists has been identified and our optimization efforts will be discussed.

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

10:30 Targeting RORγ
Daniel J. Cua, PhD, Group Leader, IMR Pathway Biology, Merck Research Laboratories, Palo Alto
I will present our work demonstrating that targeting of RORγ restrains TCR gene rearrangement and limits development of auto-reactive T cells.

11:00 The Discovery of AZD0284, an Inverse Agonist of Nuclear Receptor RORγt for the Treatment of Psoriasis
Frank Narjes, PhD, Senior Principal Scientist, Medicinal Chemistry, IMED Respiratory, Inflammation & Autoimmunity, AstraZeneca
Retinoic acid receptor-related orphan receptor C2 (RORc2, RORγt, or NR1F3) is essential for the development and differentiation of IL-17 producing TH17 cells, which are important drivers of chronic inflammation in autoimmune diseases such as psoriasis or ankylosing spondylitis. We describe the discovery of our clinical candidate AZD0284, a compound that combines good oral bioavailability with potent suppression of IL-17 production in human TH17 cells, and is currently in Phase I clinical trials.

11:30 Low Molecular Weight Modulators of RORγ: Efficacy in Autoimmune Disease Models
James Zapf, PhD, CSO and Chris Buhr, PhD, VP Medicinal Chemistry, Visionary Pharmaceuticals

12:00 pm End of Conference

> "It's a fantastic conference. It's a very comfortable environment, a very open environment. It's a very well-thought-out conference."
>
> – SIDNEY T., PROFESSOR & DIRECTOR, STEVENS INSTITUTE OF TECHNOLOGY

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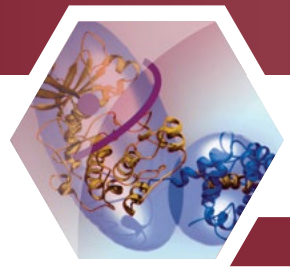

9TH ANNUAL

Kinase Inhibitor Chemistry

Emerging Approaches for the Discovery and Design of Kinase Inhibitors

April 3-4, 2018 | Hilton San Diego Bayfront | San Diego, CA

TUESDAY, APRIL 3

7:00 am Registration and Morning Coffee

OPTIMIZING NEXT-GENERATION KINASE INHIBITORS

8:00 Welcome Remarks
Kip Harry, Senior Director, Conferences, Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks
Gerhard Mueller, PhD, CSO, Gotham Therapeutics

8:10 FEATURED PRESENTATION: Selective Targeting of Kinase Catalytic and Non-Catalytic Function
Stefan Knapp, PhD, Professor, Department of Pharmaceutical Chemistry, Goethe Institut, Frankfurt
Advances in kinase structural biology led to an excellent structural coverage of the human kinase family and provided insight into the remarkable domain plasticity of the catalytic domain. Our laboratory contributed 75 of the currently ~200 known crystal structures, enabling a family-wide structural analysis for rational design of inhibitors. In this talk I will summarize strategies that led to the development of highly selective inhibitors. I will discuss the discovery of novel inhibitor binding sites including allosteric sites and the exploitation of unusual structural features for the design of highly selective kinase inhibitors.

8:40 Structure-Based Design of Long Residence Time into Novel Kinase Inhibitors
Gerhard Mueller, PhD, CSO, Gotham Therapeutics
The presentation focuses on the engineering of binding kinetic signatures into "deep-pocket-directed" scaffolds for achieving high-efficacy kinase inhibitors. We will demonstrate that a thorough understanding of the precise pharmacophoric requirements on the target's binding site is essential to pre-engineer the desired slow off-rates into new, thus literature-unprecedented scaffolds that qualify as privileged structures for the target family of kinases.

9:10 Selected Poster Presentation: Application of Sequential Palladium Catalysis for the Discovery of Janus Kinase Inhibitors
Mohamed El-Sayed, Research Assistant, Medicinal Chemistry and Molecular Pharmacology, Purdue University College of Pharmacy
The present account describes the discovery and development of a new JAK inhibitory chemotype that has produced selective JAK inhibitors, especially vs. JAK1. Sequential palladium chemistry was optimized for the rapid access to a focused library of derivatives to explore the structure-activity relationships of the new substances. Several compounds showed low nanomolar potency against the four members of the JAK family. Compounds 17d and 18 were the most active with single digit nanomolar IC50 values against JAK3 and JAK1. Compound 20a, with an azetidine amide side chain, showed the best selectivity for JAK1 kinase vs. JAK2, JAK3 and TYK2, with low nanomolar potency (3.3 nM). We confirmed efficacious inhibitor activities of many of the compounds on the proliferation and production of inflammatory cytokines by primary T cells.

9:25 Selected Poster Presentation: Discovery of Encorafenib, a Potent, Selective RAF Kinase Inhibitor for Treatment of BRAFV600E-Positive Melanoma
Shenlin Huang, Ph.D., Senior Investigator, Medicinal Chemistry, Genomics Institute of the Novartis Research Foundation
Activating mutations of BRAF, especially V600E BRAF, are found in multiple cancers, most notably in melanoma, where approximately 40% of cases are BRAF-V600E positive. Presented is encorafenib (LGX818), a selective small molecule mutant-BRAF kinase inhibitor that suppresses the RAF-MEK-ERK pathway in tumor cells expressing activating BRAF-V600 mutations. In rodent BRAF-V600 tumor xenograft models, LGX818 induces sustained tumor regression at low doses and is well-tolerated. LGX818 has shown an excellent preclinical safety profile. Multiple clinical trials are underway with LGX818 in patients harboring mutant-BRAF solid tumors.

9:40 Coffee Break

10:05 Target Residence Time-Guided Optimization of TTK Kinase Inhibitors
Rogier C. Buijsman, PhD, Head, Chemistry, Netherlands Translational Research Center B.V. (NTRC)
We studied NTRC 0066-0, a selective inhibitor of TTK, together with eleven TTK inhibitors from different chemical classes developed by others. Parallel testing showed that the cellular activity of the TTK inhibitors correlates with their binding affinity and, more strongly, with target residence time. X-ray structures revealed that the most potent inhibitors induce a unique structural conformation. Based on this insight, new TTK inhibitors were developed with longer target residence times and very potent anti-proliferative activity.

10:35 Transforming Kinase Inhibitors into New Lipophilic Salt Forms for Optimized Oral Absorption
Sponsored by Lonza Pharma & Biotech
Hywel D. Williams, PhD, Principal Scientist, Pharma Sciences, Lonza Pharma & Biotech

11:05 Determination of a Focused Mini-Kinase Panel for Early Identification of Selective Kinase Inhibitors
Scott Bembenek, PhD, Principal Scientist, Computer-Aided Drug Discovery, Janssen Research & Development
Currently, a rational, systematic, and unbiased method for choosing such a mini-kinase panel that reliably determines a compound's kinase selectivity profile does not exist. Using a novel in-house deconvolution algorithm, we performed a comprehensive analysis on our extensive kinase data set that has yielded findings far beyond those in the current literature. Indeed, one can construct a mini-kinase panel of optimal size that is very predictive when compared to the corresponding full kinase panel. Comparing this mini-kinase panel to random selection, we find an enrichment of 45.1%.

11:35 Luncheon Presentation: CSox-Based Sensors for Continuous, Homogeneous and Quantitative Monitoring of Protein Kinase and Phosphatase Activity

Sponsored by AssayQuant TECHNOLOGIES INC.

Erik Schaefer, President & CSO, AssayQuant Technologies

AssayQuant® is combining chelation-enhanced fluorescence, via the sulfonamido-oxine (Sox) chromophore, with high-throughput peptide synthesis methods to identify optimized physiologically-based substrates for measuring the activity of protein kinases and phosphatases. The result is a simple yet powerful method that allows continuous, quantitative and homogenous detection of activity using recombinant enzymes or crude cell or tissue lysates. This approach provides a quantum improvement in assay performance and productivity needed to accelerate discovery and drug development efforts.

12:20 pm Session Break

ADVANCES IN COVALENT INHIBITOR DEVELOPMENT

1:15 Chairperson's Remarks

Stefan Laufer, PhD, Chairman, Pharmaceutical & Medicinal Chemistry, Pharmacy & Biochemistry, University of Tuebingen

1:20 Presentation I: Design & Development of Highly Selective JAK3 Probes (Janus Kinase 3): Exploring the Arginine-Pocket

Stefan Laufer, PhD, Chairman, Pharmaceutical & Medicinal Chemistry, Pharmacy & Biochemistry, University of Tuebingen

Covalent Inhibitors belong to the oldest and most successful drugs. Prominent examples are e.g. Acetylsaliclic Acid, ß-Lactone Antibiotics or Gastric Proton Pump Inhibitors. A major breakthrew in cancer therapy of the last decades was targeted therapy with protein kinase inhibitors. Still unmet needs in this field are target residence time, selectivity and rapid development of target kinase mutations. A very seminal approach to address these issues was described 2013 by Liu et al. "Targeting the Cysteinome": We applied this strategy to unsolved problems in the field of JAK3, JNKs and mutant EGFR kinases. JAK3 signaling is a key driver in the development of lymphoid cells and modulation of immune response. Due to its isolated expression in lymphocytes a selective JAK3 inhibitions is considered to be a promising strategy for the development of new immunosuppressant drugs. Via a covalent-reversible inhibition approach we were able to develop new highly potent JAK3 inhibitors with high isoform specificity as well as an outstanding kinome wide selectivity. A novel binding mode was observed in the x-ray structure.

1:50 The Meisenheimer Complex as a Novel Paradigm in Drug Discovery: Targeting PLK1 through a Novel Covalent Mechanism

Campbell McInnes, PhD, Professor, Drug Discovery and Biomedical Sciences, University of South Carolina

We will describe novel inhibitors of PLK1 kinase activity that inhibit through a unique covalent strategy. The discovery and optimization of these inhibitors is described in addition to confirmation of their on-target anti-tumor mode of action through selective PLK1 inhibition.

2:20 A Kinase Platform for the Discovery of Reversible and Covalent Kinase Inhibitors

Igor Mochalkin, PhD, Associate Director, Medicinal Chemistry & Lead Optimization, EMD Serono, Inc.

This kinase platform included a combination of fragment screening, kinase-focused library design and scaffold hopping, tailored for individual kinases, kinase mini-panels and the human kinome. I will highlight our implementation of the kinase technologies that were coupled with medicinal and computational chemistry to identify and develop three clinical kinase-inhibitor candidates from EMD: evobrutinib, M7583 and M2698.

2:50 Presentation II: Triple Mutant EGFR: Report of an Irreversible EGFR Inhibitor with Low Nanomolar Activity Against L858R_T790M_C797S Resistance Mutant

Stefan Laufer, PhD, Chairman, Pharmaceutical & Medicinal Chemistry, Pharmacy & Biochemistry, University of Tuebingen

The emergence of mutations within the catalytic domain of EGFR has led to resistances against small molecular drugs. By the application of a scaffold hopping approach, we successfully developed picomolar covalent-irreversible inhibitors against gefitinib resistant EGFR mutants with high cellular activity (14 nM). Moreover we further improved the reversible binding patterns of this chemotype to yield compounds showing high activities in the low nanomalar range against the clinically challenging osimertinib resistant L858R/T790M/C797S triple mutant.

3:20 Accelerated Drug Discovery with CETSA®

Sponsored by PELAGO BIOSCIENCE

Michael Dabrowski, CEO, Pelago Bioscience

Using CETSA, researchers can now measure directly how a compound interacts with target proteins in the cell. CETSA can be used against known targets or in an unbiased proteomic approach that makes it ideal for target deconvolution, safety studies and for biomarker discovery.

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

4:30 Plenary Session Welcome Remarks from Event Director

Anjani Shah, PhD, Conference Director, Cambridge Healthtech Institute

4:35 Sponsored Plenary Keynote Introduction *(Opportunity Available)*

4:40 PLENARY KEYNOTE: Activity-Based Proteomics: Protein and Ligand Discovery on a Global Scale

Benjamin F. Cravatt, PhD, Professor and Co-Chair, Department of Molecular Medicine, The Scripps Research Institute

To address uncharacterized proteins, we have introduced chemical proteomic technologies that globally profile the functional state of proteins in native biological systems. Among these methods is activity-based protein profiling (ABPP), which utilizes chemical probes to map activity states of large numbers of proteins in parallel. I will discuss the application of ABPP to discover and functionally annotate proteins in mammalian physiology and disease, and the generation and implementation of advanced ABPP platforms for proteome-wide ligand discovery.

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

6:30 End of Day

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WEDNESDAY, APRIL 4

7:30 am Continental Breakfast Breakout Discussions

DESIGN AND DEVELOPMENT OF NOVEL ALLOSTERIC MODULATORS

8:30 Chairperson's Remarks
Ravi G. Kurumbail, PhD, Research Fellow and Structural Biology Laboratory Head, Pfizer

8:35 Fragment-Based Discovery of Inhibitors of ERK Kinase
Marc O'Reilly, PhD, Senior Director of Molecular Sciences, Astex Pharmaceuticals
This work describes the discovery of highly selective, orally bioavailable, allosteric/bitopic inhibitors of ERK kinase which show robust anti-tumor activity in a range of animal models.

9:05 Isoform-Selective Activators of AMP-Activated Protein Kinase for Metabolic Diseases
Ravi G. Kurumbail, PhD, Research Fellow and Structural Biology Laboratory Head, Pfizer
AMP-activated protein kinase (AMPK) is a heterotrimeric protein kinase that maintains cellular and whole-body energy homeostasis. We have been seeking specific activators of AMPK for the treatment of cardiovascular and metabolic diseases. High-throughput screening using a novel biochemical assay platform resulted in the identification of multiple chemotypes that target distinct AMPK subunits. We have established the molecular mode of action of these isoform-selective activators through structural, biophysical and kinetic studies.

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

KINASE INHIBITORS FOR CNS AND NEURODEGENERATIVE DISORDERS

10:30 Optimization of Brain Penetrant ATM Kinase Inhibitors for the Treatment of Huntington's Disease
Leticia Toledo-Sherman, PhD, Director of Computer-Aided Drug Design and Medicinal Chemistry, Chemistry, CHDI Foundation
The presentation will be centered on our efforts to attain potent, selective and brain penetrant ATM kinase inhibitors as proof-of-concept agents for HD. Importantly we demonstrate strong *in vitro-in vivo* correlations and a robust PK/PD relationship that warrant further studies with these compounds.

11:00 A Journey in the Kinome: Approaches, Strategies and a Bit of Luck
Sponsored by evotec
Daniele Andreotti, Director, Head, Medicinal Chemistry 3; Drug Design and Discovery, Aptuit
An overview of the main approaches and therapeutic area where eukaryotic and prokaryotic kinase inhibitors find application will be described. The presentation will be completed by reporting a successful example of Integrated Drug Discovery program. Implementation of a proper approach and strategy have allowed to identify valuable candidates within the agreed timelines and budget.

11:30 Discovery of 7-Oxo-2,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridine Derivatives as Potent, Orally Available, and Brain-Penetrating Receptor Interacting Protein 1 (RIP1) Kinase Inhibitors - Analysis of Structure-Kinetic Relationships
Masato Yoshikawa, PhD, Principal Scientist, CNS Drug Discovery Unit, Research, Takeda Pharmaceutical Company Limited
We will present a discovery of 7-oxo-2,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridine derivatives as a novel chemical series of brain-penetrating RIP1 kinase inhibitors. The optimization by utilizing SBDD approach led to the discovery of a highly potent, orally active, and brain-penetrating RIP1 kinase inhibitor with excellent PK profiles. Our preclinical candidate significantly suppressed necroptotic cell death both in mouse and human cells. Oral administration of the candidate (10 mg/kg, bid) attenuated disease progression in the mouse EAE model of multiple sclerosis.

12:00 pm End of Conference

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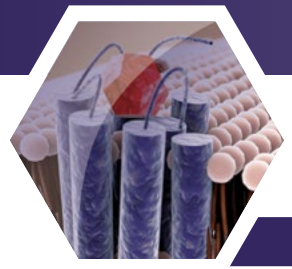


2ND ANNUAL

GPCR-Targeted Drug Design

New Structural, Pharmacological and Biophysical Insights and Tools

April 3-4, 2018 | Hilton San Diego Bayfront | San Diego, CA

TUESDAY, APRIL 3

7:00 am Registration and Morning Coffee

RECEPTOR CONFORMATIONAL STATES AND BIASED LIGANDS

8:00 Welcome Remarks
Anjani Shah, PhD, Conference Director,Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks
Andrew Alt, PhD, Associate Director, Biology, Arvinas

8:10 FEATURED PRESENTATION: β-arrestin Desensitization Cycles and Biosensor Assays
Martin Lohse, PhD, Chairman, Max Delbrück Center, Berlin, Germany
Optical analyses are providing new aspects in the analysis of GPCRs. Most notably, their activation and signaling can be monitored in real time and in intact cells by FRET microscopy. Motility and interactions can be studied by single molecule microscopy. These methods can also be used to investigate downstream signaling and to discover bias in G-protein- vs. beta-arrestin-mediated signals. They have allowed the discovery of multiple active states of beta-arrestins, suggesting that beta-arrestins undergo an activation/deactivation cycle. Differential effects of various ligands indicate that they may differ in their physiological effects by selectively stimulating distinct kinase pathways.

9:10 Fighting the Opioid Epidemic: Allosteric Modulators of Opioid Receptors and the Utility of Adding NAMs to the Therapeutic Arsenal
Andrew Alt, PhD, Director, Center for Chemical Genomics, University of Michigan
It is now emerging that determining drug target binding kinetics, next to traditional potency measures, may improve the success rate of a candidate drug moving through the clinical development. Our work provides new insights in ligand-GPCR interactions and underlines the importance of measuring binding kinetics of both drug candidates and competing endogenous ligands.Positive allosteric modulators of opioid receptors (opioid PAMs) have been proposed as a novel therapeutic approach for achieving analgesia with improved side-effect and addiction liability profile compared to traditional orthosteric opioid receptor agonists such as morphine or oxycodone. Newly discovered negative allosteric modulators (NAMs) of opioid receptors will be introduced, which may offer advantages over competitive antagonists for the acute treatment of opioid overdose.

9:40 Coffee Break

10:05 GPCR-Targeted Lead Optimization: The Importance of the Assay in Fitting Data to Models
Terry Kenakin, PhD, Professor, Department of Pharmacology, University of North Carolina School of Medicine
I will compare the muscarinic receptor Gq protein activation profiles of five exemplar molecules (slow binding agonists, partial agonists, inverse agonists, PAM-Agonists and Beta-PAMs) in calcium and IP1 assays to illustrate how quantitative comparisons to pharmacological models can both identify mechanisms of action and also convert descriptive findings to predict data for therapeutic systems. Using these models optimally allows the identification of consistent and simple scales of activity that can guide medicinal chemistry.

10:35 New Tools for GPCR Thermo-Stabilization
Seva Katritch, PhD, Assistant Professor, The Bridge Institute, University of Southern California
Engineering of GPCR constructs with improved thermostability is a key for successful structural and biochemical studies of this transmembrane protein family. Here we introduce a computational approach to effective prediction of stabilizing mutations in GPCRs, named CompoMug, which employs sequence-based analysis, structural information, and a derived machine learning predictor. Tested experimentally on the serotonin 5-HT2C receptor target, CompoMug resulted in 10 new stabilizing mutations and enabled structure determination for the 5-HT2C receptor complexes in inactive and active-like states.

11:05 GPCR Allosteric Coupling Investigated by NMR and X-Ray Diffraction
Matthew Eddy, PhD, Postdoctoral Fellow, Laboratory of Raymond Stevens, University of Southern California and The Scripps Research Institute
Drug binding in human GPCRs is allosterically connected over 30 Å to the intracellular signaling surface. Using advanced techniques for stable isotope labeling, we probe this allosteric network with NMR spectroscopy in solution for a native GPCR and variant with strikingly different signaling properties. X-ray crystal structures of the same variant reveal local conformational rearrangements in a known signaling-related structural motif. In parallel, NMR data uncover large signaling-related changes in conformational dynamics. Information from both techniques paired together provides a comprehensive picture of changes in structure and dynamics underpinning GPCR allosteric coupling.

11:35 Luncheon Presentation: Reaching beyond Developing Stable GPCR Cell Lines
Sponsored by MULTISPAN One-Stop shop for GPCR Research
Lisa Minor, Scientific Consultant, Multispan, Inc.
Developing high quality assays is paramount for drug discovery screening. Multispan devoted significant effort in developing signaling and phenotypic assays using endogenous targets such as RXFP1 in THP-1, CGRP in SK-N-MC, AMPK in C2C12, and DNA-PK in HELA cells. We also developed stable cell line assays for CGRP, AM, and Amylin by studying and overcoming endogenous RAMP expression and designed a 32-GPCR panel comprising CNS and cardiovascular liability targets. In addition to radioligand binding, we established a FACS-based quantification of GPCR expression to benchmark target expression against physiological level in native cells.

12:20 pm Session Break

GPCRs IN CANCER AND OTHER DISEASES

1:15 Chairperson's Remarks
JoAnn Trejo, PhD, MBA, Professor and Vice Chair, Department of Pharmacology, Associate Dean for Health Sciences Faculty Affairs, University of California, San Diego

1:20 GPCRs as Targets in Cancer
Paul A. Insel, MD, Distinguished Professor, Pharmacology and Medicine; Co-Director, Medical Scientist MD/PhD Training Program, University of California, San Diego
Emerging data suggest that GPCRs contribute to malignancy and certain GPCRs have higher expression in tumors compared to normal tissue. Using multiple approaches to assess GPCRs in human tumors, cancer cells and cancer-associated fibroblasts (CAFs) in the tumor microenvironment, we find that tumors, cancer cells and CAFs have higher expression of many GPCRs. Confirmatory, validation data exist for multiple such GPCRs in pancreatic cancer, a highly lethal cancer in need of new, effective therapies.

1:50 Illuminating the Onco-GPCRome
J. Silvio Gutkind, PhD, Professor, Department of Pharmacology; Associate Director of Basic Science, Moores Cancer Center, UCSD
Recent large cancer sequencing initiatives have revealed that more than 25% of all human malignancies harbor mutations in G proteins and GPCRs, and that certain GPCR families are aberrantly expressed in multiple human neoplasia. We will present new evidence supporting the potential clinical benefit of targeting GPCRs, G proteins, and their regulated signaling circuitry for cancer prevention and treatment. How GPCRs modulation can be exploited to increase the response to new immunotherapies will be discussed.

2:20 Anti-Leukemic Activity of Imipridone ONC212 via Selective Targeting of Orphan GPCR GPR132/G2A
Varun Vijay Prabhu, PhD, Associate Director, Research and Development, Oncoceutics, Inc.
Imipridones are a new class of anti-cancer small molecules that share a unique tri-heterocyclic core structure and selectively engage GPCRs. Experimental GPCR profiling using the PathHunter® β-Arrestin assay (DiscoverX) and multidose validation revealed that imipridone ONC212 selectively targets orphan GPCR GPR132/G2A at nanomolar concentrations. BIOSENS-ALL BRET assay (Domain) showed that ONC212 promotes Gq family activation downstream of GPR132. ONC212 was non-toxic to normal cells at therapeutic concentrations and demonstrated robust *in vivo* safety/efficacy in leukemia xenograft models.

2:50 Therapeutic Promise of Allosteric Modulators of Angiotensin II Receptor
Sadashiva Karnik, PhD, Professor, Molecular Cardiology, Lerner Research Institute, Cleveland Clinic
Novel allosteric modulators were discovered based on crystal structure and computer assisted drug development. These novel molecules showed high specificity and efficacy in pharmacological and signaling studies. *In vivo* evaluation in animal models are in progress. This will be the first report of allosteric chemotypes for any angiotensin receptor.

3:20 Sponsored Presentation *(Opportunity Available)*

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

4:30 Plenary Session Welcome Remarks from Event Director
Anjani Shah, PhD, Conference Director, Cambridge Healthtech Institute

4:35 Sponsored Plenary Keynote Introduction *(Opportunity Available)*

4:40 PLENARY KEYNOTE: Activity-Based Proteomics: Protein and Ligand Discovery on a Global Scale
Benjamin F. Cravatt, PhD, Professor and Co-Chair, Department of Molecular Medicine, The Scripps Research Institute
To address uncharacterized proteins, we have introduced chemical proteomic technologies that globally profile the functional state of proteins in native biological systems. Among these methods is activity-based protein profiling (ABPP), which utilizes chemical probes to map activity states of large numbers of proteins in parallel. I will discuss the application of ABPP to discover and functionally annotate proteins in mammalian physiology and disease, and the generation and implementation of advanced ABPP platforms for proteome-wide ligand discovery.

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

6:30 End of Day

WEDNESDAY, APRIL 4

7:30 am Continental Breakfast Breakout Discussions

ENDOSOMAL SIGNALING

8:30 Chairperson's Remarks
Irina Kufareva, PhD, Project Scientist, The Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego

> "I met some of my best collaborators here. This is a good networking tool. I like the meeting; it's very good."
>
> – DONALD D., PROFESSOR, UCSD

8:35 **Ubiquitin-Mediated Inflammatory Signaling by GPCRs**
JoAnn Trejo, PhD, MBA, Professor and Vice Chair, Department of Pharmacology, Associate Dean for Health Sciences Faculty Affairs, University of California, San Diego
Ubiquitination of 40 mammalian GPCRs has been reported, but despite the rich complexity of GPCR signaling, ubiquitination is attributed largely to GPCR degradation. We discovered that ubiquitination of GPCRs promotes p38 activation on endosomes via recruitment of TAB2, which co-associates with TAB1 that directly binds to p38a. TAB1-dependent p38 activation is critical for PAR1-mediated endothelial inflammatory responses. The mechanisms by which GPCR-induced p38 endosomal inflammatory signaling is regulated is not known and will be discussed.
Decoding the Layered Internet-like Architecture of a Cell's Signaling Network:Precisionalized Drug Discovery in the Era of Network Medicine

9:05 **Decoding the Layered Internet-like Architecture of a Cell's Signaling Network:Precisionalized Drug Discovery in the Era of Network Medicine**
Pradipta Ghosh, MD, Professor, Departments of Medicine and Cell and Molecular Medicine, UC San Diego
We posit that the architecture and the principles of information transfer in the intracellular communication are in many ways similar to those in the global communication network, the Internet, spurring the Intranet of Cells (IoC) metaphor. In particular, as in telecommunications, flexibility, evolvability and robustness in the IoC are gained at the expense of speed, and appear to be mediated by the layered protocol architecture at the signaling stations. Our IoC initiative is to organize the cell's information and make it accessible and useful.

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

NEW GPCR SCREENING AND BINDING ASSAYS AND TOOLS

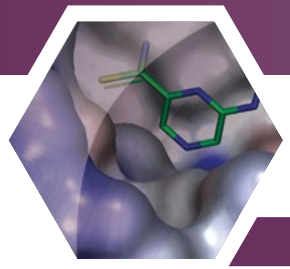
10:30 **Discovery of Small Molecule Protease-Activated Receptor 2 (PAR2) Antagonists**
Dean G. Brown, PhD, Director of External Chemistry, Hit Discovery, Discovery Sciences, IMED Biotech Unit, AstraZeneca
We employed two screening strategies to identify antagonists at protease activated receptor (PAR2), one being a DNA-encoded library screen on PAR2 and the second a fragment screen using a stabilized PAR2 GPCR receptor. From these efforts, we identified two lead series of compounds, each of which bind to distinct and previously unknown allosteric sites. These results illustrate the power of integrating stabilized GPCR technologies into established screening paradigms.

11:00 **Binding and Functional Analysis - Complementary Approaches in Safety Pharmacology using GPCRs** *Sponsored by* eurofins | Pharma Discovery Service
Thierry Jolas, Ph.D., Study Director, Eurofins Pharma Discovery Services
In vitro pharmacological profiling is an integral part of drug discovery and development, and provides critical information at multiple key decision points in the process. Using several examples, I will show how a combined approach of adopting both binding and functional assays may provide a more holistic assessment of test compounds activity.

11:30 **Kinetic Drug Discovery for GPCRs**
Sam Hoare, PhD, Founder and Chief Scientist, Pharmacology Data Analysis, Pharmechanics, LLC
Novel paradigms are needed for translating the raw data emerging from new molecular biosensor and reader technology-based assays into meaningful pharmacological activity parameters that can be used for structure-activity analysis. We have developed a new kinetic data analysis framework that, using standard curve-fitting software, yields values of the rate of onset of the response, and the total signal produced. Here we will show the resulting structure-activity kinetics for beta2 adrenoceptor signaling, and for biased agonism at the D2 dopamine receptor.

12:00 pm **End of Conference**

> "Up-to-date discussion on late breaking strategies for novel kinase inhibitor design."
>
> – ANN A., SENIOR SCIENTIST, PFIZER



13TH ANNUAL

Fragment-Based Drug Discovery

Hits to Leads and Lessons Learned

April 3-4, 2018 | Hilton San Diego Bayfront | San Diego, CA

TUESDAY, APRIL 3

7:00 am Registration and Morning Coffee

CHEMISTRY CHALLENGES FOR GROWING FRAGMENTS

8:00 Welcome Remarks
Anjani Shah, PhD, Conference Director, Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks
Daniel A. Erlanson, PhD, Co-Founder, Carmot Therapeutics, Inc.

8:10 Creation of a Novel Class of Potent and Selective MTH1 Inhibitors Using Fragment-Based Design
Jenny Viklund, PhD, Director, Protein Science and Drug Design, Sprint Bioscience
This presentation describes our fragment-based approach to create potent and selective inhibitors of MTH1 that also have promising drug-like properties. MTH1 is an enzyme involved in degradation of oxidized dGTP to prevent its incorporation into DNA. Enzymes such as MTH which are involved in sanitization of the nucleotide pool have been shown to be important for tumor cell survival.

8:40 Fragment to Lead: SAR and Optimization of Novel Bromodomain Inhibitors with High fsp3 Character
Justin Dietrich, PhD, Senior Scientist III, Discovery Chemistry and Technology, AbbVie, Inc.
This presentation will cover a recent application of AbbVie's revamped fragment library featuring an example where a fragment with high fsp3 character was quickly advanced to lead with high BEI, LE, and LipE as well as good oral bioavailability. The unique properties associated with fragments with high sp3 character and some lessons learned on the efficiency of chemistry to iterate 3d fragment hits will also be discussed.

9:10 Fragment-Based Screening for Metallo-ß-lactamases Inhibitors: SPR and NMR Combined Approach
Sponsored by evotec
Silvia Davalli, Senior Manager, Head, NMR Spectroscopy; Drug Design and Discovery, Aptuit
Metallo-β-lactamases are associated with multidrug resistance in Gram-negative bacteria and their development is a major health concern as there are no clinically-approved drugs up to now. To address the need for novel structurally-diverse inhibitors, we have screened our internal fragment library: information from NMR and SPR techniques are exploited by computational analysis.

9:40 Coffee Break

NOVEL SPR AND NMR APPLICATIONS TO FBDD

10:05 Enabling Alternative Binding Sites with Novel Fragment Screening Approaches Using Surface Plasmon Resonance
Kevin M. O'Malley, PhD, Senior Research Investigator, Lead Discovery, LDO, Bristol-Myers Squibb R&D
Surface Plasmon Resonance (SPR) is an industry standard method for the identification and characterization of fragment hits. Its label free detection using changes in mass make it ideal to definitively confirm target engagement. Typical uses have been to interrogate known binding/active sites. Probing alternative sites can have the advantage of providing novel chemotypes with different modes of interaction with target. Here we describe methods of probing alternate epitopes using conventional and emerging SPR approaches.

10:35 Using NMR-Based Activity Assays to Identify Fragment Leads Against Two Trichomonas Vaginalis Enzymes
Brian Stockman, PhD, Associate Professor and Chair, Chemistry, Adelphi University
Trichomonas vaginalis is classified as a neglected parasitic infection by the CDC, with about 5% of clinical cases resistant to current treatments. Two essential nucleoside ribohydrolase enzymes from *T. vaginalis* were screened against a fragment library using NMR-based activity assays. Distinct classes of inhibitors with ligand efficiencies greater than 0.5 were identified. Fragment expansion experiments have further improved ligand efficiencies and provided direction to ongoing medicinal chemistry efforts designed to discover nM inhibitors of these enzymes.

11:05 Nanoscale Encapsulation for Optimized NMR Fragment Based Drug Discovery
Josh Wand, PhD, Professor, Biochemistry & Biophysics, University of Pennsylvania
Encapsulation of single protein molecules in reverse micelles is a new and potentially transformative technology. Encapsulation significantly enhances fragment based screening using NMR spectroscopy. The technology in the context of several examples will be described.

11:35 Luncheon Presentation: A Complete Pipeline for Biophysics Based Drug Discovery
Sponsored by ZoBio
Gregg Siegal, CEO, ZoBio
ZoBio has built an integrated technology pipeline that enables a wide array of targets for FBLD and maximizes the chance of successfully generating high quality leads. I'll discuss all the key elements, including: building a fragment library, using high throughput protein engineering to solve structure problems and better understand target biology, why we use orthogonal fragment screening, and the advantages of having both NMR and X-ray structural biology capabilities.

12:20 pm Session Break

FRAGMENT-ASSISTED DRUG DISCOVERY

1:15 Chairperson's Remarks
Derek Cole, PhD, Director, Medicinal Chemistry, Takeda

Cambridge HEALTHTECH Institute
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1:20 FEATURED PRESENTATION: The Convoluted Journey of an ERK2 Fragment Series (with an HTS Detour)
Huifen Chen, PhD, Senior Scientist, Department of Biophysics, Genentech
ERK1/2 represent an essential downstream node in the Ras/Raf/MEK/ERK (MAPK) signal transduction pathway, and have attracted significant interest as potential anticancer targets. Both fragment and high-throughput screens were carried out in parallel to discover novel ERK1/2 inhibitors. In this presentation, I discuss the journey of a fragment-based series along with how learnings from the fragment series were incorporated into the HTS-derived series which led to a clinical candidate GDC-0994.

1:50 Fragment-Based Discovery of Inhibitors of ERK Kinase
Marc O'Reilly, PhD, Senior Director of Molecular Sciences, Astex Pharmaceuticals
This work describes the discovery of highly selective, orally bioavailable, allosteric/bitopic inhibitors of ERK kinase which show robust anti-tumour activity in a range of animal models.

2:20 Discovery of a Ketohexokinase (KHK) Inhibitor for the Treatment of NAFLD/NASH: Fragment-to-Candidate via Structure-Based Drug Design and Parallel Chemistry
Kim Huard, PhD, Senior Principal Scientist, Medicine Design, Pfizer, Inc.
Identification of a selective ketohexokinase (KHK) inhibitor was sought to help elucidate the effect of KHK inhibition on metabolic disorders. In our efforts towards this goal, key structural features interacting with KHK were discovered through fragment-based screening and used to mine our compound collection for attractive chemical starting points. This fragment-to-candidate story will present the fragment-based screen triage, compound optimization via structure-based drug design (SBDD), *in vivo* target validation and clinical candidate selection.

2:50 Identification of eFT508, an Oral, Potent and Highly Selective Inhibitor of Mitogen-Activated Protein Kinase Interacting Kinase (MNK) 1 and 2, via a Disciplined, Iterative Structure-Based Drug Design Strategy
Paul Sprengeler, PhD, Research Fellow, Medicinal Chemistry, eFFECTOR Therapeutics, Inc.
eFT508, an exquisitely selective, potent dual MNK1/2 inhibitor, was designed to assess the potential for control of oncogene signaling at the level of mRNA translation. The crystal structure-guided design beginning with fragments and fragment-like molecules leverages stereoelectronic interactions unique to MNK. eFT508 has potent *in vivo* anti-tumor activity in models of DLBCL and solid tumors and is currently being evaluated in Phase 2 clinical trials in solid tumors and lymphoma.

3:20 Present and Futuristic Collaborative Drug Discovery Informatics Innovations (CDD Vault + Bioassay Express)
Sponsored by
CDD VAULT
Barry Bunin, CEO, Collaborative Drug Discovery, Inc.
CDD Vault software, activity & registration, visualization, inventory, and ELN capabilities all address today's markets. For tomorrow's research: open source descriptors and model sharing capabilities allow for platform-independent collaborations. We've also developed BioAssay Express, human-readable assay text to computer-readable format to augment bioassay needs.

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

4:30 Plenary Session Welcome Remarks from Event Director
Anjani Shah, PhD, Conference Director, Cambridge Healthtech Institute

4:35 Sponsored Plenary Keynote Introduction
(Opportunity Available)

4:40 PLENARY KEYNOTE: Activity-Based Proteomics: Protein and Ligand Discovery on a Global Scale
Benjamin F. Cravatt, PhD, Professor and Co-Chair, Department of Molecular Medicine, The Scripps Research Institute
To address uncharacterized proteins, we have introduced chemical proteomic technologies that globally profile the functional state of proteins in native biological systems. Among these methods is activity-based protein profiling (ABPP), which utilizes chemical probes to map activity states of large numbers of proteins in parallel. I will discuss the application of ABPP to discover and functionally annotate proteins in mammalian physiology and disease, and the generation and implementation of advanced ABPP platforms for proteome-wide ligand discovery.

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

6:30 End of Day

Cambridge HEALTHTECH Institute
A Division of Cambridge Innovation Institute

WEDNESDAY, APRIL 4

7:30 am Continental Breakfast Breakout Discussions

NON-NMR APPROACHES FOR FBDD

8:30 Chairperson's Remarks
Huifen Chen, PhD, Senior Scientist, Discovery Chemistry, Genentech

8:35 Hot-Spotting with Thermal Scanning: A Ligand- and Structure-Independent Assessment of Target Ligandability
Fredrik Edfeldt, PhD, Associate Principal Scientist, Biophysics, Discovery Sciences, AstraZeneca R&D, Sweden
Evaluating the ligandability of a protein is essential when defining hit-finding strategies or to prioritize amongst drug targets. We demonstrate that high-throughput thermal scanning can be used as a simple and generic biophysical fragment screening method for this purpose. We have applied the method to a large set of proteins and show that the assessment is predictive for the success of HTS. We have also made use of urea and D2O to improve assay sensitivity.

9:05 Weak Affinity Chromatography (WAC): A Novel Approach to Fragment-Based Drug Discovery
Sten Ohlson, PhD, Professor, School of Biological Sciences, Nanyang Technological University
Weak Affinity Chromatography (WAC) is an established analytical affinity technique for specific and gentle separation and analysis of biomolecules. Since its inception in 1990 it has among other applications been successfully used as an efficient tool in drug discovery, mainly for fragment screening. WAC advantages include speed, high quality fragment affinity information, reliable fragment-to-target binding kinetics information and enabling use of a standard LC/MS platform. Examples will be given on screening of membrane proteins (aquaporins), proteases, kinases, coagulation proteins, chaperones and protein-protein interaction (PPI).

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

FRAGMENTS FOR PPIs

10:30 Fragment-Based Discovery of a Chemical Probe for the NSD3-PWWP-1 Domain
Jark Böttcher, Principal Scientist, Medicinal Chemistry, Boehringer Ingelheim RCV GmbH & Co KG
We describe the fragment-based discovery of molecules binding to the proposed methyl-lysine binding site of the PWWP-1 domain of NSD3. Supported by a virtual screening approach and subsequent structure-based optimization, the initial hits were optimized into a chemical probe with confirmed binding in cellular assays. The probe and the related negative control can be used to explore the functions of the PWWP-1 domain.

11:00 Lead Generation without an X-Ray Crystal Structure: An NMR Method to Probe Protein-Ligand Complexes
Julien Orts, PhD, Professor, Laboratory of Physical Chemistry, Swiss Federal Institute of Technology ETH
My talk is about a NMR method to solve protein-ligand complex structure. I will present two or three examples of this method applied to finding inhibitors against specific PPI targets.

11:30 *In silico* Fragment Screening to Identify Cryptic Pockets and Allosteric Sites for PPI Inhibitor Development
Ben Cossins, PhD, Principal Scientist, UCB Pharma
Drug development is increasingly difficult and expensive. Valuable targets are not always amenable to modulation by small molecules and resources are often directed towards seemingly intractable targets. We have been building and applying molecular dynamics based fragment screening and *de novo* design approaches to try and understand ligandability and functionality for protein-protein interaction targets. We believe this approach can steer us towards hit compounds for tractable PPI targets.

12:00 pm End of Conference

> "I really like this conference. I always learn new, latest developments that are occurring in the field."
>
> – MICHAEL F., PRINCIPAL SCIENTIST, ABBVIE

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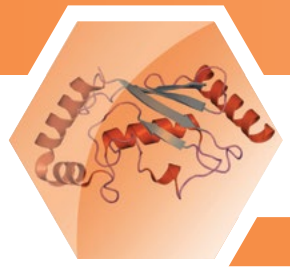

INAUGURAL

Ubiquitin Proteasome System Inhibitors

Discovery and Development of Small Molecules Targeting DUBs and Ligases

April 4-5, 2018 | Hilton San Diego Bayfront | San Diego, CA

WEDNESDAY, APRIL 4

12:30 pm Registration

12:45 Dessert Break in the Exhibit Hall with Poster Viewing

HIJACKING THE UPS FOR TARGETED PROTEIN DEGRADATION

1:30 Welcome Remarks
Kip Harry, Senior Director, Conferences, Cambridge Healthtech Institute

1:35 Chairperson's Opening Remarks
Alexander Statsyuk, PhD, Assistant Professor, Department of Pharmacological and Pharmaceutical Sciences, University of Houston

1:40 Target Protein Degradation for New Therapeutics
Shaomeng Wang, PhD, Warner-Lambert/Parke-Davis Professor, Medicine; Professor, Medicine, Pharmacology and Medicinal Chemistry; Director, Center for Therapeutics Innovation, University of Michigan
Recently, a new small-molecule approach has been employed to target degradation of BET proteins through the design of bifunctional, Proteolysis-Targeting Chimera (PROTAC) molecules. Based upon our new classes of highly potent small-molecule BET inhibitors, we have designed and optimized highly potent and efficacious small-molecule degraders of BET proteins. We have performed critical and extensive evaluation of our BET degraders for their therapeutic potential and mechanism of action in models of acute leukemia and solid tumors.

2:10 PROTACs: The Chemical Equivalent of CRISPR
Dan Bondeson, Research Scientist, Crews Lab, Yale University
Induced protein degradation offers several advantages over traditional inhibition strategies and has emerged recently as a potential therapeutic option. For the past 16 years, we have helped develop this fast growing field, shepherding our initial chemical biology concept into a drug development strategy that is on the verge of clinical validation. PROTACs with high target selectivity, potency, and oral bioavailability will be discussed as well as a system to address the 'PROTACability' of particular E3 ligases.

2:40 Covalent Inhibitors and Degraders of Challenging Targets in Cancer
Dennis Dobrovolsky, Research Scientist, Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School
This presentation will discuss new pharmacological strategies towards targeting kinases and other targets. Small molecules capable of inducing protein degradation through the recruitment of E3 ligases will be discussed with a focus on kinases. A general approach for identifying the most easily degradable kinase targets will be presented. Chemical design principles for developing degraders will be discussed. New approaches for developing covalent kinase inhibitors will also be discussed.

3:10 Protein Ubiquitination in Immune Homeostasis and Dysregulation
Yun-Cai Liu, PhD, Professor La Jolla Institute for Allergy and Immunology
Effective immune responses in our body are critical in defending invading pathogens, whereas such responses are balanced by immune tolerance mechanisms to prevent from attacking our own tissues. Loss of such balance could result in excessive tissue damage or malignant tumor formation. Our research for the last two decades has documented that E3 ubiquitin ligases play an essential role in lymphocyte activation and tolerance induction. We previously showed that the E3 ubiquitin ligase VHL-hypoxic inducing factor (HIF) pathway plays a key role in controlling the stability and function of regulatory T cells by modulating interferon-g production. We recently extended our studies to other cell types including innate lymphoid type 2 cells, and found that the VHL-HIF axis is important in regulating their development and function via switching the cellular glucose metabolism from oxidative phosphorylation to hypoxic glycolysis during lung inflammation. The latest results of our on-going research will be presented in this meeting. The anticipated results will provide us with a unique opportunity in targeting the E3 ligases in different cell types for potential therapeutic intervention of human inflammatory diseases and cancer.

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

4:30 Targeted Protein Degradation by Small Molecules
Alessio Ciulli, PhD, Professor, Chemical & Structural Biology, School of Life Sciences, University of Dundee
The application of small molecules to induce selected protein degradation is emerging as a transformative new modality of chemical intervention in drug discovery. We have previously shown that linking a VHL ligand that we had discovered with a pan-BET inhibitor creates highly selective PROTAC molecule MZ1. MZ1 triggers preferential intracellular degradation of Brd4, leaving the homologous BET members untouched, and exhibits greater anti-proliferative activity in leukemia cell lines than pan-BET inhibition.

5:00 Selected Poster Presentations

Ubiquitin Carboxyl-terminal H-L5 Inhibitor Diminishes TGFβ-1 Signaling and Ameliorates Pulmonary Fibrosis
Yutong Zhao, MD, PhD, Associate Professor of Medicine and Cell Biology, Co-director of Acute Lung Injury, Center of Excellence Department of Medicine University of Pittsburgh School of Medicine

DYRK2, a Novel Therapeutic Target in 26S Proteasome Dependent Neoplastic Malignancies
Sourav Banerjee PhD, Post-doctoral Scholar, Department of Pharmacology, University of California San Diego

5:30 Breakout Discussions

6:15 End of Day

6:30 Dinner Short Courses*
**Separate registration required; please see page 3 for details.*

Cambridge HEALTHTECH Institute
A Division of Cambridge Innovation Institute

THURSDAY, APRIL 5

8:00 am Breakfast Presentation: Improvements in NMR Approaches to Fragment Based Screening
Sponsored by BRUKER
Donna Baldisseri, Senior Applications Scientist, Bruker BioSpin
FBDD is a powerful search engine for identification of fragments that bind to disease relevant target proteins ultimately leading to drug candidates. NMR-based FBDD screening requires compound library validation, preparation of hundreds of samples per campaign, automated acquisition, processing of thousands of spectra, and their analysis for binding assessment. Here is described the streamlined solutions offered by Bruker, automating this pipeline to improve the speed and productiveness of FBDD screening for the pharmaceutical industry.

8:45 Plenary Session Welcome Remarks from Event Director
Anjani Shah, PhD, Conference Director, Cambridge Healthtech Institute

8:50 Plenary Keynote Introduction
Chris Petersen, CTO, Scientist.com

8:55 PLENARY KEYNOTE: Targeting Ras and MYC for the Treatment of Cancer
Stephen Fesik, PhD, Professor of Biochemistry, Pharmacology, and Chemistry, Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University School of Medicine
Two of the most important targets in cancer are Ras and MYC. However, both of these highly validated cancer targets are thought to be undruggable. In this presentation, I will discuss our approaches for targeting both of these proteins directly and indirectly using fragment-based methods and structure-based design.

9:45 Coffee Break in the Exhibit Hall with Poster Viewing

DESIGN AND DEVELOPMENT OF NOVEL DEUBIQUITINASE (DUB) INHIBITORS

10:40 Chairperson's Remarks
Tauseef R. Butt, PhD, President and CEO, Progenra, Inc.

10:45 Small Molecule Ubiquitin Protease (USP7) Inhibitors with Immune Cell-Based Anti-Tumor Activity Superior to That of Biologicals
Tauseef R. Butt, PhD, President and CEO, Progenra, Inc.
In immune competent animal models, USP7 inhibitors are potent anti-tumor agents, not only blocking tumor growth but also eliminating tumor metastasis. These results constitute the first example of a small molecule single agent that works by targeting both the tumor itself and the host immune system and also by eliminating tumor metastasis. In animal models, the USP7 inhibitor demonstrates activity that is superior to that of PD1 and CTLA4 antibodies.

11:15 Evaluation and Characterization of Small Molecule Inhibitors of Deubiquitinating Enzyme USP14 as Potential Anti-Cancer Agents
Stina Lundgren, PhD, Associate Principal Scientist/ Project Leader, Medivir AB
Over the years, USP14 has been reported to regulate the stability of a variety of proteins as well as modulating signal transduction in multiple cellular pathways, thereby effecting a range of cellular processes including Wnt-signaling and autophagy. USP14 aberrant expression and activity has been suggested to play an important role in tumorigenesis and neurodegenerative diseases. As part of Medivir DUB drug discovery efforts targeting DUBs, we have characterized a set of small molecule USP14 inhibitors We present data evaluating the effect of these USP14 inhibitors on cellular proliferation and Wnt signaling and compare them to the effect of siRNA knockdown of USP14.

11:45 Bio-Techne - Your Partner in UPS-Related Research and Drug Development
Sponsored by BostonBiochem a biotechne brand
Bradley Brasher, PhD, Managing Director, Boston Biochem
I will illustrate how Bio-Techne companies including Boston Biochem, Tocris, R&D Systems, Novus, and Protein Simple support the research and development of small molecule deubiquitinase inhibitors and PROTACs compounds. Additionally, I will detail how Boston Biochem can provide custom proteins and proteomics services for building and monitoring *in vitro* assays.

12:00 pm Mining the Deubiquitinase Family for Novel Drugs Utilizing FORMA's Drug Discovery Engine
Stephanos Ioannidis, PhD, Head, Early Portfolio, FORMA Therapeutics
The deubiquitinating enzymes (DUBs), by their reversal of the ubiquitination/polyubiquitination process, are key enzymes regulating protein homeostasis. As such, modulators of DUB function have the potential to be important therapeutics in oncology, immunology, neurodegenerative and other medical disorders involving pathological or dysregulated proteins. FORMA Therapeutics deploys multiple drug discovery screening platforms to explore broad target families on scale. Panels of functional cellular and enzymatic assays, including related target family selectivity screens, were established to mine the DUBome for novel chemical matter.

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

1:30 Dessert Break in the Exhibit Hall with Poster Awards

INSIGHTS INTO DEUBIQUITINASE ENZYMES AND INHIBITORS

2:15 Chairperson's Remarks
Tauseef R. Butt, PhD, President and CEO, Progenra, Inc.

2:20 DUB Inhibitors in Syngeneic Cancer Models and in Preclinical Studies
Wayne W. Hancock, M.D., Ph.D., Professor, Pathology and Chief of Transplant Immunology, Children's Hospital of Philadelphia and University of Pennsylvania
When it comes to trash talking about cells, there are lots to gossip about and reasons to do so. I will briefly review the key interactions between the trash collectors and the trash recyclers within cells, and how this has gone from esoterica to essential in the era of immune-oncology. DUBs help determine the outcomes of checkpoint blockade inhibition and are key to the functions of each of the main players in the immune response to cancer. While the effects of DUB inhibitors in reductionist xenograft models are salutary, the more relevant actions in syngeneic tumor models and in patients involve balancing the effects of DUB inhibitors on the immune system with their effects on tumor cells, and these are not things that can be predicted by their structures or staring at their ADME/tox profiles.

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2:50 USP7-Specific Inhibitors Target and Modify the Enzyme's Active Site via Distinct Chemical Mechanisms
Irina Bezsonova, PhD, Assistant Professor, Department of Molecular Biology and Biophysics, University of Connecticut
USP7 is a deubiquitinating enzyme that plays a pivotal role in multiple oncogenic pathways and therefore is a desirable target for new anti-cancer therapies. However, the lack of structural information about the USP7-inhibitor interactions has been a critical gap in the development of potent inhibitors. USP7 is unique among USPs in that its active site is catalytically incompetent, and is postulated to rearrange into a productive conformation only upon binding to ubiquitin.

3:20 Chemical Libraries to Unlock Deubiquitylase (DUB) Targeted Drug Discovery
Sponsored by UBIQUIGENT
Jason Brown, PhD, Scientific Director, Ubiquigent Ltd
Ubiquigent is a world leading provider of ubiquitin system targeted drug discovery tools and services. Within the ubiquitin signalling cascade the deubiquitylase (DUB) enzyme family offers a deep seam of drug target opportunities addressing an array of therapeutic areas. We will discuss Ubiquigent's commercially accessible first-in-class novel DUB targeted hit-finding chemical library DUBtarget™-001 and its characterisation employing our integrated service platforms featuring the DUBprofiler™ screening and selectivity and REDOXprofiler™ hit triage capabilities.

3:50 Refreshment Break

TARGETING THE PPIs OF E3 LIGASES

4:20 HECT E3 and RBR E3 Ligases as Drug Targets to Treat Cancer and Neurodegenerative Diseases: Basic Science and New Screening Technologies
Alexander Statsyuk, PhD, Assistant Professor, Department of Pharmacological and Pharmaceutical Sciences, University of Houston
E3 ligases (>600 known) are the key mediators of protein degradation pathways, and E3 ligase inhibitors or activators are promising drug leads. In addition, E3 ligases can be executors that mediate the degradation of PROTAC targets. In this presentation, we specifically discuss emerging biochemical mechanisms and biological roles of HECT and RBR E3 ligases, their therapeutic potential to treat cancers and neurodegenerative diseases, and current screening technologies to discover initial drug leads for this class of drug targets.

4:50 Redirecting the Cereblon-CRL4 Ubiquitin Ligase With Cereblon Modulator Compounds
Mary Matyskiela, PhD, Senior Scientist, Structural and Chemical Biology, Celgene
Cereblon modulators bind cereblon to confer differentiated substrate specificity to the CRL4CRBN E3 ubiquitin ligase. CC-220 is a cereblon modulator in Phase II clinical development that exhibits improved degradation of Ikaros and Aiolos. CC-885, a cereblon modulator with potent anti-tumor activity, mediates the cereblon-dependent ubiquitination and proteasomal degradation of the translation termination factor GSPT1. Crystallographic studies of the cereblon-DDB1-CC-885-GSPT1 complex revealed that GSPT1 binds cereblon and CC-885 through a surface turn containing a glycine residue at a key position. Mutational analysis and modeling demonstrate that the cereblon substrate Ikaros depends upon a similar structural feature for cereblon binding. These findings define a structural degron underlying cereblon 'neosubstrate' selectivity, and pave the way for the development of new cereblon modulators.

5:20 Cep78, a Novel Inhibitor of the HECT E3 Ubiquitin Ligase EDD-DYRK2-DDB1DCAF1
William Tsang, PhD, Research Unit Director, Cell Division and Centrosome Biology, Montreal Clinical Research Institute
EDD-DYRK2-DDB1DCAF1 is a multi-subunit HECT E3 ubiquitin ligase whose physiological functions are not fully understood. We found that EDD-DYRK2-DDB1DCAF1 is present at the centrosome, an organelle crucial for cell division, and that its enzymatic activity is regulated by a novel centrosomal protein called Cep78 in human cells. By using a combination of biochemistry, molecular biology, and cell biology, we dissected the mechanism by which EDD-DYRK2-DDB1DCAF1 is inhibited by Cep78.

5:50 End of Conference

> "What I really like at this conference is that there are parallel sessions. There is always a presentation at any time of the day that I find interesting."
>
> – STEFAN J., PRODUCT MANAGER, BRUKER BIOSPIN

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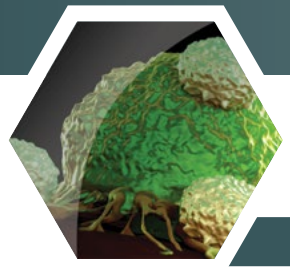

2ND ANNUAL

Small Molecules for Cancer Immunotherapy

Discovery and Development of Immune-Modulatory Small Molecules

April 4-5, 2018 | Hilton San Diego Bayfront | San Diego, CA

WEDNESDAY, APRIL 4

12:30 pm Registration

12:45 Dessert Break in the Exhibit Hall with Poster Viewing

SMALL MOLECULES TARGETING PD-1/ PD-L1 AND IDO

1:30 Welcome Remarks
Kip Harry, Senior Director, Conferences, Cambridge Healthtech Institute

1:35 Chairperson's Opening Remarks
Alexander Dömling, PhD, Professor and Chair, Department of Drug Design, University of Groningen

1:40 Small-Molecule Inhibitors of PD-1/PD-L1
Alexander Dömling, PhD, Professor and Chair, Department of Drug Design, University of Groningen
My research group is leading in the synthesis of macrocyclic compounds with non-peptidic character. We have not only devised 12 novel convergent straightforward synthetic ways to assemble very large macrocyclic libraries but we also applied them to antagonize protein-protein interactions such as PD1-PD-L1.

2:10 Tetraiodothyroacetic Acid (Tetrac), a Small Molecule Thyroid Hormone Antagonist, Disables Immune Checkpoint Defenses of Cancer Cells
Paul Davis, MD, Professor, Department of Medicine, Pharmaceutical Research Institute, Albany Medical College
We have shown that the PD-1/PD-L1 immune checkpoint is regulated non-immunologically by thyroid hormone. A thyroid hormone antagonist, tetrac, acts as a hormone receptor on an integrin expressed by cancer cells to downregulate expression of PD-L1 and PD-1 genes. beta-Catenin activation mediates T cell exclusion from the cancer microenvironment and tetrac blocks catenin activation non-immunologically by inducing expression of miR-21 and CBY1 (Chibby). Thus, acting outside the traditional immune system and at the level of gene expression, tetrac disables immune defenses of tumor cells.

2:40 FEATURED PRESENTATION: Small Molecule Antagonists Targeting PD-1/ PD-L1 and Other Immune Checkpoint Pathways
Murali Ramachandra, PhD, CSO, Aurigene Discovery Technologies Limited
We are developing small molecule oral agents dually targeting PD-L1 and another pathway to increase the response rate, and with a relatively shorter pharmacokinetic exposure for better management of irAEs. We have identified candidates potently targeting PD-L1 and VISTA or PD-L1 and TIM-3 pathways along with desirable physico-chemical profile, exposure upon oral dosing and pharmacological properties. CA-170, the first candidate from this approach dually targeting PD-L1 and VISTA, is now undergoing clinical trials.

3:10 Epigenetic Control of Immune Checkpoint Inhibitor Responses
Diana Hargreaves, PhD, Assistant Professor, Molecular and Cell Biology, Salk Institute for Biological Sciences
Mutations in subunits of the SWI/SNF chromatin remodeling complex are known to potentiate responses to checkpoint therapies and are thus attractive targets for the development of small molecules for cancer therapy. Here we describe a key role for the SWI/SNF subunit ARID1A in controlling chromatin accessibility and histone modifications at transcriptional enhancers and discuss our efforts to identify novel SWI/SNF complex inhibitors.

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

4:30 Using a Network-Driven Drug Discovery (NDD) Approach in the Identification and Optimisation of Novel Immune-Modulatory Small Molecules
Sree Vadlamudi, PhD, Programme Manager, Discovery, e Therapeutics plc
The majority of drug discovery approaches involve the search for a single binding target in a well-characterised pathway. But while pathways are easy to envisage, they do not reflect the complexity of biological systems. A more realistic way to describe the underlying interactions which occur is as a network. We have successfully implemented and validated a highly productive network-driven drug discovery (NDD) approach to identify NCEs in diverse areas of biology. We will describe a case study highlighting the application of our proprietary NDD methodology in the discovery and optimisation of small molecules with a novel mechanism of action (MOA) for modulating tryptophan catabolism in tumour and immune cell populations. Our lead molecules, covered by two patents, show potency in cell-based assays that is comparable or superior to the existing clinical candidates in development.

5:00 A Small Molecule Multiple Checkpoint Inhibitor
Floyd Taub, MD, CEO, Medical, AxImmune
Ax 101 has been shown to decrease markers of severe checkpoint inhibition including PD1, Tim 3 and Lag 3. This correlates with tumor inhibition in animals of myeloma, melanoma, bladder cancer and breast cancer. It also correlates with all human Phase I/II lymphoma patients who are immune eligible meeting irRECIST and some meeting classic RECIST.

5:30 Breakout Discussions

6:15 End of Day

6:30 Dinner Short Courses*
**Separate registration required; please see page 3 for details.*

THURSDAY, APRIL 5

8:00 am Breakfast Presentation: Improvements in NMR Approaches to Fragment Based Screening
Sponsored by BRUKER
Donna Baldisseri, Senior Applications Scientist, Bruker BioSpin
FBDD is a powerful search engine for identification of fragments that bind to disease relevant target proteins ultimately leading to drug candidates. NMR-based FBDD screening requires compound library validation, preparation of hundreds of samples per campaign, automated acquisition, processing of thousands of spectra, and their analysis for binding assessment. Here is described the streamlined solutions offered by Bruker, automating this pipeline to improve the

speed and productiveness of FBDD screening for the pharmaceutical industry.

8:45 Plenary Session Welcome Remarks from Event Director
Anjani Shah, PhD, Conference Director, Cambridge Healthtech Institute

8:50 Plenary Keynote Introduction
Chris Petersen, CTO, Scientist.com

8:55 PLENARY KEYNOTE: Targeting Ras and MYC for the Treatment of Cancer
Stephen Fesik, PhD, Professor of Biochemistry, Pharmacology, and Chemistry, Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University School of Medicine
Two of the most important targets in cancer are Ras and MYC. However, both of these highly validated cancer targets are thought to be undruggable. In this presentation, I will discuss our approaches for targeting both of these proteins directly and indirectly using fragment-based methods and structure-based design.

9:45 Coffee Break in the Exhibit Hall with Poster Viewing

SMALL MOLECULES TARGETING THE TUMOR MICROENVIRONMENT

10:40 Chairperson's Remarks
Suresh Kumar, PhD, Senior Director, Research and Development, Progenra

10:45 A New Approach for the Discovery of Immune Stimulating Drugs
Dennis A. Carson, MD, Director Emeritus, Moore University of California, San Diego Cancer Center, Sanford Consortium for Regenerative Medicine

11:15 Inhibiting Treg Trafficking into the Tumor Microenvironment
David Wustrow, Vice President, Drug Discovery, FLX Bio, Inc.
Recent longitudinal studies in patients receiving IO agents demonstrate an influx of Treg in responding patients which may dampen optimal anti-tumor responses. Understanding the mechanisms of Treg recruitment into the TME thereby preventing their ability to induce immune tolerance. This talk will describe the discovery of the key mechanism of such Treg recruitment as well as *in vitro* and *in vivo* validation of this small molecule approach to selectively decreasing immune tolerance in the TME.

11:45 Accelerated Drug Discovery with CETSA®
Sponsored by PELAGO BIOSCIENCE
Michael Dabrowski, CEO, Pelago Bioscience
Using CETSA, researchers can now measure directly how a compound interacts with target proteins in the cell. CETSA can be used against known targets or in an unbiased proteomic approach that makes it ideal for target deconvolution, safety studies and for biomarker discovery.

12:00 pm Targeting Tumor Microenvironment with Deubiquitinase Inhibitors for Cancer Immunotherapy
Suresh Kumar, PhD, Senior Director, Research and Development, Progenra
Immune suppressive Tregs and MDSCs in the tumor microenvironment correlate with poor prognosis. Suppression of Tregs or impairment of Treg function is an attractive cancer immunotherapy approach. Deubiquitinase USP7 is critical for Treg function by regulating Foxp3 and TIP60. Progenra has developed potent USP7 inhibitors that impair Treg functions and are efficacious in various syngeneic solid tumor models. USP7 inhibitors alone or in combination can improve the efficacy and expand the scope of cancer immunotherapy.

12:30 Lunch & Learn: Immune Metabolism: Targeting Mitochondria to Promote Antitumor Immunity
Sponsored by BIODURO
Brett Hall, PhD, CEO, Asellus Therapeutics
An expanding body of research has established that mitochondria are central players in coordinating immune response. Asellus is working on small molecule drug programs that promote antitumor immunity through targeted modulation of mitochondria function. We will discuss preclinical progress on one of our drug programs, AT-S-977.

1:30 Dessert Break in the Exhibit Hall with Poster Awards

KINASE IMMUNOMODULATORS

2:15 Chairperson's Remarks
Donald Durden, MD, Professor, Department of Pediatrics, University of California, San Diego; Director of Operations, SignalRx Pharmaceuticals

2:20 Discovery of Scaffold/Platform for the Development of nM Potent Triple Inhibitor of PI3K/BRD4/CDK4/6 (Kinase/Epigenetic) Inhibitor, SRX3177 for Maximum Cancer Cell Synthetic Lethality, Safety and Efficacy
Donald Durden, MD, Professor, Department of Pediatrics, University of California, San Diego; Director of Operations, SignalRx Pharmaceuticals
A novel thienopyranone molecular scaffold has been developed *in silico* to selectively inhibit PI3 kinase (PI3K) as well as two other targets, the bromodomain protein, BRD4 and CDK4/6. Molecular modeling studies employing crystal structure analysis and robust PI3K, BRD4 and CDK4/6 homology models have been developed and will be presented to describe how these single small molecules can bind to inhibit such distinctly different proteins and their functions. As a cancer therapeutic, this triple inhibition mechanism allows for a unique and powerful way to modulate critical components of cancer cells.

2:50 Purine Nucleoside Phophorylase Inhibitors as Novel, First-in-class Small Molecule Immunotherapy
Shanta Bantia, PhD, President and CEO, Nitor Therapeutics
We have discovered, contrary to all previous literature, that purine nucleoside phosphorylase (PNP) inhibitors are immune potentiators and represent a new class of orally bioavailable, small molecule immuno-oncology therapeutics. PNP inhibitors activate the immune system through modulation of an endogenous metabolite. Increase in the endogenous metabolite, guanosine, with PNP inhibition leads to activation of TLR2, 4 and 7. Potential attributes for differentiation and value for PNP inhibitor (NTR001) are: (1) Immune activation occurring in tumor micro-environment (TME) more so than in other tissues (because of increased apoptosis and necrosis in TME causing increased levels of guanosine) and hence less likelihood of immune related adverse effects that is commonly seen with other immunotherapies (2) Rapid path to clinic as human safety is known and doses are defined

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(3) Evidence of immune activation in clinical studies and the concept of activation of immune system by PNP inhibitors confirmed in preclinical models of vaccines and cancer.

3:20 **Selective Inhibitors of CLK and DYRK kinases**
Lijun Sun, PhD, Director, Center for Drug Discovery and Translational Research, Beth Israel Deaconess Medical Center; Associate Professor, Harvard Medical School
CDC2-like kinase (CLK) and dual specific tyrosine phosphorylation-regulated kinase (DYRK) control the mRNA splicing events via priming phosphorylation of key SF members of the spliceosome. CLK and DYRK are aberrantly activated in a number of cancers and are attractive targets for developing anticancer therapy. We describe our SAR results of a class of novel water-soluble benzimidazoles as selective CLK/DYRK inhibitors. *In vitro* activity in the NCI60 panel screen of the advanced lead candidates, as well as *in vivo* efficacy in established prostate cancer tumor models, will be presented.

3:50 **Refreshment Break**

NOVEL IMMUNOMODULATORY SMALL MOLECULES

4:20 **Tumor Immune Modulation following Intratumoral Therapy with Small Molecule TLR7/8 Ligands**
David Ferguson, PhD, Professor, Medicinal Chemistry, University of Minnesota
The basic structural features of small molecule ligands that confer selectivity to Toll-like receptors 7 and 8 will be discussed in the context of immunomodulation and the design of cancer vaccines. An SAR analysis will be presented to identify structural features that confer selectivity to TLR7 and TLR8 and ligand specific activation of key cytokines in producing antigen specific cellular responses in model systems. Finally, *in vivo* data will be shown that demonstrate the potential of TLR7/8 stimulation in designing advanced vaccines for cancer treatment.

4:50 **Tumor Immune Modulation following Intratumoral Therapy with Small Molecule TLR7/8 Ligands**
John Vasilakos, PhD, Senior Research Immunologist and Business Director for TLR Agonists, TLR Department, Drug Delivery Systems Division, 3M
TLR7/8 ligands exhibit anti-tumor activity when injected into tumors, and synergize with checkpoint blockade therapies. Anti-tumor activity of TLR7/8 ligands requires or is associated with the infiltration of activated CD8 T cells, formation of lymphoid aggregates, and expression of cytokines and chemokines associated with Th1 immunity, CTL activity, T cell chemotaxis, and type I IFN inducible gene expression.

5:20 **The Imipridone ONC201, a Selective DRD2 Antagonist, Exerts Immunostimulatory Activity in Advanced Cancer Patients**
Joshua Allen, PhD, Vice President, Research and Development, Oncoceutics
ONC201 is an orally active small molecule antagonist of the G protein-coupled receptor DRD2 currently in Phase II clinical trials for advanced cancer. DRD2 is expressed by immune cells and ONC201 has shown immunostimulatory effects in preclinical studies, including increased intratumoral NK cell infiltration in xenografts. In agreement with preclinical observations, increase in circulating and intratumoral NK cells, cytokines and effector molecules was observed in prostate, endometrial, glioblastoma and mantle cell lymphoma patients.

5:50 **End of Conference**

> **"I get in three days an absolute high-level overview about what's going on in my field."**
>
> – STEFAN L., CHAIRMAN, PHARMACEUTICAL & MEDICINAL CHEMISTRY, UNIVERSITY OF TUEBINGEN

Macrocyclics & Constrained Peptides

Cell-Penetrating 'Bigger' Molecules

April 4-5, 2018 | Hilton San Diego Bayfront | San Diego, CA

WEDNESDAY, APRIL 4

12:30 pm Registration

12:45 Dessert Break in the Exhibit Hall with Poster Viewing

DESIGN RULES FOR MACROCYCLES

1:30 Welcome Remarks
Anjani Shah, PhD, Conference Director, Cambridge Healthtech Institute

1:35 Chairperson's Opening Remarks
Scott Lokey, PhD, Professor, Chemistry and Biochemistry, University of California, Santa Cruz

1:40 Lessons for the Design of Synthetic Macrocycles from Machine Learning
Adrian Whitty, PhD, Professor, Biochemistry, Boston University

2:10 Physical Chemical Properties for Drug Design in Beyond Rule of Five Chemical Space
Marina Shalaeva, PhD, Principal Scientist, Medicinal Design, Pfizer
New concepts and methods are being developed for evaluation and modulation of properties of Bro5 compounds to achieve acceptable PK/PD in drug candidate. In particular, the PLRP-S method for estimating lipophilicity and ionization in nonpolar membrane-like environment is described. A fast chromatographic assay is used to asses lipophilicity-ionization patterns of lipophilic, low solubility Bro5 compounds in combination with pKa by MCE, while EPSA and ElogD are used to drive passive permeability and drug efficiency (lipE).

2:40 Lipophilic Permeability Efficiency (LPE) Enables the Identification and Quantification of Structural Effects on Macrocycle Permeability
Matthew R. Naylor, PhD, LIFA Postdoctoral Fellow, Eli Lilly & Co.
Macrocycle scaffold structure determines the balance between lipophilicity and aqueous solubility in the pursuit of bRo5 therapeutics capable of passive cell permeability. Current techniques to identify such structure are time-intensive (NMR analysis) or challenging on large peptides (*in silico* prediction). Combining a simple hydrocarbon lipophilicity measurement with a predictor of aqueous solubility, Lipophilic Permeability Efficiency (LPE) quantifies the intrinsic ability of diverse bRo5 scaffolds to hide backbone or sidechain polarity for cell permeability.

3:10 Conformational Sampling of Macrocycles in Solution
Sponsored by OpenEye
Paul Hawkins, PhD, Head, Scientific Solutions, OpenEye Scientific Software
Some types of macrocyclic molecules have been shown to be orally bioavailable ligands for targets such as GPCRs and protein-protein interfaces, which requires then to be able to permeate cell membranes effectively. The means by which high molecular weight macrocycles are able to be membrane permeable has been the subject of some recent study, but no clear conclusions have yet been reached. In this presentation we discuss how to model effectively the conformational properties of macrocycles in different environments and how experimental data gathered in solution, particularly from NMR, can be used to improve that sampling.

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

4:30 Property-Based Drug Design beyond Ro5 - Lessons Learned from AbbVie's Drugs and Compound Collection
Phil Cox, PhD, Senior Principal Scientist, Chemistry Group Leader, Discovery Chemistry and Technology, AbbVie, Inc.
This presentation will focus on the lessons learned from an initiative to analyze AbbVie's internal database of compounds beyond Ro5 (including macrocycles).

5:00 Rationalizing the Passive Membrane Permeability of Cyclic Peptides
Sereina Riniker, PhD, Assistant Professor, Laboratory of Physical Chemistry, ETH Zürich
The hypothesis for the passive membrane permeability of cyclic peptides involves the interconversion between "open" conformations and "closed" conformations prior to the entering of the membrane. Using kinetic models based on molecular dynamics (MD) simulations in polar and apolar environments, a rationale for the "permeability cliff" presented by the natural product cyclosporine A and its synthetic derivative cyclosporine E as well as for a recently published series of cyclic decapeptides is provided.

5:30 Breakout Discussions

6:15 End of Day

6:30 Dinner Short Courses*
**Separate registration required; please see page 3 for details.*

THURSDAY, APRIL 5

8:00 am Breakfast Presentation: Improvements in NMR Approaches to Fragment Based Screening
Sponsored by BRUKER
Donna Baldisseri, Senior Applications Scientist, Bruker BioSpin
FBDD is a powerful search engine for identification of fragments that bind to disease relevant target proteins ultimately leading to drug candidates. NMR-based FBDD screening requires compound library validation, preparation of hundreds of samples per campaign, automated acquisition, processing of thousands of spectra, and their analysis for binding assessment. Here is described the streamlined solutions offered by Bruker, automating this pipeline to improve the speed and productiveness of FBDD screening for the pharmaceutical industry.

8:45 Plenary Session Welcome Remarks from Event Director
Anjani Shah, PhD, Conference Director, Cambridge Healthtech Institute

8:50 Plenary Keynote Introduction
Chris Petersen, CTO, Scientist.com

8:55 PLENARY KEYNOTE: Targeting Ras and MYC for the Treatment of Cancer
Stephen Fesik, PhD, Professor of Biochemistry, Pharmacology, and Chemistry, Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University School of Medicine
Two of the most important targets in cancer are Ras and MYC. However, both of these highly validated cancer targets are thought to be undruggable. In this presentation, I will discuss our approaches for targeting both of these proteins directly and indirectly using fragment-based methods and structure-based design.

9:45 Coffee Break in the Exhibit Hall with Poster Viewing

BEYOND NATURAL PEPTIDES AND AMINO ACIDS

10:40 Chairperson's Remarks
Maxwell D. Cummings, PhD, Senior Principal Scientist, Computational Chemistry, Discovery Sciences, Janssen R&D

10:45 FEATURED PRESENTATION: The RaPID Discovery of Bioactive Pseudo-Natural Peptides
Hiroaki Suga, PhD, Professor, Department of Chemistry, School of Science, The University of Tokyo
This lecture will describe the most recent development in the genetic code reprogramming technology that enables us to express pseudo-natural peptides. The technology involves (1) efficient macrocyclization of peptides, (2) incorporation of non-standard amino acids, such as N-methyl amino acids, (3) reliable synthesis of libraries with the complexity of more than a trillion members, (4) rapid discovery of potent bioactive pseudo-natural peptides by the RaPID system (or PDPS).

11:15 Lead Optimization of Natural-Product Derived NaV1.7 Inhibitory Disulfide-Rich Peptides
Kaustav Biswas, PhD, Principal Scientist, Hybrid Modality Engineering, Amgen, Inc.
My talk details Amgen's program directed at inhibition of the voltage-gated sodium channel NaV1.7 for pain and itch using hits from a venom screen. We identified novel toxin peptides from tarantula venom which have disulfide-rich folded motifs. Using a combination of positional scanning and peptide-ion channel molecular docking studies, we will discuss the discovery of synthetic analogues with activity in *ex vivo* and *in vivo* behavioral NaV1.7-dependent models.

11:45 Sponsored Presentation *(Opportunity Available)*

12:00 pm Discovery of Potent and Orally Bioavailable Macrocyclic Peptide-Peptoid Hybrid CXCR7 Modulators
Markus Boehm, PhD, Associate Research Fellow, Medicinal Chemistry, Pfizer
While several small molecules have been identified that modulate the activity of CXCR7, an attractive drug target for a variety of disease indications, peptidic macrocycles may provide additional advantages in terms of potency, selectivity, and reduced off-target activity. We report on a series of peptidic macrocycles that bind to CXCR7 and also incorporate an N-linked peptoid functionality in order to overcome the poor permeability associated with peptides. The peptoid group also enabled us to explore side chain diversity well beyond that of natural amino acids.

12:30 Luncheon Presentation: Evaluation of Free Energy Calculations for the Prioritization of Macrocyclic Cyclophilin Inhibitors
Sponsored by SCHRÖDINGER
Janet Paulsen, PhD, Senior Scientist, Applications Science, Schrödinger
Macrocycles are often used to drug difficult targets, such as PPIs or balance desirable drug properties. Synthesis of these molecules can require significant effort with no guarantee that the molecule will have improved properties or meet pro ject goals. Here, I will present a blinded retrospective investigation, performed in collaboration with Gilead, targeting cyclophilin for Hepatitis C. FEP+ successfully predicted relative binding free energies, rank-ordered compounds and explained non-intuitive SAR for a class of mini-sanglifehrins.

1:30 Dessert Break in the Exhibit Hall with Poster Awards

CYCLIC PEPTIDES: DRUG DEVELOPMENT CHALLENGES

2:15 Chairperson's Remarks
Adrian Whitty, PhD, Professor, Biochemistry, Boston University

2:20 Cell Penetration Profiling for Biotherapeutics
Joshua Kritzer, PhD, Associate Professor, Chemistry, Tufts University
Several classes of biomolecules have emerged as exciting potential therapies, but their development has been impeded by imprecise measurements of intracellular delivery. The Kritzer lab has devised a new method for quantitating cell penetration, the ChloroAlkane Penetration Assay (CAPA). CAPA is inexpensive and high-throughput, and it can quantitate penetration to individual cellular compartments. We are using CAPA to comprehensively profile cell penetration for diverse biomolecules and drug delivery systems.

2:50 Catching Cyclic Peptides in Action at the Ribosome
Jordan Carelli, PhD, formerly Graduate Student, Jack Taunton Lab, UCSF; currently Senior Scientist, Oncology RU, Pfizer
Ternatin-4 and didemnin B are unrelated cyclic peptides that kill cancer cells by binding the eukaryotic elongation factor 1A (eEF1A)•aa-tRNA•GTP ternary complex. I will present our efforts in the Taunton lab to elucidate the molecular mechanisms by which ternatin-4 and didemnin B inhibit protein translation. Despite sharing an allosteric binding site on eEF1A, ternatin-4 and didemnin B differentially impact eEF1A conformational dynamics *in vitro*, and have distinct effects on cancer-derived and non-malignant cells.

3:20 Polar Hinges as Functionalized Conformational Constraints in (Bi)Cyclic Peptides
Alex Hoose, PhD, Post-doctoral Research Associate, Liskamp Group, School of Chemistry, University of Glasgow
We wish to devise (cyclic) peptides and peptidomimetics as protein-protein interactions (PPI) inhibitors. Polar hinges have been developed for cyclization of peptides leading to bicyclic peptides and cyclized peptides with improved solubility and biological activity. Increasingly, we note that a good aqueous solubility of peptides is an absolute prerequisite not only to be able to handle and purify our target peptides but it is also crucial for biological activity characterization.

3:50 Refreshment Break

4:20 Cyclotide Antagonists of the HDM2-HDMX RING-Mediated E3 Ligase
Julio Camarero, PhD, Professor, Pharmacology and Pharmaceutical Sciences, University of Southern California
The cyclotide scaffold has a tremendous potential for the development of therapeutic leads based on their extraordinary stability and potential for grafting applications. We will show an example, where a large cyclotide-based genetically encoded library was used to screen for low nanomolar antagonists for the Hdm2-HdmX RING-mediated E3 ligase activity. We will also present different strategies to improve the cellular uptake and pharmacokinetic profiles of bioactive cyclotides.

4:50 Constrained Oligomers Targeting the Ubiquitin-Proteasome Pathway
Thomas Kodadek, PhD, Professor of Chemistry; Associate Dean of Graduate and Post-Doctoral Studies, The Scripps Research Institute

5:20 Chemo-enzymatic Synthesis of Highly Constrained Multicyclic Peptides
Marcel Schmidt, Industrial PhD Candidate, Van't Hoff Institute of Molecular Sciences, University of Amsterdam
The increasing number of macrocyclic peptides currently being investigated as prospective therapeutics requires efficient, cost-effective routes for their synthesis. We have developed a flexible and broadly applicable chemo-enzymatic strategy that enables the efficient, scalable assembly of (multi) cyclic peptide macrocycles. We successfully employed omniligase-1-catalyzed peptide backbone cyclization for the synthesis of a plethora of peptides, ranging from naturally occurring multicyclic peptides (e.g. cyclotide MCoTI-II) to multicyclic peptides containing non-natural scaffolds with bifunctional biological activity (e.g. tri- and tetracycles).

5:50 End of Conference

Cambridge HEALTHTECH Institute
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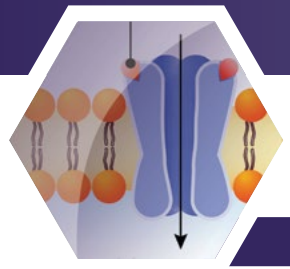

INAUGURAL

Targeting Complex Membrane Proteins

Biophysical Techniques, Structure-Based Drug Design and Other Advances

April 4-5, 2018 | Hilton San Diego Bayfront | San Diego, CA

WEDNESDAY, APRIL 4

12:30 pm Registration

12:45 Dessert Break in the Exhibit Hall with Poster Viewing

STRUCTURE-BASED DESIGN FOR COMPLEX MEMBRANE PROTEINS

1:30 Welcome Remarks
Anjani Shah, PhD, Conference Director, Cambridge Healthtech Institute

1:35 Chairperson's Opening Remarks
Sid Topiol, PhD, CSO, 3D-2drug, LLC; Professor and Director, Structural and Computational Drug Discovery, Stevens Institute of Technology

1:40 FEATURED PRESENTATION: Structure, Activation and Inhibition of Chemokine Receptors
Tracy M. Handel, Professor and Chair, Division of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, School of Medicine, University of California, San Diego
Chemokine receptors and their endogenous protein ligands are key to the etiology of many inflammatory diseases. Preclinical studies have demonstrated the therapeutic potential of many chemokine receptors, yet successful drug discovery has been slow with only two FDA-approved small molecule drugs. Fortunately, recent structural information should reverse this trend. In this presentation, our current understanding of the structure and activation mechanisms of chemokine receptors by chemokines, and strategies for receptor inhibition with small molecules, will be summarized.

2:10 The Shifting Landscape of Structure-Based Drug Design through Developments in Cryo Electron Microscopy
Stephen Muench, PhD, Assistant Professor, Department of Membrane Biology, School of Biomedical Sciences, University of Leeds
Membrane proteins represent over 30% of the genome and make up ~60% of therapeutic targets. However, despite their importance, our structural and biochemical understanding is still lacking. This talk will detail how new developments in electron microscopy and extraction methodologies have opened up new opportunities for studying membrane proteins and driving therapeutic design. In particular, it will discuss how we are now driving drug design through electron microscopy on a range of membrane protein targets.

2:40 Solute Carrier Transporters: An Emerging Drug Target Class
Alan Wickenden, PhD, Scientific Director, Discovery Sciences, Janssen Research & Development, LLC

3:10 Sponsored Presentation *(Opportunity Available)*

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

ALLOSTERIC MODULATION AND BIASED SIGNALING: NOT JUST FOR GPCRs?

4:30 Allosteric Modulation in and by Transporters of GPCR Ligands
Sid Topiol, PhD, CSO, 3D-2drug, LLC; Professor and Director, Structural and Computational Drug Discovery, Stevens Institute of Technology
Allosteric modulation of protein action has become increasingly more sought after as a means to achieve advantageous features such as ligand selectivity and tone. For endogenous amine GPCRs, these attributes are effectively achieved via independent proteins such as the SERT transporter. Recent X-ray structural reports for dDAT and hSERT elucidate the structural basis for drug binding at these targets. Further, the transporters themselves offer allosteric sites which are shown to enrich drug discovery opportunities.

5:00 Signaling Bias across Receptor Classes
Brian J. Arey, PhD, Director, Mechanistic Pharmacology, Leads Discovery and Optimization, Bristol-Myers Squibb Co.
Signaling bias, or functional selectivity, of GPCRs is now a well-accepted phenomenon. With growing access to crystal structures of GPCRs in liganded and un-liganded states, we have begun to get a clearer picture of the conformational rearrangements that give rise to activation/selectivity in receptor signaling. However, understanding of signaling bias as it relates to other receptor classes has not been thoroughly addressed. This presentation will discuss commonalities that occur in activation of receptors across receptor classes that suggest this phenomenon is not restricted to GPCRs.

5:30 Breakout Discussions

6:15 End of Day

6:30 Dinner Short Courses*
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THURSDAY, APRIL 5

Sponsored by BRUKER

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9:45 Coffee Break in the Exhibit Hall with Poster Viewing

NEW DRUG DISCOVERY APPROACHES FOR ION CHANNEL AND TRANSPORTERS

10:40 Chairperson's Remarks
Alan Wickenden, PhD, Scientific Director, Discovery Sciences, Janssen Research & Development, LLC

10:45 Structural Insights from the Co-Crystal of the Glycine Receptor Ion Channel Bound to Its Modulator
Xin Huang, PhD, Principal Scientist, Department of Molecular Engineering, Amgen
Glycine receptors (GlyRs) mediate inhibitory neurotransmission in the central nervous system. Selective activation of GlyRs has been hypothesized as an alternative approach to treat neuropathic pain. Here we present crystal structures of GlyRa3 with both positive and negative modulators. Our structures provide new insights into molecular recognition of these modulators and their modulation mechanisms. These results also offer promise of rational structure-based design of new classes of GlyR modulators.

11:15 Positive Allosteric Modulators of AMPA Receptors: A Model for PPI Stabilization Studies
Christopher Ptak, PhD, Postdoctoral Research Associate, Laboratory of Robert Oswald, Department of Molecular Medicine, Cornell University, College of Veterinary Medicine
AMPA receptor positive allosteric modulators represent a potential class of nootropic drugs. These modulators act by stabilizing a weak domain-domain dimer that participates in the receptor's activated state conformation. X-ray crystal structures illuminate the additional bridging contacts formed by the modulator across the dimer interface and have been exploited to develop new modulators with nanomolar affinity. Further, the use of small angle X-ray scattering and NMR spectroscopy provide insight into PPI-stabilizer binding models and the effect of allostery and stoichiometry.

11:45 Sponsored Presentation *(Opportunity Available)*

12:00 pm Developing Novel Pain Drugs by Selectively Targeting Nav1.7
David Hackos, PhD, Senior Scientist, Neuroscience, Genentech
Nav1.7 is a sodium ion channel that plays a role in pain sensing. We and others have identified small molecule compounds that bind to a novel site within the 4th voltage-sensing domain that lock the channel into an inactivated state. We solved the structure of the binding site for this class of compounds (Ahuja et al., Science 2015) which led to key insights into the mechanism and the pharmacology of these selective sodium channel inhibitors.

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

1:30 Dessert Break in the Exhibit Hall with Poster Awards

BIOPHYSICAL TOOLS FOR MEMBRANE PROTEINS

2:15 Chairperson's Remarks
Aaron Thompson, PhD, Scientist II, Department of Structural Biology, Dart Neuroscience; former Postdoctoral Fellow of Ray Stevens Laboratory

2:20 Biophysical Characterization of GPCRs with Crystallization-Enhancing Modifications
Matthew Eddy, PhD, Postdoctoral Fellow, Laboratory of Raymond Stevens, University of Southern California and The Scripps Research Institute
We present two studies where biophysical techniques provide new insight into structure-function relationships of human GPCRs and their implications for drug discovery. First, NMR studies of a GPCR fusion protein used for X-ray crystallography document how the fusion protein affects the signaling-related conformational equilibrium, highlighting potential instances where drug-ligand interactions can be affected. Second, NMR, X-ray diffraction, and other biophysical methods are applied to GPCR variants with mutations in a known allosteric center, and we explore the potential utility of these variants to accelerate GPCR drug discovery.

2:50 Nanodiscs for Biophysical Characterization of Membrane Proteins
Ilia Denisov, PhD, Laboratory of Stephen Sligar, Department of Biochemistry, University of Illinois at Urbana-Champaign
The Nanodisc platform has enjoyed wide applicability as it provides a self-assembled system that renders typically insoluble yet biologically and pharmacologically relevant membrane protein targets such as receptors, transporters, enzymes, and viral antigens soluble in aqueous media. It has also provided a means for understanding the mechanism of cancer signaling complexes, such as KRas4b and its effectors, which all form on a membrane surface. I will present our latest discoveries enabled by Nanodiscs.

3:20 Using Label-Free Impedimetric Monitoring to Profile the Pharmacology of Cell-Surface Receptors *in Vitro*
Joachim Wegener, PhD, Professor, Division Cell-Based Sensors, Fraunhofer Research Institution for Microsystems and Solid-State Technologies (EMFT), University of Regensburg
This presentation will highlight several different approaches how non-invasive impedance measurements can be used to characterize the pharmacology of GPCRs and other cell-surface receptors that can be switched from OFF to ON states or changed in their activity by ligand binding. Impedance approaches are especially suited for difficult-to-purify proteins because they can be analyzed label-free in their native state in the membrane of living cells at endogenous

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expression levels. The non-invasive nature of the measurement allows following the cell response to receptor activation and the intracellular signal amplification in real time.

3:50 **Refreshment Break**

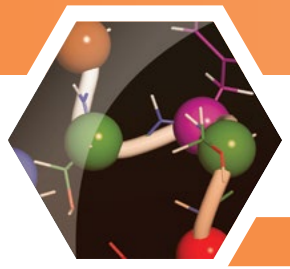
CANCER-RELATED MEMBRANE TARGETS

4:20 **Structure-Based Drug Design for Cancer-Related Membrane Proteins**
Avner Schlessinger, PhD, Assistant Professor, Pharmalogical Sciences, Mount Sinai School of Medicine
Solute carrier (SLC) transporters play a major role in mediating nutrient delivery in reprogrammed cancer metabolism networks. We use computational methods including homology modeling and virtual screening, which are followed by experimental testing, to discover novel small molecule ligands for cancer-related transporters. Our results provide useful tool compounds to characterize the role of SLC transporters in cancer, as well as a framework for developing efficacious lead compounds against emerging drug targets.

4:50 **Applying Mammalian Membrane Two-Hybrid (MaMTH) Assay Identifies Novel Cancer Targets & Therapeutics**
Igor Stagljar, PhD, Professor, Department of Molecular Genetics, Department of Biochemistry, University of Toronto
I will demonstrate how the Mammalian Membrane Two-Hybrid (MaMTH) assay can efficiently be used as a drug discovery assay for identification of inhibitory compounds that change the phosphorylation status of the human Epidermal Growth Factor Receptor (EGFR) in the context of living cells and in the low nanomolar range, an advance which may open up a whole new approach to drug development and lead to more effective treatments for lung cancer patients.

5:20 **Thyroid Hormone Analogues as Angiogenic Agents via the Integrin Receptor**
Paul Davis, MD, Professor, Department of Medicine, Pharmaceutical Research Institute, Albany Medical College
Acting via a specific integrin receptor on tumor cells, thyroid hormone (T4) and its antagonist (tetrac), modulate transcription of genes for cytokines and chemokines. T4 and tetrac also regulate expression of the PD-L1 gene--thus modifying the inflammatory process and angiogenesis.

5:50 **End of Conference**



Biophysical Approaches for Drug Discovery

New Methods for Medicinal Chemists

April 6, 2018 | Hilton San Diego Bayfront | San Diego, CA

FRIDAY, APRIL 6

7:25 am Registration and Morning Coffee

EMERGING TOOLS FOR DRUG DISCOVERY – BIOPHYSICAL AND BEYOND

7:55 Welcome and Opening Remarks
Anjani Shah, PhD, Conference Director, Cambridge Healthtech Institute
Chris Smith, PhD, Director, Medicinal Chemistry, COI Pharmaceuticals

8:00 FEATURED PRESENTATION: Development of Cryo-Electron Microscopy for Pharmaceutical Drug Design: From Implementation to Optimization
Christopher Arthur, PhD, Principal Scientist Specialist, Structural Biology, Genentech

8:30 Application of Encoded Library Technology to Lead Generation at GSK
Svetlana Belyanskaya, PhD, Encoded Library Technologies, R&D Platform Technology & Science, GSK Boston
Affinity-based screening of DNA-encoded chemical libraries is routinely employed within GSK for lead generation. The platform has evolved over its application to a quantitative on-DNA binding assay of billions of compounds simultaneously. A case study will be presented to illustrate the process of selection design and execution including the high throughput chemistry and hit confirmation using affinity selection mass spectrometry used to follow up screens.

9:00 Coffee Break

9:30 Native Mass Spectrometry and Collision-Induced Unfolding for Drug Discovery and Development
Varun V. Gadkari, PhD, Postdoctoral Research Fellow, Laboratory of Brandon Ruotolo, Department of Chemistry, University of Michigan

10:00 Identifying and Testing the Optimal Conditions for Kinetic Fragment-based Screening; a Novel TR-FRET Based Approach
David Sykes, MS, Experimental Officer, Laboratory of Dmitry Veprintsev, Molecular and Cellular Pharmacology, University of Nottingham
Developing new approaches for studying drug-receptor kinetics is key to improving screening efficiency. I will describe a novel TR-FRET based competition-association kinetic binding approach testing the kinetics of a commercially available library of ~1400 low molecular weight fragments at the dopamine D2 receptor, a prototypical GPCR. A range of off-rates were obtained including examples with surprisingly slow off-rates. This approach offers the potential to discover chemical starting points for the development of kinetically optimized medicines.

10:30 Second-Harmonic Generation for Conformation-Selective Drug Discovery: PPI Case Studies
Joshua Salafsky, PhD, Founder & CSO, Biodesy, Inc.
I will review the state of the art in SHG technology with a number of case studies. In particular, I will discuss the sensitivity of SHG to subtle but biologically important allosteric conformational changes that occur in protein-protein interactions. Various approaches for setting up a protein-protein assay screen will be discussed as well.

11:00 Measure What Matters, When It Matters
Delphine Collin, PhD, Vice President, Discovery and Biophysics, HarkerBIO, LLC
By changing their conformation, proteins can carry out their functions and modulate the functions of other molecules. As structure based drug discovery's appreciation of proteins as dynamic, flexible molecules grows, so does the importance of probing conformational changes to the unliganded form of a protein. Triaging our toolbox of orthogonal techniques, including second harmonic generation measurements, we can investigate and measure protein structural motion.

11:15 Luncheon Presentation *(Opportunity Available)* **or Enjoy Lunch on Your Own**

12:00 pm Session Break

ORTHOGONAL BIOPHYSICAL APPROACHES

1:00 Chairperson's Remarks
Phillip Schwartz, PhD, Senior Scientist, Structural Biology and Biophysics, Takeda California

1:05 Takeda's Tool Kit of Biophysical Methods
Pedro Serrano, PhD, Principal Scientist, Structural Biology and Biophysics, Takeda SD

1:35 A Systematic Approach for Prosecuting Fragment Hits in the Absence of Structural Information
Bradley Doak, PhD, Research Fellow, Medicinal Chemistry, Monash University
Developing fragment hits into lead-like structures can be difficult, especially when no structural information is available. We aim to standardize the evaluation and development of these fragment hits, with or without structural information, through exploration of vectors around the fragment. Here we present case studies that used chemoinformatic tools for finding purchasable analogues as well as designing standardized libraries of reagents to explore and validate vectors for expansion.

2:05 Measuring Biomolecular Interactions of GPCRs Using a Variety of Biophysical Techniques
Phillip Schwartz, Ph.D., Senior Scientist, Structural Biology and Biophysics, Takeda California
Drug discovery efforts are undergoing a renaissance in GPCR-related research as orphan receptors become de-masked and our understanding of how to study these difficult targets improves. Identifying preparations amenable to biophysical characterization is a critical step in pursuing GPCR drug development. I will discuss the application of three biophysical techniques (surface palsmon resonance, second harmonic generation and nuclear magnetic resonance) to GPCRs.

2:35 Networking and Discussion Session

3:05 Refreshment Break

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ADDRESSING CHALLENGING TARGETS WITH BIOPHYSICAL APPROACHES

3:35 Coupling Biophysical Approaches with Molecular Simulations to Optimize Compounds for Challenging Disease Targets

Woody Sherman, PhD, CSO, Silicon Therapeutics

We describe our drug discovery projects that combine experimental and simulation methods to develop novel medicines for diseases with targets that are currently considered challenging. Our INSITE computational platform accurately treats the underlying physics of molecular recognition (i.e. protein dynamics, water thermodynamics, and quantum mechanical effects) and integrates with experimental techniques such as X-ray crystallography, NMR, ITC, and second harmonic generation.

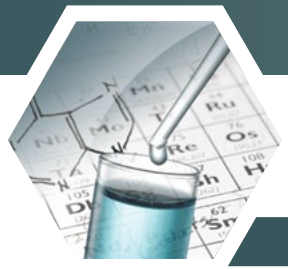
4:05 Liquid Chromatography- Mass Spectrometry (LC-MS)-Based Metabolomics in Pharmacological Lead Generation: From a Single Metabolic Node to Network Analysis

Gang Xing, PhD, Principal Scientist, Internal Medicine Research Unit, Pfizer Worldwide Research & Development, Pfizer, Inc.

The study of metabolic disease is complicated by sophisticated pathway networks contributing both catabolically and anabolically to a single molecular entity. LC-MS offers the ability to detect and quantify biomarkers with both specificity at single nodes and comprehensive coverage of large, chemically diverse networks, empowering not only SAR-based lead compound generation but also unknown pathway explorations. Case studies on both topics will be presented.

4:35 End of Conference

> "There's lots of interesting talks, but from quite a diverse set of people, which makes for an interesting meeting"
>
> – BEN D., RESEARCH FELLOW, VERNALIS RESEARCH



INAUGURAL

SYMPOSIUM

Lead Optimization for Drug Metabolism & Safety

Tools and Strategies for Incorporating Safety into Drug Design

April 6, 2018 | Hilton San Diego Bayfront | San Diego, CA

FRIDAY, APRIL 6

7:25 am Registration and Morning Coffee

UNDERSTANDING DRUG METABOLISM AND DRUG-DRUG INTERACTIONS

7:55 Welcome and Opening Remarks
Tanuja Koppal, PhD, Conference Director, Cambridge Healthtech Institute
John C. L. Erve, PhD, DABT, Consultant, Jerve Scientific Consulting, Inc.

8:00 FEATURED PRESENTATION: Addressing Biotransformation Issues in Early Discovery
Deepak Dalvie, PhD, Senior Director, DMPK, Celgene
Drug metabolism plays an important role in the discovery and development of a drug candidate. Addressing metabolism issues early on can result in candidates with less metabolism as well as bioactivation liabilities. Strategies and examples of role of metabolism in early discovery will be discussed in this talk.

8:30 Principles of Metabolite Identification by Mass Spectrometry for Drug Discovery and Development
John C. L. Erve, PhD, DABT, Consultant, Jerve Scientific Consulting, Inc.
Metabolite identification (Met ID) studies are an important component for both drug discovery and drug development efforts. Mass spectrometry, particularly high mass accuracy techniques, is the primary tool for Met ID studies. Chemists often rely on internal or external scientists to perform metabolite identification and characterization but will benefit by understanding how it is done. This talk will cover strategies used to identify drug metabolites allowing chemists to better understand the strengths and limitations of these studies.

9:00 Coffee Break

IMPACT OF DRUG TRANSPORT AND CLEARANCE

9:30 Detection and Assessment of Reactive Drug Metabolites in Drug-Mediated Hepatotoxicity
Mark Grillo, PhD, Staff Scientist, Drug Metabolism & Pharmacokinetics, MyoKardia, Inc.
A number of toxic drugs undergo bioactivation to chemically-reactive metabolites that bind covalently to endogenous macromolecules, proteins, DNA leading to organ toxicity and carcinogenesis. Current experimental techniques used to detect and assess the potential liabilities of reactive metabolites and how information from mechanistic *in vitro* studies can be employed to redesign candidate drugs leading to blocked or minimized bioactivation and decreased toxification will be discussed.

10:00 Application of Drug Transporters in Drug Discovery
Caroline Lee, PhD, Executive Director, Ardea Biosciences Inc., a member of the AstraZeneca Group
Transporters play a key role in the disposition of drugs. Transporters contribute to drug efficacy, drug interactions and may limit desired drug exposure. The rationale and identification of the transporters to implement in drug discovery will be discussed as well as the difficulties that may be encountered in translating *in vitro* data to clinical outcome.

10:30 Addressing the Challenges of Low Clearance and Intracellular Free Drug Concentration
Li Di, PhD, Research Fellow, Pharmacokinetics, Dynamics and Metabolism, Pfizer Inc.
Low clearance compounds continue to increase in drug discovery and lack of low clearance tools can lead to over-prediction of clearance, dose and under-prediction of half-life. Intracellular free drug concentration is most relevant for development of PK/PD relationships and prediction of drug-drug interactions. This presentation will discuss approaches to address these challenges and their applications in drug discovery.

11:00 Elucidating Mechanism-of-Toxicity of FAAH Inhibitors via Proteome-Screening *Sponsored by* CYCLICA
Stephen MacKinnon, PhD, Director, Research and Development, Cyclica Inc.
Cyclica has developed a protein structure-based and AI-augmented drug discovery platform (Ligand Express) that provides a unique panoramic view of small-molecules in development, by identifying on-/off-targets that may be expected as well as those that are unanticipated. Accordingly, Ligand Express can augment R&D programs by elucidating MoA of small molecules.

11:15 Luncheon Presentation *(Opportunity Available)* **or Enjoy Lunch on Your Own**

12:00 pm Session Break

CASE STUDIES: STRATEGIES FOR OPTIMIZING DMPK PROPERTIES

1:00 Chairperson's Remarks
Mark Grillo, PhD, Staff Scientist, Drug Metabolism & Pharmacokinetics, MyoKardia, Inc.

1:05 Use of Integrated DMPK Approaches to Facilitate Design of Brain Penetrant Kinase Inhibitors
Xingrong Liu, PhD, Principal Scientist, Drug Metabolism and Pharmacokinetics, Genentech, Inc.

1:35 A Proposed ADME Optimization Workflow for Covalent Inhibitors
Mehran Moghaddam, PhD, MBA, Founder and CEO, OROX Biosciences
With the renewed interest in covalent inhibitors comes the responsibility to advance only compounds with drug-like properties in discovery programs. The traditional small molecule reversible drug discovery workflow includes target identification and validation, lead identification, lead optimization and profiling and optimizing for ADME properties are paramount in obtaining acceptable efficacy and safety. This presentation will contrast the ADME workflow for discovery of covalent verses reversible inhibitors.

2:05 Predicting Human PK and Exposure in Discovery to Inform Lead Optimization and Candidate Selection
Natalie Hosea, PhD, DMPK San Diego Site Head, Takeda
Prediction of human pharmacokinetics and drug-related exposure underpins early decision-making in drug discovery. More specifically, early human predictions enable identification of key liabilities for focused optimization strategies as well as enabling assessment of early safety information when coupled with pharmacology information. In this section, case studies on the application of predictions to optimization strategies and compound advancement will be discussed.
Continued on next page...

2:35 Co-Presentation: Strategies and Application of CYP Inhibition and Phenotyping Assays to Optimize SYK Inhibitor Drug-Drug Interaction Risk Profiles
David M. Stresser, PhD, Principal Research Scientist, AbbVie, Inc.
Michael Hoemann, PhD, Senior Scientist, Department of Chemistry, AbbVie, Inc.
Cytochrome P450 interaction liabilities receive higher scrutiny in therapeutic areas requiring low tolerance for drug-drug interactions. In these competitive market areas, rapid access to robust CYP metabolism and inhibition data is crucial to a program's success. We will review early 'perpetrator' and 'victim' assays and how they were used at AbbVie to successfully address a significant FmCYP3A4 and time-dependent inhibition liability in a Spleen Tyrosine Kinase (SYK) program.

3:05 Refreshment Break

NEW ASSAYS FOR ADMET PREDICTIONS AND EARLY DOSING

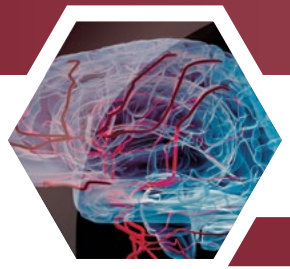
3:35 Kriging - A New Approach for Building ADMET Prediction Models
Istvan Enyedy, PhD, Principal Scientist, Medicinal Chemistry, Biogen
Kriging is using the correlation of the distance between molecules with the difference between their activity/ADMET properties for *in silico* predictions. We have considered this algorithm since it allows us to easily build, evaluate, and maintain models and has a report format that allows users to judge the accuracy of the predictions. The performance of eighteen models and how training sets impact it will be presented.

4:05 Sensitive *in vitro* Screening for Structure/Tissue Toxicity Assessment with Rapid-Turnaround Time
Ian Sweet, PhD, Associate Professor, Department of Medicine, University of Washington
I will present sensitive technology we have developed that continuously measures time courses of pharmacologically relevant drug effects on solid tissue samples. The accuracy and throughput is well suited to quantify and rank effects and toxicity of drug metabolites, chemical libraries and lead candidates. Data generated will be useful for the analysis of drug effects on human vs. animal tissue, target organs and drug-drug interactions.

4:35 *In vitro* Tools for Successful Prediction of Human Hepatic Clearance
Jasleen Sodhi, Graduate Student, Laboratory of Dr. Leslie Benet, Pharmaceutical Sciences and Pharmacogenomics Program, Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco
Accurate prediction of human pharmacokinetic properties is critically important in drug discovery. Of particular importance is the prediction of hepatic clearance, which largely determines drug exposure and contributes to projections of dose, drug half-life and bioavailability. This talk will cover common *in vitro* techniques used to predict hepatic clearance of new chemical entities and the fundamentals of *in vitro* to *in vivo* extrapolation (IVIVE) of drug clearance.

5:05 End of Conference

> "Great opportunity to share and discuss cutting-edge approaches/aspects in drug discovery."
>
> – FABRIZIO G., PRINCIPAL SCIENTIST, ASTRAZENECA



INAUGURAL

SYMPOSIUM

Blood-Brain Penetrant Inhibitors

Tools, Strategies, and Design of Brain Penetrant Inhibitors

April 6, 2018 | Hilton San Diego Bayfront | San Diego, CA

FRIDAY, APRIL 6

7:25 am Registration and Morning Coffee

DISCOVERY AND DEVELOPMENT OF BRAIN PENETRANT INHIBITORS FOR CANCER

7:55 Welcome and Opening Remarks
Kaitlin Kelleher, Conference Director, Cambridge Healthtech Institute
William F. Elmquist, PharmD, PhD, Professor and Head, Department of Pharmaceutics; Director, Brain Barriers Research Center, University of Minnesota

8:00 Brain Tumor Interactions: A Complex, Dynamic System Influencing Efficacy and Resistance
William F. Elmquist, PharmD, PhD, 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. While molecularly targeted anti-cancer agents have impressive inhibitory action against signaling pathways that drive tumor growth, they have been ineffective in treating brain tumors. The mechanisms responsible for this failure must be explored before progress can be made, and inadequate drug delivery across an intact BBB is one critical factor for primary tumors and micro-metastases in the brain.

8:30 Roche Delivery Platforms for Biotherapeutics to Treat Brain Tumors
Eduard Urich, PhD, Pre-Clinical Project Leader and Senior Scientist, Roche Pharmaceutical Research and Early Development, NORD Discovery & Translational Area, Roche
I will describe an overview of our recent novel antibody engineering platforms, including our Brain Shuttle technology that utilizes receptor-mediated transcytosis to cross an intact BBB. Experimental data will illustrate the absolute requirement to cross the BBB to remove tumor cells within the brain parenchyma.

9:00 Coffee Break

DISCOVERY AND DEVELOPMENT OF BRAIN PENETRANT INHIBITORS FOR CANCER *(CONT.)*

9:30 Inhibition of Wnt Pathway in Brain Cancers
Elmar Nurmemmedov, PhD, MBA, Assistant Professor, Director of Drug Discovery, Translational Neurosciences and Neurotherapeutics, John Wayne Cancer Institute
Wnt signaling pathway controls a variety of cellular events including cell proliferation, anti-cancer immunity and DNA damage response. In brain cancers, Wnt pathway is particularly involved in acquired resistance to chemotherapy. Targeted inhibition of Wnt pathway is shown to sensitive deadly brain tumors to chemotherapy and thereby extend patient survival. Development of brain-penetrant Wnt inhibitors is a new therapeutic direction that will benefit brain cancer patients.

10:00 Discovery and Synthesis of the Macrocyclic EML4-ALK Inhibitor, Lorlatinib (PF-06463922)
Paul Richardson, PhD, Director, Process and Analytical Technologies, Oncology Medicinal Chemistry, Pfizer
This talk will center on the design of PF-06463922, focusing on the optimization of the properties to achieve brain penetration. In addition, the synthesis of PF-06463922 will be discussed with the key step herein being the ring closure to form the final 12-membered macrocycle. The development, optimization and subsequent scale-up of a novel direct arylation route to achieve this will be presented, leading to a sequence that is three steps shorter and is expected to provide a higher overall throughput of the desired API.

10:30 Discovery of Selective Orexin-1 Receptor Antagonists
Terry Lebold, PhD, Senior Scientist, Neuroscience Chemistry, Janssen Research & Development
Presented here will be the discovery, synthetic methods and SAR associated with novel selective orexin-1 receptor antagonists and their evaluation in preclinical models of panic, anxiety and addiction. In addition, we will highlight our first candidate for pre-clinical development, JNJ-54717793.

11:00 Sponsored Presentation *(Opportunity Available)*

11:15 Luncheon Presentation *(Opportunity Available)* **or Enjoy Lunch on Your Own**

12:00 pm Session Break

BRAIN PENETRANT INHIBITORS FOR NEURODEGENERATIVE DISEASE AND PSYCHIATRIC DISORDER

1:00 Chairperson's Remarks
Zoran Rankovic, Director, CBT Chemistry Centers, St. Jude Children's Research Hospital

1:05 Art and Science of CNS Drug Design
Zoran Rankovic, Director, CBT Chemistry Centers, St. Jude Children's Research Hospital
This presentation focuses on the interplay between the physicochemical and CNS pharmacokinetic parameters, and medicinal chemistry strategies towards molecules with optimal brain exposure. Since the challenge of CNS drug discovery could be effectively addressed only with an in-depth understanding of the structure-brain exposure relationships built on reliable and meaningful pharmacokinetic data, the importance of modern CNS pharmacokinetic concepts including the "free drug" hypothesis are also discussed.

1:35 Yeast-Based Phenotypic Screening to Identify Brain Penetrant Inhibitors
Matt Lucas, PhD, Director, Medicinal Chemistry, Yumanity Therapeutics
Phenotypic screening has undergone a revival in the last decade. In this presentation, I will share some of our learnings from Yumanity's phenotypic screening platform to bias towards the identification of scaffolds that are brain penetrant with potential utility to treat protein misfolding diseases.

2:05 Kinase Inhibitors as Therapeutics for Alzheimer's Disease: Development of Casein Kinase 1d Inhibitors

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That Lead To Inhibition of Tau Phosphorylation at Ser202 and Ser396
Jayalakshmi Sridhar, PhD., Assistant Professor, Chemistry, Xavier University
Several protein kinases play an important in the progression of neurodegenerative disorders such as Alzheimer's disease. Many of these are targets for potential therapeutics. Our research group has found one such target as Casein kinase 1delta which phosphorylates the tau protein leading to neuro-fibrillary tangles that is a hallmark of Alzheimer's disease.

2:35 Networking and Discussion Session

3:05 Refreshment Break

BRAIN PENETRANT INHIBITORS FOR NEURODEGENERATIVE DISEASE AND PSYCHIATRIC DISORDER *(CONT.)*

3:35 Laminin Actively Regulates Blood Brain Barrier Integrity
Yao Yao, PhD, Assistant Professor, Pharmaceutical and Biomedical Sciences, University of Georgia
Laminin, a large family of trimeric proteins, is the only component required for the formation of the basement membrane (BM)---the non-cellular component of the blood brain barrier (BBB). It has been shown that different cells synthesize distinct laminin isoforms at the BBB. Using conditional knockout mutants, we reported that loss of astrocytic laminin leads to BBB disruption and intracerebral hemorrhage, whereas ablation of pericytic laminin results in a much milder BBB breakdown phenotype. These results suggest that laminin/BM also contributes to the maintenance of BBB integrity, and may be targeted for drug delivery to the CNS.

4:05 Serial Cerebrospinal Fluid Collection in Early Clinical Development May Provide Pharmacokinetic and Pharmacodynamic Insights for CNS Drugs
Stanford Jhee, PharmD, Corporate Vice President, Scientific Affairs, PAREXEL International
One of the main objectives of CNS Phase I clinical development is determination of CNS penetration and its pharmacokinetic and pharmacodynamics profiles. This can be compared to that of preclinical and plasma levels. An indwelling catheter in the lumbar region can provide a safe and tolerable method to collect serial CSF in humans. Such data is a valuable translational information that can be directly be applied to early clinical drug development. Our methods and experience over the last 15 years will be presented with selected data presented.

4:35 T-Type Calcium Channel Blockers for the Treatment of Generalized Epilepsies
Olivier Bezençon, Senior Group Leader, Chemistry, Idorsia Pharmaceuticals Ltd
The discovery and optimization of new, brain-penetrant T-type calcium channel blockers are presented. Optimized compounds with excellent efficacy in a rodent model of generalized absence-like epilepsy are discovered. Along the fine optimization (target potency, brain penetration, and solubility), an Ames negative aminopyrazole as putative metabolite of this compound series was successfully identified. These efforts culminated in the selection of a compound that was elected as a clinical candidate.

5:05 End of Conference

Hotel & Travel Information

Conference Venue & Hotel:
Hilton San Diego Bayfront
One Park Blvd.
San Diego, CA 92101
Phone: 619-564-3333

Discounted Room Rate: $265 s/d
Discounted Cut-off Date:
February 26, 2018

For more reservation information: Visit the Hotel & Travel page of DrugDiscoveryChemistry.com

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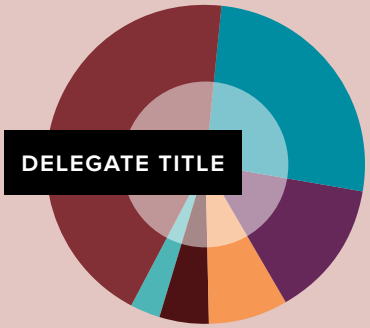
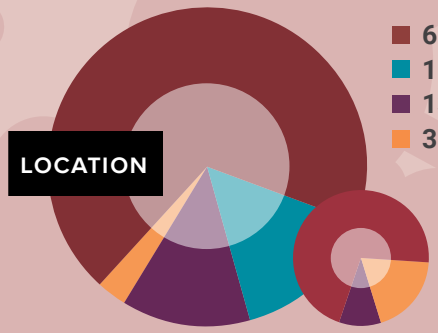


DELEGATE TITLE

- 39% Scientist/Technologist
- 29% Executive/Director
- 12% Sales & Marketing
- 10% Professor
- 6% Manager
- 4% Assistant

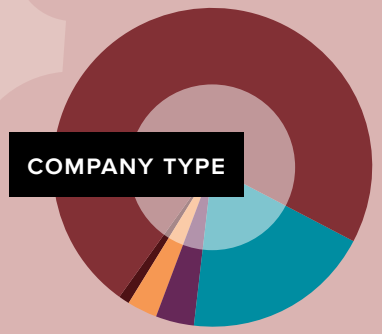


LOCATION

- 69% United States
- 15% Europe
- 13% Asia
- 3% Rest of World

US BREAKDOWN

- 48% West Coast
- 41% East Coast
- 11% Midwest



COMPANY TYPE

- 73% Biotech & Pharma
- 19% Academic & Government
- 4% Press, Services, & Societies
- 3% Healthcare
- 1% Financial

CURRENT SPONSORS & EXHIBITORS AS OF NOVEMBER 17, 2017

- Acrotein ChemBio Inc.
- Analyticon Discovery LLC
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- ZoBio

Cambridge HEALTHTECH Institute
A Division of Cambridge Innovation Institute

Drug Discovery Chemistry

April 2-6, 2018 | Hilton San Diego Bayfront | San Diego, CA

PRICING & REGISTRATION INFORMATION

PREMIUM CONFERENCE PRICING, *BEST VALUE* *(Includes access to two conferences, two short courses, and one symposium)*

	Commercial	Academic, Government, Hospital Affiliated
Advance Rate until March 30	$3249	$2099
Registrations after March 30	$3349	$2199

STANDARD CONFERENCE PRICING *(Includes access to two conferences, excludes short courses and symposia)*

Advance Rate until March 30	$2449	$1199
Registrations after March 30	$2649	$1299

BASIC CONFERENCE PRICING *(Includes access to one conference, excludes short courses and symposia)*

Advance Rate until March 30	$1849	$999
Registrations after March 30	$1949	$1099

SHORT COURSE PRICING *(April 2 & 4)*

1 Short Course	$699	$399
2 Short Courses	$999	$699
3 Short Courses	$1199	$799

SYMPOSIUM PRICING *(April 6)*

1 Symposium	$999	$599

PROGRAM SELECTIONS

Afternoon Short Courses *(April 2)*
SC1: Ligand-Receptor Molecular Interactions and Drug Design
SC2: Advancing Tools and Technology for Fragment-Based Design
SC3: Drug Metabolism and Its Impact on Decisions in Lead Discovery and Drug Development
SC4: Diversity-Oriented Platforms for Ligand Discovery

Dinner Short Courses *(April 2)*
SC5: Immunology Basics for Chemists
SC6: Introduction to Allosteric Modulators and Biased Ligands of GPCRs
SC7: Introduction to Targeted Covalent Inhibitors
SC8: Introduction to the Ubiquitin Proteasome System

Concurrent Conferences *(April 3-4)*	Concurrent Conferences *(April 4-5)*	Concurrent Symposia *(April 6)*
C1: Protein-Protein Interactions	**C6:** Ubiquitin Proteasome System Inhibitors	**S1:** Biophysical Approaches for Drug Discovery
C2: Inflammation & Autoimmune Inhibitors	**C7:** Small Molecules for Cancer Immunotherapy	**S2:** Lead Optimization for Drug Metabolism & Safety
C3: Kinase Inhibitor Chemistry	**C8:** Macrocyclics & Constrained Peptides	**S3:** Blood-Brain Penetrant Inhibitors
C4: GPCR-Targeted Drug Design	**C9:** Targeting Complex Membrane Proteins	
C5: Fragment-Based Drug Discovery		

Dinner Short Courses *(April 4)*
SC9: Impact of Convergence of Immunology & Epigenetics in Drug Discovery
SC10: Enabling Macrocyclic Compounds for Drug Discovery: Opportunities, Challenges & Strategies
SC11: Trends in Physical Properties of Drugs
SC12: Covalent Fragments: Applications in Target-Based and Phenotypic Screens

CONFERENCE DISCOUNTS

Poster Submission – Discount ($50 Off): Poster abstracts are due by **February 23, 2018.** 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 Elizabeth Lemelin at 781-972-5488.

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.

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.