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12TH ANNUAL

Drug Discovery Chemistry

APRIL 23-27, 2017

SHERATON SAN DIEGO HOTEL & MARINA · SAN DIEGO, CA

OPTIMIZING SMALL MOLECULES FOR TOMORROW'S THERAPEUTICS

APRIL 24-25:


Inflammation Inhibitors


Protein-Protein Interactions, Part 1


GPCR-Targeted Drug Design


Blood-Brain Penetrant Inhibitors

APRIL 25-26:


Kinase Inhibitor Chemistry


Protein-Protein Interactions, Part 2


Fragment-Based Drug Discovery


Macrocyclics & Constrained Peptides

SYMPOSIA APRIL 27:


Biophysical Approaches for Drug Discovery


Small Molecules for Cancer Immunotherapy

PLENARY KEYNOTES

PROTACs: Inducing Protein Degradation as a Therapeutic Strategy

Craig M. Crews, Ph.D., Professor, Chemistry & Pharmacology, Yale University

Drug Discovery and Pan-Assay Interference Compounds (PAINS)

Jonathan B. Baell, Ph.D., Faculty of Pharmacy and Pharmaceutical Sciences, Monash University

EVENT FEATURES

- More than 140 presentations
- 700+ high-level participants
- 70+ posters
- Interactive roundtable, breakout & panel discussions
- "Track-hop" between concurrent meetings
- Exclusive exhibit & poster viewing hours
- Dedicated networking opportunities
- 12 interactive short courses

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CONFERENCE-AT-A-GLANCE

SUNDAY, APRIL 23	PRE-CONFERENCE SHORT COURSES*			
MONDAY, APRIL 24	INFLAMMATION INHIBITORS	PROTEIN-PROTEIN INTERACTIONS, PART 1	GPCR-TARGETED DRUG DESIGN	BLOOD-BRAIN PENETRANT INHIBITORS
TUESDAY, APRIL 25	INFLAMMATION INHIBITORS	PROTEIN-PROTEIN INTERACTIONS, PART 1	GPCR-TARGETED DRUG DESIGN	BLOOD-BRAIN PENETRANT INHIBITORS
	KINASE INHIBITOR CHEMISTRY	PROTEIN-PROTEIN INTERACTIONS, PART 2	FRAGMENT-BASED DRUG DISCOVERY	MACROCYCLICS & CONSTRAINED PEPTIDES
	DINNER SHORT COURSES*			
WEDNESDAY, APRIL 26	KINASE INHIBITOR CHEMISTRY	PROTEIN-PROTEIN INTERACTIONS, PART 2	FRAGMENT-BASED DRUG DISCOVERY	MACROCYCLICS & CONSTRAINED PEPTIDES
THURSDAY, APRIL 27	SMALL MOLECULES FOR CANCER IMMUNOTHERAPY		BIOPHYSICAL APPROACHES FOR DRUG DISCOVERY	

Separate registration is required

PLENARY KEYNOTES

APRIL 24, 2017 | 4:30 PM

PROTACs: Inducing Protein Degradation as a Therapeutic Strategy

Craig M. Crews, Ph.D., Professor, Chemistry & Pharmacology, Yale University

APRIL 26, 2017 | 8:30 AM

Drug Discovery and Pan-Assay Interference Compounds (PAINS)

Jonathan B. Baell, Ph.D., Faculty of Pharmacy and Pharmaceutical Sciences, Monash University

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Short Courses*

APRIL 23 & 25, 2017

*Separate registration is required

SUNDAY, APRIL 23, 2017

AFTERNOON COURSES | 2:00 - 5:00 pm

SC1: Trends in Physical Properties of Drugs

Instructors:

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

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

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

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

SC2: GPCR Structure Based Drug Discovery

Instructors:

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

Aaron Thompson, Ph.D., Scientist II, Department of Structural Biology, Dart Neuroscience; former Postdoctoral Fellow of Ray Stevens Laboratory

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

SC3: Designing Peptide Therapeutics for Specific PPIs

Instructor:

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

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

SC4: RNA as a Small Molecule Drug Target

Instructor:

John "Jay" Schneekloth Jr., Ph.D., Investigator, Chemical Biology Laboratory; Head, Chemical Genetics Section, Center for Cancer Research, National Cancer Institute, NIH

Additional Instructors to be Announced

- Types of RNA that are druggable
- Strategies for identifying biologically active, RNA-binding small molecules
- Future of RNA as a drug target

DINNER COURSES | 6:00 - 9:00 pm

SC5: Immunology Basics for Chemists

Instructors:

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

Thomas Sundberg, Ph.D., 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

SC6: Introduction to Allosteric Modulators and Biased Ligands of GPCRs

Instructors:

Annette Gilchrist, Ph.D., Professor, Pharmacology, Midwestern University

Sid Topiol, Ph.D., CSO, 3D-2drug, LLC; Professor and Director, Structural and Computational Drug Discovery, Stevens Institute of Technology

- Overview of allosteric modulators and pathway biased ligands
- Approaches for screening and validation
- Insights into GPCR structural "pressure points"
- Structure based options for docking and design of allosteric and biased ligands

SC7: Ligand-Receptor Molecular Interactions and Drug Design

Instructor:

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

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

SC8: Drug Metabolism and Its Impact on Decisions in Lead Discovery

Instructors:

Mark Grillo, Ph.D., Staff Scientist, Drug Metabolism & Pharmacokinetics, MyoKardia, Inc.

Adrian J. Fretland, Ph.D., Associate Director, DMPK Oncology iScience, AstraZeneca

- Enzymes involved in the metabolism of drugs
- Metabolism-based drug-drug interactions
- Understanding how drug structure impacts important PK parameters
- Common assays for predicting clearance and drug-drug interactions
- Understanding how drug metabolism concepts are applied during lead optimization

TUESDAY, APRIL 25, 2017

DINNER COURSES | 6:00 - 9:00 pm

SC9: Impact of Convergence of Immunotherapy and Epigenetics on Drug Discovery

Instructors:

Seng-lai 'Thomas' Tan, Ph.D., Senior Director and Head of Immunology, FORMA Therapeutics

Edward Holson, Ph.D., CSO, KDAc Therapeutics

- Understanding how epigenetic pathways intersect and interact with the immune system
- Exploiting immunoepigenetics to enhance the efficacy of current drug treatments
- Recent scientific and pre-clinical data to support combination therapies
- Case studies highlighting promises and challenges

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

Instructors:

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

Mark Peterson, Ph.D., 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: Advancing Tools and Technology for Fragment-Based Design

Instructors:

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

Daniel A. Erlanson, Ph.D., 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

SC12: Introduction to Targeted Covalent Inhibitors

Instructors:

Brian Gerstenberger, Ph.D., Principal Scientist, Medicinal Chemistry, Pfizer

Mark Schnute, Ph.D., 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
- Mechanism of drug resistance

Eighth Annual

Inflammation Inhibitors

Small Molecule Approaches for Oral-Based Therapeutics

MONDAY, APRIL 24

7:00 am Registration and Morning Coffee

INFLAMMATION DRUG TARGETS FOR SMALL MOLECULES: BEYOND KINASES AND NUCLEAR RECEPTORS

8:00 Chairperson's Opening Remarks
Jennifer Venable, Ph.D., Associate Scientific Director, Medicinal Chemistry, J&J

8:10 FEATURED PRESENTATION: Development of Immunoproteasome Subunit Selective Inhibitors
Dustin McMinn, Ph.D., Director, Head of Medicinal Chemistry, Kezar Life Sciences, Inc.

Selective immunoproteasome inhibition blocks inflammatory cytokine production and alters pro-inflammatory T-cell plasticity without affecting cell viability. Animal models of rheumatoid arthritis, type-I diabetes, multiple sclerosis, IBD, and lupus maintain normal immune function while responding well to small-molecule immunoproteasome inhibitors. Kezar's first candidate from this compound class, KZR-616, entered Phase I clinical trials in summer of 2016. Our design toward KZR-616 and other selective immunoproteasome inhibitors will be discussed.

8:40 STING (Stimulator of Interferon Genes)-Dependent Pathways and New Drug Targets
Sasha (Alexander) Poltorak, Ph.D., Associate Professor, Integrative Physiology and Pathobiology, Tufts University

We present evidence that activation of STING in T cells not only induces a type I IFN response atypical of these cells, but also activates cell stress and apoptotic pathways, triggering profound T cell death. These observations imply that STING-targeted therapeutics may potentially lead to T cell deficiencies, or, conversely could be beneficial for the elimination of pathological T cells in the case of autoimmune disease, T cell lymphomas, or organ transplantation.

9:10 Sponsored Presentation *(Opportunity Available)*

9:40 Coffee Break

10:05 Discovery of NF-kappa-B-Inducing Kinase (NIK) Inhibitors
Walter Keung, Ph.D., Senior Scientist, Medicinal Chemistry, Takeda California

NF-kB-inducing kinase (NIK, MAP3K14) is a key component of the non-canonical NF-kB pathway, and a central node in pathways commonly activated in autoimmune and inflammatory disorders. Here, we describe a fragment and structure based approach to the optimization of novel and selective series of NIK inhibitors, which capitalized on an unexpected flipped binding mode. Broader pharmacological profiling of these molecules will also be described.

10:35 Biomarker Discovery and Development of PTG-200, an Oral Peptide Antagonist of IL-23 Receptor
Larry Mattheakis, Ph.D., Vice President, Biology, Protagonist Therapeutics

Clinical studies show that blocking IL-23 function has therapeutic applications in inflammatory bowel disease. We have developed PTG-200, a potent peptide that binds and blocks downstream signaling of the IL-23 receptor, expressed on gut innate lymphoid cells. PTG-200 is orally stable and in rat colitis models results in significant improvements in disease, including histopathology. We also identified biomarkers that are PTG-200 dose dependent and correlate with efficacy; their potential clinical applications will be discussed.

11:05 KPT-350, a Selective Inhibitor of Nuclear Export (SINE) Compound, Targets Multiple Autoimmune Processes in Lupus
Margaret Lee, Ph.D., Director, Biology, Karyo Pharma

Exportin-1 (XPO1) is the sole nuclear exporter of multiple anti-inflammatory regulatory proteins and transcription factors relevant to systemic lupus erythematosus (SLE) disease pathology. KPT-350 is an orally bioavailable, reversible, small-molecule inhibitor of XPO1 with potent effects on murine lupus *in vivo*. KPT-350 treatment reduces germinal center reactions, auto reactive plasma cells, pro-inflammatory cytokines and autoantibodies leading to improvements in nephritis and proteinuria in lupus prone mice. Thus inhibition of XPO1 represents a novel therapeutic approach for SLE.

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

12:20 pm Session Break

TARGETING ROR/NUCLEAR RECEPTORS FOR INFLAMMATION AND AUTOIMMUNITY

1:15 Chairperson's Remarks
John Robinson, Ph.D., Director, Medicinal Chemistry, Array Biopharma

1:20 FEATURED PRESENTATION: Discovery of a Series of Thiazole RORγt Inverse Agonists
Steven Goldberg, Ph.D., Associate Scientific Director, Immunology, Janssen R&D

Differentiation of naïve T-cells into IL-17 producing Th17 cells is regulated by the nuclear receptor transcription factor retinoic acid receptor-related orphan receptor γt (RORγt). Blocking the production of pro-inflammatory cytokines by RORγt modulation has the potential to be an effective treatment for autoimmune diseases. A promising series of thiazole RORγt inverse agonists has been identified and our optimization efforts will be discussed.

1:50 Small Molecule Modulators of RORγ
Robert Hughes, Ph.D., Senior Associate Director, Small Molecule Discovery Research, Boehringer-Ingelheim

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

2:20 From Multiple Hit Series to the Clinical Candidate for RORγt Using DNA Encoded Library Technology
Sanne Glad, Ph.D., Principal Scientist, Project Leader, Lead Discovery Nuevolution

The nuclear hormone receptor RORγt is a master regulator of IL-17A production, which triggers inflammatory disease. We have identified nanomolar potent small molecule inverse agonists from screening 830 million DNA-encoded compounds against the RORγt-ligand binding domain. Hit-to-lead optimization led to a preclinical candidate with attractive DMPK properties, high oral bioavailability, strong *in vivo* efficacy across several anti-inflammatory animal models, and a benign safety profile.

2:50 VTP-43,742: An Oral RoRγt Inverse Agonist in Clinical Development; Discovered by *in silico* Structure Based Drug Design
David A. Claremon, Ph.D., Vice President, Chemistry, Vitae Pharmaceuticals, an Allergan Affiliate

3:20 Sponsored Presentation *(Opportunity Available)*

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

4:30 PLENARY KEYNOTE PRESENTATION
PROTACs: Inducing Protein Degradation as a Therapeutic Strategy
Craig M. Crews, Ph.D., Lewis B. Cullman Professor of Molecular, Cellular, and Developmental Biology; Professor, Chemistry & Pharmacology, Yale University
Enzyme inhibition has proven to be a successful paradigm for pharmaceutical development, however, it has several limitations. As an alternative, for the past 16 years, my lab has focused on developing Proteolysis Targeting Chimera (PROTAC), a new 'controlled proteolysis' technology that overcomes the limitations of the current inhibitor pharmacological paradigm. Based on an "event-driven" paradigm, PROTACs offer a novel, catalytic mechanism to irreversibly inhibit protein function, namely, the intracellular destruction of target proteins.

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

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6:30 Close of Day

TUESDAY, APRIL 25

7:30 am Continental Breakfast Breakout Discussions

NEXT-GENERATION INTRACELLULAR KINASE INHIBITORS FOR INFLAMMATION

8:30 Chairperson's Remarks
Seng-lai 'Thomas' Tan, Ph.D., Senior Director and Head of Immunology, FORMA Therapeutics

8:35 A Twisted Road to the Discovery of BMS-986142: Using Locked Atropisomers to Drive Potency in a Reversible Inhibitor of Bruton's Tyrosine Kinase (BTK)
Joseph Tino, Ph.D., Senior Principal Scientist, Immunoscience Discovery Chemistry, BristolMyers Squibb
Bruton's tyrosine kinase (BTK) plays a central role in multiple cell types linked to autoimmune diseases. BTK inhibitors are anticipated to be important clinical options for fighting rheumatoid arthritis and lupus. This presentation details the structure-activity relationships leading to a novel series of carbazole and tetrahydrocarbazole based, reversible inhibitors of BTK. Improvements in potency and selectivity by locking the two atropisomeric centers will be featured. With an excellent efficacy and tolerability profile, BMS-986142 has advanced into clinical studies.

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

9:05 A First-in-Class Allosteric Inhibitor of TYK2 as a Potential Treatment for Inflammatory Autoimmune Diseases
Stephen Wrobleski, Principal Investigator, Immunoscience Chemistry, Bristol-Myers Squibb
Tyrosine kinase 2 (TYK2) is a member of the JAK family of kinases and is involved in signaling through the receptors for several pro-inflammatory interferons and interleukins. BMS-986165 is a highly potent and exquisitely selective TYK2 inhibitor that binds to the unique pseudokinase domain of TYK2 and functions through an allosteric mechanism. I will describe the medicinal chemistry efforts and structure-based optimization strategies that led to the identification of BMS-986165 as a promising clinical candidate with first-in-class potential.

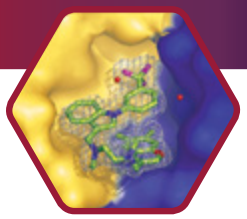
9:35 Coffee Break in the Exhibit Hall with Poster Viewing

10:30 ARRY-624: A TYK2-leaning, JAK Inhibitor: A First-in-Class Small Molecule Selectively Targeting the IL-12/23 Pathways
John Robinson, Ph.D., Director, Medicinal Chemistry, Array Biopharma
Pan JAK inhibitors block signaling of >20 cytokines & growth factors, effect both NK and CD8+ T-cell populations, and exhibit increased risk of infection & malignancy clinically. We hypothesized that a Tyk2-targeted kinase inhibitor, such as ARRY-624, which does not engage JAK1/3, may lead to differentiated efficacy and clinical safety vs. currently available treatment options. This profile allows for selective modulation of IL-12 (Th1) and IL-23 (Th17) pathways, while sparing IL-2/IL-7 and IL-15 (g-chain-utilizing cytokines).

11:00 Inhibition of Autoimmune Pathways with Dual Inhibition of JAK1 and TYK2
Brian Gerstenberger, Ph.D., Principal Scientist, Medicinal Chemistry, Pfizer

11:30 Discovery and Profiling of Novel, Intestinally-Restricted Oral Pan-JAK Inhibitors for the Treatment of Inflammatory Bowel Diseases
Jennifer Kozak, Ph.D., Research Scientist, Medicinal Chemistry, Theravance Biopharma
There remains a significant need for improved therapies to treat inflammatory bowel diseases, including ulcerative colitis (UC). The oral JAK inhibitor tofacitinib has demonstrated clinical effectiveness in treating UC patients in Phase 3 trials, although its usage may be limited by adverse events resulting from systemic drug levels. Here we report the structure-based design and profiling of a series of novel, pan-JAK inhibitors designed to be intestinally-restricted thereby minimizing systemic side effects.

12:00 pm Close of Conference



Tenth Annual

Protein-Protein Interactions, Part 1

Targeting PPIs for Therapeutic Interventions

MONDAY, APRIL 25

7:00 am Registration and Morning Coffee

TARGETING PPIs FOR IMMUNOLOGY AND INFECTIOUS DISEASES

8:00 Chairperson's Opening Remarks

Laura Silvian, Ph.D., Principal Scientist and Head, Physical Biochemistry, Biogen

8:10 Complement Factor D Inhibitors: Blocking Interactions with Factor B via Fragment-Based Approaches

Fredrik Edfeldt, Ph.D., Associate Principal Scientist, Biophysics, Discovery Sciences, Astra Zeneca R&D

Complement Factor D (CFD) is an atypical self-inhibited Ser-protease that is activated only when binding to Complement Factor B. Our approach has been to block enzymatic activity by targeting and stabilizing the inactive form of CFD. When other hit-finding methods failed, we succeeded using fragment-based approaches. Initially we identified a weak (2 mM) fragment hit by SPR. Structure based design was then used to develop inhibitors with a roughly 20000-fold improvement in affinity from the starting point.

8:40 Using Encoded Library Technologies to Discover Small Molecule Inhibitors of RSV Protein Complexes

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

Respiratory Syncytial Virus (RSV) remains a significant unmet cause of severe respiratory infections. RSV-N (nucleoprotein) is a critical component of the virus' replication machinery, encapsulating the viral RNA genome and forming interactions with other viral proteins (P and L) that form the viral replication complex. DNA encoded library technology (ELT) was used to identify a potent inhibitor of the N/P protein/protein interaction capable of blocking viral replication of cells.

9:10 Sponsored Presentation *(Opportunity Available)*

9:40 Coffee Break

10:05 p53/Rb Reactivation Modulators for HPV-Positive Head and Neck Cancer

Paramjit Arora, Ph.D., Professor, Department of Chemistry, New York University

The incidence of human papillomavirus (HPV)-positive head and neck squamous cell carcinoma (HNSCC) has rapidly increased over the past 30 years, prompting the suggestion that an epidemic may be on the horizon. We are exploring if targeting the E6-p300 interaction is an effective approach to reactivate p53/Rb in HPV-positive HNSCC. Through rational design we have uncovered small molecules inhibitors that reactivate p53 and potentiate the anticancer activity of cis-platinum in HPV-positive HNSCC

10:35 Rational Design of Human Cyclophilin Inhibitors as Pan-Viral Agents

Jean-Francois Guichou, Ph.D., Professor, Structural Biology Department, Center of Structural Biochemistry, University of Montpellier, France

Cyclophilins are peptidyl-prolyl cis/trans isomerases (PPIase) that catalyse the interconversion of the peptide bond at proline residues. Several cyclophilins play a pivotal role in the life cycle of a number of viruses. The existing cyclophilin inhibitors, all derived from cyclosporine A or sanglifehrin A, have several disadvantages. Here we use a fragment-based drug discovery approach using nucleic magnetic resonance, X-ray crystallography and structure-based compound optimization to generate a new family of non-peptidic, small-molecule cyclophilin inhibitors.

11:05 Inhibiting Interaction of IL17A and Its Receptor

Sepideh Afshar, Ph.D., Principal Research Scientist, Department of Protein Engineering, Eli Lilly and Company

11:35 Luncheon Presentation: Discovery of Novel Small-Molecule Protein-Protein Interaction Inhibitors using DNA-Encoded Chemical Libraries

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X-CHEM PHARMACEUTICALS

Anthony D. Keefe, Senior Director, Lead Discovery, X-Chem Pharmaceuticals

X-Chem operates a proprietary DNA-encoded chemistry platform that has been successfully applied to a wide range of target classes and therapy areas and currently numbers over 100 billion compounds. Of the twenty-eight programs that we have licensed to our collaboration partners approximately one third are for inhibitors of protein-protein interactions. This number reflects both the effectiveness of our platform and the wide-ranging interest among our collaboration partners for this class of target and mode of action. This presentation will introduce the generation of DNA-encoded chemical libraries and how affinity-mediated methodologies may then be used to find potent inhibitors from within them. Examples will also be shown in which multiple DNA-encoded library screens are run in parallel and simultaneously generate data that informs upon the specificity, affinity and binding site of individual library members. Additionally, a number of our successful individual protein-protein interaction programs will be introduced.

12:20 pm Session Break

BEYOND ACTIVE-SITE BINDING

1:15 Chairperson's Remarks

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

1:20 Development of Cytotoxic Bicyclic Peptide Drug Conjugates and Applications in Molecular-Targeted Cancer Therapy

Daniel Teufel, Ph.D., Head of Chemistry, Bicycle Therapeutics

The Bicycle platform is presented where linear peptide libraries, genetically encoded in bacteriophage, are post-translationally cyclised with homo-trifunctional organochemical scaffolds, yielding large bicyclic peptide libraries. These constrained peptide libraries have been screened against a range of targets, including receptors, interleukins, enzymes and serine proteases. This presentation describes the identification and development of a novel peptide macrocycle (2.5 kDa) targeting tumour-overexpressed MT1-MMP, and its applications as a cytotoxic drug conjugate in molecular targeted chemotherapy.

1:50 Junctional Epitope Antibodies as Tools for Screening against PPI Targets

Chiara Valenzano, Ph.D., Principal Scientist, Structural Biology, UCB Pharma

The transient interaction between proteins regulates the majority of biological cellular processes. Here we introduce VHH6, a junctional epitope antibody capable of specifically recognizing a neo-epitope when two proteins interact to form a complex. Orthogonal biophysical techniques have been used to prove the "junctional epitope" nature of VHH6, a camelid single domain antibody recognizing the IL-6–gp80 complex. X-ray crystallography, HDX-MS and SPR analysis confirmed that the CDR regions of VHH6 interact simultaneously with IL-6 and gp80, locking the two proteins together.

2:20 Dynamic Injection SPR for Rapid Protein-Protein Binding Site Identification

Clare Wilson, Ph.D., Postdoctoral Research Fellow, Division of Cardiovascular & Diabetes Research, University of Leeds

Using dynamic injection SPR (diSPR) based on a SensiQ Pioneer platform, we have localized an important binding site between fibrinogen and its associated transglutaminase. This site may now be targeted by small

molecule compounds to disrupt this interaction to reduce clot stability, providing a novel therapeutic approach to the development of novel anti-thrombotic therapeutics.

2:50 Inhibiting Kinases at Their Substrate Recognition Sites: Structure-Activity and Selectivity of Polo Box-Targeted PLK1 Inhibitors

Campbell McInnes, Ph.D., Associate Professor, Drug Discovery and Biomedical Sciences, University of South Carolina

Protein-protein interactions involved in kinase regulation and substrate recognition have significant potential in drug discovery due to their unique features and therefore allow selectivity and potency of inhibition by avoiding the catalytic site. Since these interfaces typically involve shallow clefts and more diffuse interactions, they are more challenging than the ATP binding site. We have developed and validated a general strategy for protein-protein interactions in the development of non-ATP competitive inhibitors of protein kinase oncology targets through the substrate recruitment site.

3:20 Sponsored Presentation *(Opportunity Available)*

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

4:30 PLENARY KEYNOTE PRESENTATION

PROTACs: Inducing Protein Degradation as a Therapeutic Strategy

Craig M. Crews, Ph.D., Lewis B. Cullman Professor of Molecular, Cellular, and Developmental Biology; Professor, Chemistry & Pharmacology, Yale University

Enzyme inhibition has proven to be a successful paradigm for pharmaceutical development, however, it has several limitations. As an alternative, for the past 16 years, my lab has focused on developing Proteolysis Targeting Chimera (PROTAC), a new 'controlled proteolysis' technology that overcomes the limitations of the current inhibitor pharmacological paradigm. Based on an "event-driven" paradigm, PROTACs offer a novel, catalytic mechanism to irreversibly inhibit protein function, namely, the intracellular destruction of target proteins.

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

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6:30 Close of Day

TUESDAY, APRIL 25

7:30 am Continental Breakfast Breakout Discussions

APOPTOSIS AND PPI INHIBITORS

8:30 Chairperson's Remarks

Kevin Lumb, Ph.D., Scientific Director, Discovery Sciences, Janssen R&D

8:35 FEATURED PRESENTATION: IAP Antagonists Synergize with Cancer Immunotherapies

Eric LaCasse, Ph.D., Research Scientist, Apoptosis Research Centre, Children's Hospital of Eastern Ontario

This presentation reviews the current state and future directions for inhibitor-of-apoptosis (IAP) members. These small-molecule IAP antagonists kill tumor cells in conjunction with TNFalpha while also stimulating immune cells. Immune stimulants are able to induce endogenous TNFalpha which synergizes with these IAP antagonists. In addition, these compounds can provide co-stimulatory signals to T-cells which in the presence of immune checkpoint inhibitor biologics allows for a full-fledged immune response against the tumor.

> "Great opportunity to share and discuss cutting-edge approaches/aspects in drug discovery."
>
> *- Fabrizio G., Principal Scientist, AstraZeneca*

9:05 The Development of Orally Bioavailable Antagonists of Inhibitor of Apoptosis Proteins (IAPs) for the Treatment of Cancer

Lewis Gazzard Ph.D., Senior Scientist, Discovery Chemistry, Genentech, Inc.

Apoptosis is a tightly regulated process critically dependent on the balance between anti- and pro-apoptotic factors. The inhibitor of apoptosis (IAP) proteins block progression into apoptosis, and are upregulated in many cancers to tip this balance in favor of survival, while the endogenous IAP antagonist SMAC acts to promote cell death. The development of small molecule SMAC mimetics and the identification of two orally bioavailable clinical candidates for the treatment of cancer will be described.

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

10:30 Discovery of a Potent Inhibitor of an Anti-Apoptotic PPI Target

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

A number of therapeutically important targets involve disrupting interactions between two proteins ("PPI targets"). Disruption of this type of interface was initially regarded as "undruggable", but a growing body of literature shows that these interactions can be successfully inhibited by small molecule ligands. We will discuss our experiences and successful approaches to identifying ligands and inhibitors of PPI targets.

11:00 Next-Generation Cereblon Modulators

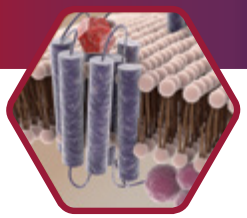
Phillip Chamberlain, Ph.D., Principal Scientist, Biochemistry and Structural Biology, Celgene

11:30 Design, Synthesis and Characterization of Modulators of the Inhibitor of Apoptosis (IAP) Family Proteins

Nicholas D. P. Cosford, Ph.D., Professor, Cancer Metabolism& Signaling Networks Program; Associate Director, Translational Research, Sanford Burnham Prebys Medical Discovery Institute

The inhibitor of apoptosis (IAP) proteins are critical regulators of cellular processes in humans. Compounds that modulate IAPs have potential as therapeutic agents to treat cancer and diseases of the immune system. The systematic rational design and synthesis of monovalent Smac mimetics in different structural classes will be presented. The application of IAP modulators to the treatment of cancer and HIV/AIDs will be discussed.

12:00 pm Close of Conference



Inaugural

GPCR-Targeted Drug Design

with a Focus on Biased Signaling and Biophysical Techniques

MONDAY, APRIL 24

7:00 am Registration and Morning Coffee

BIASED AGONISM AT THE OPIOID RECEPTOR

8:00 Chairperson's Opening Remarks
Roger K. Sunahara, Ph.D., Professor of Pharmacology, University of California San Diego

8:10 Positive Allosteric Modulators of Opioid Receptors
Andrew Alt, Ph.D., Associate Director, Biology, Arvinas
Positive allosteric modulators (PAMs) of opioid receptors block pain by amplifying the activity of endogenous opioid agonists which are naturally released in pain states. However, PAMs have no effect in tissues where agonists are not present. Therefore, opioid PAMs may exhibit significantly improved side effect and abuse liability profiles compared to current opioid medications. The current preclinical data supporting a rationale for developing opioid receptor PAMs as novel pain medications will be presented.

8:40 Conserved Allosteric Sodium in Class A GPCRs: Role in Function and Ligand Design
Seva Katritch, Ph.D., Assistant Professor, The Bridge Institute, University of Southern California
Class A GPCRs feature a highly conserved polar cavity in the center of 7TM bundle, harboring a sodium ion and water cluster with highly unusual properties. We will describe structural and pharmacological evidence for this Na+ cluster and its conservation in many GPCRs, as well as the recent efforts in elucidating its role in receptor function. We will also discuss emerging applications of the allosteric sodium site in GPCR stabilization and ligand discovery.

9:10 Sponsored Presentation *(Opportunity Available)*

9:40 Coffee Break

10:05 Structural Insights into Opioid Receptor Signaling
Aashish Manglik, M.D., Ph.D., Stanford Distinguished Fellow, Department of Molecular and Cellular Physiology, Former Member of Brian Kobilka Group, Stanford University School of Medicine
Despite two centuries of medicinal chemistry since the isolation of morphine from the opium poppy, the ideal opioid analgesic devoid of liabilities like addiction and respiratory depression remains elusive. I will describe our efforts to understand the structural and biophysical basis of opioid receptor activation and how these insights have enabled the discovery of a novel Gi biased opioid agonist that provides pain relief without key dose limiting side effects.

10:35 Kratom Alkaloids: Novel Molecular Frameworks for Next-Generation Opioid Modulators
Andrew Kruegel, Ph.D., Associate Research Scientist, Department of Chemistry, Columbia University
The *Mitragyna speciosa* plant (kratom) has been used in traditional medicine in Southeast Asia for hundreds of years. Alkaloids isolated from this plant and their synthetic derivatives act as opioid receptor modulators with pharmacological properties distinct from traditional opioids, namely they elicit potent analgesic effects in rodents while avoiding the major negative side effects of respiratory depression, tolerance/dependence, and reward. The design, synthesis, and pharmacological evaluation of new analgesics in this class will be discussed.

11:05 Opioid Receptor Trafficking and Signaling
Manoj Puthenveedu, Ph.D., Associate Professor, Department of Biological Sciences, Carnegie Mellon University
Membrane trafficking, by determining the number of receptors available on the cell surface, can regulate the strength of cellular responses to signals. Emerging data suggest that trafficking can also tune cellular responses by regulating receptor location, and therefore the site of signal origin, in the cell. In this context, I will present our work on how trafficking changes sub-cellular localization of opioid receptors and thereby regulates opioid signaling.

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

12:20 pm Session Break

PHARMACOLOGICAL GPCR INSIGHTS

1:15 Chairperson's Remarks
Tracy Handel, Ph.D., Professor, UCSD Skaggs School of Pharmacy & Pharmaceutical Sciences, UCSD Health Sciences

1:20 FEATURED PRESENTATION: Receptor Allostery by Cations, Small Molecules and G proteins
Roger K. Sunahara, Ph.D., Professor of Pharmacology, University of California San Diego
The relationship between G protein binding and the hormone binding site, where G proteins potently enhance the affinity of hormone agonists, is an allosteric one. Here we describe a major role of additional co-factors, cations, as allosteric modulators in the stabilization of inactive and active states of GPCRs. These data highlight the complex nature of the cooperativity existing between hormones, cations and G proteins in stabilizing specific GPCR conformations and illustrate a significant impact on drug discovery and development.

1:50 Diverse Mechanisms for Nuclear Localization of GPCRs: Impact on Function
Sylvain Chemtob, M.D., Ph.D., Professor of Pediatrics and Ophthalmology, University of Montreal
Mechanisms that govern localization of GPCRs at the cell nucleus remain mostly unknown and vary. For instance, stimulation of coagulation factor II receptor-like 1 (F2rl1) leads to its translocation from plasma membrane to the cell nucleus using a microtubule-dependent shuttle that requires sorting nexin 11 (Snx11). Whereas stimulation of platelet-activating factor (PAFR) does not affect its cellular distribution. But its C-terminal motif, along with Rab11a and importin-5 are critical for nuclear localization of PAFR.

2:20 Biophysical Basis for Sustained G Protein Signaling by Internalized GPCRs
Alex Thomsen, Ph.D., Postdoctoral Fellow, Lefkowitz Lab, Department of Medicine, Duke University
Some GPCRs activate G-proteins from within internalized cellular compartments resulting in sustained G-protein signaling rather than β-arrestin-mediated desensitization. Using a variety of biochemical, biophysical, and cell-based methods we recently demonstrated the existence, functionality, and architecture of internalized receptor "megaplexes" composed of a single GPCR, β-arrestin, and G-protein. Formation of such megaplexes provides a mechanistic explanation for how a GPCR, while being internalized through interaction with β-arrestin maintains its ability to activate G-protein from internalized compartments.

2:50 The Structural and Functional Basis of Chemokine Receptor Signaling
Tracy Handel, Ph.D., Professor, UCSD Skaggs School of Pharmacy & Pharmaceutical Sciences, UCSD Health Sciences

3:20 3DM Protein Family Analysis System Applied to the GPCR Protein Family
Sponsored by bio-prodict
Henk-Jan Joosten, Ph.D., CEO, Bio-Prodict
Proteins fall in large protein-families and vast amounts of data are available for one protein family (e.g. sequences, literature, structural data, alignment data, SNP data, mutation data, binding data, etc). 3DM, a protein-superfamily analysis platform, automatically collects all data and contains many state-off-the-art tools enabling complex analysis of super-family data.

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

4:30 PLENARY KEYNOTE PRESENTATION
PROTACs: Inducing Protein Degradation as a Therapeutic Strategy
Craig M. Crews, Ph.D., Lewis B. Cullman Professor of Molecular, Cellular, and Developmental Biology; Professor, Chemistry & Pharmacology, Yale University
Enzyme inhibition has proven to be a successful paradigm for pharmaceutical development, however, it has several limitations. As an alternative, for the past 16 years, my lab has focused on developing Proteolysis Targeting Chimera (PROTAC), a new 'controlled proteolysis' technology that overcomes the limitations of the current inhibitor pharmacological paradigm. Based on an "event-driven" paradigm, PROTACs offer a novel, catalytic mechanism to irreversibly inhibit protein function, namely, the intracellular destruction of target proteins.

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

6:30 Close of Day

TUESDAY, APRIL 25

7:30 am Continental Breakfast Breakout Discussions

DESIGNING GPCR-TARGETED COMPOUNDS

8:30 Chairperson's Remarks
Sid Topiol, Ph.D., CSO, 3D-2drug, LLC; Professor and Director, Structural and Computational Drug Discovery, Stevens Institute of Technology

8:35 GPCR Structural Biology for Drug Discovery: Through the Protein Science Lens
Sujata Sharma, Ph.D., Director, Screening and Protein Science, Merck and Company

9:05 Compound Mechanism of Action: "The Known Unknown" and How That Affects Lead Optimization
Brian J. Murphy, Ph.D., Senior Principal Scientist, Fibrosis Drug Discovery, Disease Sciences and Biologics, R&D, Bristol-Myers Squibb
I will present three vignettes of programs whose progress was slowed by testing compounds that had little to no a priori chance of working *in vivo*. Had greater attention been paid to the pharmacological properties of the compounds (allostery, kinetics, reserve), the selection of compounds for *in vivo* testing would have been more judicious and the programs could have proceeded to clinical candidate selection significantly more quickly and efficiently.

> "This meeting was an eye-opener for me to see how collectively drug delivery scientists can work with medicinal chemists to bring new pharmaceutical products more effectively to the market."
>
> *- Hayat O., Professor, University of Illinois at Chicago*

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

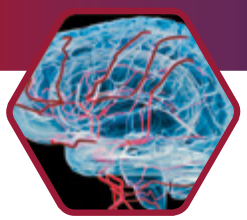
BIOPHYSICAL TECHNIQUES FOR STUDYING GPCR DYNAMICS

10:30 Biophysical Characterization of GPCRs: SPR and Other Techniques
Phillip Schwartz, Ph.D., Senior Scientist, Biophysical Chemistry, 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. We are pioneering the application of numerous biophysical techniques including SPR, SHG, DSF, NMR, HDX and BSI to study GPCRs. Data from a variety of these techniques will be compared and contrasted using a number native ligands and tool compounds.

11:00 Conformational Dynamics of G Protein-Coupled Receptors as Studied by NMR Spectroscopy in Solution
Matthew Eddy, Ph.D., Postdoctoral Fellow, Laboratory of Raymond Stevens, The Bridge Institute, University of Southern California
Application of nuclear magnetic resonance (NMR) spectroscopy to studies of G protein-coupled receptors (GPCRs) has been challenging due to difficulties producing sufficient quantities of isotope labeled functional receptors. Here we present a novel approach to heterologous production of wild type, labeled human GPCRs at sufficient quantities and quality for high resolution NMR spectroscopy. Data obtained with our method provide novel insights into intrinsic ligand activity that may aid in developing new design criteria for drugs that target GPCRs.

11:30 Ligand-observed NMR for Ligand Selectivity and Fragment Screening of Specific GPCR Subtypes
Daniel Scott, Ph.D., Laboratory Head, The Florey Institute of Neuroscience and Mental Health, The University of Melbourne
We evolved ultra-stable α1A-AR and α1B-AR variants using Cellular High-throughput Encapsulation, Solubilization and Screening (CHESS) to enable the analysis of ligand binding and fragment screening using ligand observed NMR techniques. α1A- and α1B-adrenoceptors (α1A-AR and α1B-AR) are closely related G protein-coupled receptor (GPCRs) that modulate the cardiovascular and nervous systems in response to binding epinephrine and norepinephrine.

12:00 pm Close of Conference



Second Annual

Blood-Brain Penetrant Inhibitors

Discovery and Design of Selective and Potent Inhibitors Crossing the Blood-Brain Barrier

MONDAY, APRIL 24

7:00 am Registration and Morning Coffee

FEATURED SESSION: DISCOVERY AND DEVELOPMENT OF BRAIN PENETRANT INHIBITORS FOR CANCER

8:00 Chairperson's Opening Remarks

William F. Elmquist, Pharm.D., Ph.D., Professor and Head, Department of Pharmaceutics; Director, Brain Barriers Research Center, University of Minnesota

8:10 BBB – Brain Tumor Interactions: A Complex, Dynamic System Influencing Efficacy and Resistance

William F. Elmquist, Pharm.D., Ph.D., Professor and Head, Department of Pharmaceutics; Director, Brain Barriers Research Center, University of Minnesota

This talk will focus on the issues surrounding effective drug delivery to the invasive cells in brain tumors, both primary and metastatic. 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.

8:40 Small Molecule Kinase Inhibitors for Brain Cancer: Limitations, Challenges and Opportunities

Timothy P. Heffron, Ph.D., Senior Scientist, Discovery Chemistry, Genentech, Inc.

In addition to each of the factors that affect the identification of a successful oncology drug candidate, drug discovery aimed at treating neurological cancers must also consider the presence of the blood-brain barrier (BBB). High expression of transporters at the BBB limits most kinase inhibitors from freely reaching CNS malignancies within the brain. This talk will discuss the unmet need for neuro-oncology treatments, the significant opportunities that remain for new kinase inhibitors in this space and the unique challenges and considerations for brain penetrant kinase inhibitor programs.

9:10 Prediction of Drug Efficiency: Aptuit's Experience in CNS Drug Design & Discovery

Sponsored by aptuit

Alfonso Pozzan, Ph.D., Manager & Principal Scientific Investigator, Computational Chemistry, Aptuit

The selection of high-quality drug candidates is recognized as the most important decision in Drug Discovery. In '97, Lipinski paved the way towards a more rational use of physicochemical descriptors to predict the quality of such molecules. As an evolution of this concept, we have introduced in 2010 an *in vitro/in vivo* Drug Efficiency (Deff) coefficient and now an *in silico* Deff predictor to be used during the Drug Design phase.

9:40 Coffee Break

10:05 Discovery and Synthesis of the Macrocyclic EML4-ALK Inhibitor, Lorlatinib (PF-06463922)

Paul Richardson, Ph.D., 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.

10:35 Discovery and Evaluation of Clinical Candidate AZD3759, a Potent, Oral Active, Central Nervous System Penetrant, Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor

Qingbei Zeng, Ph.D., Principal Scientist, Innovation Center China, AstraZeneca

Herein, we report the discovery of (4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl (2R)-2,4-dimethylpiperazine-1-carboxylate 1m (AZD3759), an investigational drug currently in Phase I clinical trial, which has excellent central nervous system penetration and which induces profound regression of brain metastases in a mouse model.

11:05 Galotinib, Targeting Brain Metastasis for Non-Small Cell Lung Cancer

Xiaoyang Xia, Ph.D., CEO, Teligene

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

12:20 pm Session Break

BRAIN PENETRANT INHIBITORS FOR NEURODEGENERATIVE AND PSYCHIATRIC DISORDERS

1:15 Chairperson's Remarks

Edward Holson, Ph.D., CSO, KDAc Therapeutics

1:20 Brain Penetrant HDAC Inhibitors to Treat CNS Disorders

Edward Holson, Ph.D., CSO, KDAc Therapeutics

1:50 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, importance of modern CNS pharmacokinetic concepts including the "free drug" hypothesis, are also discussed.

2:20 Addressing the Inflammatory Aspects of Amyloidosis Using CNS Penetrant p38 Kinase Inhibitors

Michael Burnet, Ph.D., Managing Director, Synovo GmbH

We screened appropriate inhibitor sets for CNS penetration in a murine amyloidosis model (APPPS) to select appropriate compounds for study. The centrally available p38 inhibitors reversed this phenomenon providing treated animals with a similar life expectancy to non-diabetic littermates. The substances had no effect on diabetic parameters, and given that the amyloid deposition is largely central in this model, we are investigating the CNS component of this effect. These data suggest that centrally active p38 inhibitors have the potential to treat dementias complicated by Type II diabetes.

2:50 Strategy and Tactics for the Discovery of Kinase Inhibitors: A Lundbeck Perspective

Klaus Baek Simonsen, Ph.D., Vice President, Discovery Chemistry, DMPK and Molecular Screening, Lundbeck

This talk will highlight our drug discovery philosophy and strategies towards the discovery of new CNS drugs for kinases. The various challenges within drug discovery in general and CNS in particular will be discussed together with contemporary understanding of drug discovery and medicinal chemistry scholarship, translatability and project execution for this target class. Our strategy and search for novel kinase inhibitors will be illustrated with examples form two active programs including LRRK2.

3:20 Sponsored Presentation *(Opportunity Available)*

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

4:30 PLENARY KEYNOTE PRESENTATION

PROTACs: Inducing Protein Degradation as a Therapeutic Strategy

Craig M. Crews, Ph.D., Lewis B. Cullman Professor of Molecular, Cellular, and Developmental Biology; Professor, Chemistry & Pharmacology, Yale University

Enzyme inhibition has proven to be a successful paradigm for pharmaceutical development, however, it has several limitations. As an alternative, for the past 16 years, my lab has focused on developing Proteolysis Targeting Chimera (PROTAC), a new 'controlled proteolysis' technology that overcomes the limitations of the current inhibitor pharmacological paradigm. Based on an "event-driven" paradigm, PROTACs offer a novel, catalytic mechanism to irreversibly inhibit protein function, namely, the intracellular destruction of target proteins.

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

Sponsored by

ASINEX

6:30 Close of Day

TUESDAY, APRIL 25

7:30 am Continental Breakfast Breakout Discussions

PHENOTYPIC APPROACHES TOWARD DISCOVERY OF BLOOD-BRAIN PENETRANT INHIBITORS

8:30 Chairperson's Remarks

Matt Lucas, Ph.D., Director, Medicinal Chemistry, Yumanity Therapeutics

8:35 Yeast-Based Phenotypic Screening to Identify Brain Penetrant Inhibitors

Matt Lucas, Ph.D., 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.

9:05 A Human-Analog Platform for the Study of Drug Effects on the CNS and PNS across the Blood-Brain Barrier

James J. Hickman, Ph.D., Founding Director, NanoScience Technology Center and Professor, Nanoscience Technology, Chemistry, Biomolecular Science, Material Science and Electrical Engineering, University of Central Florida

In this system, the BBB consists of human stem cell-derived endothelial cells and astrocytes on opposing sides of a thin carbon-based membrane. The neuronal cultures represent the central nervous system with hippocampal neurons or the peripheral nervous system with motoneurons. The setup allows for the continuous monitoring of the trans-endothelial electrical resistance as well as the recording of neuronal activity in response to compounds or compound combinations.

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

10:30 Intact BBB vs. Disease-Altered BBB in ALS

Svitlana Garbuzova-Davis, Ph.D., D.Sc., Professor, Center of Excellence for Aging and Brain Repair, Department of Neurosurgery and Brain Repair, University of South Florida

My laboratory is focused on translational research examining the therapeutic effects of transplanting human umbilical cord blood in mouse models of ALS and Sanfilippo Syndrome. One current focus of mine is deciphering the mechanisms of the blood-CNS barrier damage in ALS and stroke and engendering barrier repair to restore neurovascular unit functionality in patients with these or other neurovascular diseases.

11:00 Therapeutic Targeting of Oxygen-Sensing Prolyl Hydroxylases Abrogates ATF4-Dependent Neuronal Death and Improves Outcomes after Brain Hemorrhage in Several Rodent Models

Rajiv R. Ratan, M.D., Ph.D., Director, Laboratory for Redox Biology and Neural Protection and Repair Burke Medical Research Institute; Professor, Neurology and Neuroscience, Brain and Mind Research Institute, Weill Cornell Medicine

Protection from oxidative death *in vitro* or from ICH *in vivo* by adaptaquin was associated with suppression of activity of the prodeath factor ATF4 rather than activation of an HIF-dependent prosurvival pathway. Together, these findings demonstrate that brain-specific inactivation of the HIF-PHD metalloenzymes with the blood-brain barrier-permeable inhibitor adaptaquin can improve functional outcomes after ICH in several rodent models.

11:30 Understanding the Biology of the Central Nervous System (CNS) Barriers under Homeostatic and Inflammatory Conditions

Jorge Iván Alvarez, Ph.D., Assistant Professor of Pathobiology, University of Pennsylvania

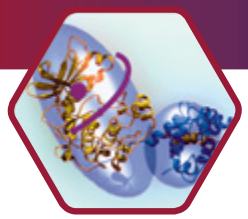
Research in the Alvarez lab is aiming to understand the biology of the Central Nervous System (CNS) barriers under homeostatic and inflammatory conditions. These barriers selectively restrict the molecular and cellular trafficking between the periphery and the CNS, but also serve as a signaling interface that actively regulates exchanges between both compartments. They are composed of the blood-brain barrier (BBB), the blood-meningeal barrier (BMB) and the blood-cerebrospinal fluid barrier (BCB).

12:00 pm Close of Conference

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

TRACK HOPPING

Attendees at Drug Discovery Chemistry are permitted to "track-hop" between concurrent programs. Though you register for a particular conference(s) or symposium, in reality you gain access to all concurrent conference tracks or symposia. For the best value, sign up for a Premium registration, and gain access to all eight conference tracks, both symposia, plus two short courses of your choice.



Eighth Annual

Kinase Inhibitor Chemistry

Emerging Approaches for the Discovery and Design of Kinase Inhibitors

TUESDAY, APRIL 25

12:30 pm Registration

TRENDS IN KINASE INHIBITOR DISCOVERY AND DEVELOPMENT

1:30 Chairperson's Remarks

Gerhard Mueller, Ph.D., Senior Vice President, Medicinal Chemistry, MercaChem BV

1:40 Diversity of Kinase Inhibition Modalities and Their Implications to the Hydrophobic Spine Topology

Gerhard Mueller, Ph.D., Senior Vice President, Medicinal Chemistry, MercaChem BV

A brief overview of the heterogeneity of inhibition modes will be given, followed by introducing the concept of the hydrophobic spine as a regulatory element in kinase activation. Distortion of the hydrophobic spine topology offers new opportunities to engineer selectivity, and to optimize binding kinetic attributes. The prospective engineering of binding kinetic signatures into inhibitors by applying "deep-pocket-directed" scaffolds is exemplified by a lead finding campaign that yielded novel, selective, and highly efficacious CDK-8 inhibitors.

2:10 Comparison of Methods for Determination of Drug-Target Engagement in Live Cells

Aleksandra Baranczak, Ph.D., Senior Scientist, Discovery Chemistry and Technology, AbbVie

While the list of potential techniques that enable studies of target engagement is continuously expanding, identification of the best method to evaluate interactions between a ligand and its cellular binding partner(s) remains far from straightforward. We will discuss the applicability of various methods for determining target engagement of reversible and irreversible inhibitors of soluble and membrane kinases in live cells. The strengths and limitations of all methods will be analyzed, as well as their adaptability to high-throughput format assay development.

2:40 Determination of a Focused Mini-Kinase Panel for Early Identification of Selective Kinase Inhibitors

Scott Bembenek, Ph.D., 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%.

Sponsored by CHEMICAL COMPUTING GROUP

3:10 MOEsaic: Exploring SAR through the application of Interactive Matched Molecular Pair Profiles

Alain Ajamian, MBA, Ph.D., Director, Business Development, Chemical Computing Group

With larger data sets and parallel development of different structural series, managing and analyzing structure activity/property relationship data in medicinal chemistry projects is becoming ever more challenging. Tools and methods for the efficient visualization, analysis and profiling of structures thus remain of deep interest. In this work, we will describe a new application, MOEsaic, which can be used to quickly interrogate SAR data through the application of interactive MMP analysis and R-group profiling.

Sponsored by CHIRAL TECHNOLOGIES INC DAICEL GROUP

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

4:30 Off-Target Effects of 31 FDA-Approved Small Molecule Kinase Inhibitors on AMP-Activated Protein Kinase

Qiang Shi, Ph.D., Principal Investigator, National Center for Toxicological Research (NCTR), FDA

The clinical use of many small molecule kinase inhibitors (KIs) is often limited by severe organ toxicities, particularly hepatotoxicity and cardiotoxicity. Off-target inhibition of AMP-activated protein kinase (AMPK) contributes to the pathogenesis of sunitinib-induced cardiotoxicity, while secondary activation of AMPK protects regorafenib-induced hepatocyte toxicity. We examined the effects of 31 FDA-approved small molecule kinase inhibitors on AMPK.

5:00 CASE STUDY: Discovery of a Potent and Selective Sphingosine Kinase 1 Inhibitor through the Molecular Combination of Chemotype Distinct Screening Hits

Mark E. Schnute, Ph.D., Medicine Design, Pfizer

Inhibition of S1P signaling has been proposed as a strategy for treatment of inflammatory diseases and cancer. Two different formats of an enzyme-based high-throughput screen yielded two attractive chemotypes capable of inhibiting S1P formation in cells. The molecular combination of these screening hits led to a compound with two orders of magnitude improved potency. Through the modification of tail region substituents, the specificity of inhibition for SphK1 and SphK2 could be modulated yielding SphK1 selective, potent SphK1/2 dual, or SphK2 preferential inhibitors.

5:30 Breakout Discussions

6:15 Close of Day

6:30 Dinner Short Courses*

*Separate registration required; please see page 3 for details.

WEDNESDAY, APRIL 26

8:00 am Plenary Breakfast Presentation *(Sponsorship Opportunity Available)*

8:30 PLENARY KEYNOTE PRESENTATION

Drug Discovery and Pan-Assay Interference Compounds (PAINS)

Jonathan B. Baell, Ph.D., Faculty of Pharmacy and Pharmaceutical Sciences, Monash University

I will discuss issues around the PAINS filter that we published in 2010 and since then has generated much discussion in the industry. The PAINS filter helped explain the difficulties with certain compounds that many hit-to-lead medicinal chemists around the world, principally in academia and small biotechs but to some extent in big pharma also, were encountering. However, because some known drugs contain PAINS, there is the fear that such filters may be too stringent.

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

ADVANCES IN COVALENT INHIBITOR DEVELOPMENT

10:30 Chairperson's Remarks

Stefan Laufer, Ph.D., Chairman, Pharmaceutical & Medicinal Chemistry, Pharmacy & Biochemistry, University of Tuebingen

10:45 Highly Selective JAK3-Inhibitors with a Covalent-Reversible Binding Mode Targeting a Nitrile Induced Arginine Pocket

Stefan Laufer, Ph.D., Chairman, Pharmaceutical & Medicinal Chemistry, Pharmacy & Biochemistry, University of Tuebingen

JAK3 functions are restricted to immune cells suggesting it as a primary target. However, the high degree of structural conservation makes isoform

selective targeting a challenging task. Here we present picomolar inhibitors with unprecedented selectivity for JAK3. Selectivity was achieved by concurrent covalent-reversible targeting of a JAK3-specific cysteine residue and a novel induced binding pocket yielding versatile tool compounds for the elucidation of JAK3 specific functions.

11:15 Design and Development of Novel Covalent Kinase Inhibitors

Michael Friedman, Ph.D., Principal Scientist, AbbVie

This presentation will detail AbbVie's approach for the design and development of novel covalent kinase inhibitors. Examples from recently developed inhibitors will be given.

11:45 3DM Protein Family Analysis System Applied to the Kinase Protein Family

Sponsored by bio-prodict

Henk-Jan Joosten, Ph.D., CEO, Bio-Prodict

Proteins fall in large protein-families and vast amounts of data are available for one protein family (e.g., sequences, literature, structural data, alignment data, SNP data, mutation data, binding data, etc.). 3DM, a protein-superfamily analysis platform, automatically collects all data and contains many state-of-the-art tools enabling complex analysis of super-family data.

12:00 pm FEATURED PRESENTATION: Tailoring Residence Time Utilizing Reversible Covalent Cysteine Targeting

Michael Bradshaw, Ph.D., Associate Director, Principia Biopharma

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

12:30 Luncheon Presentation: Modern Drug Research Informatics Applications to CNS, Infectious, Neglected, Rare, and Commercial Diseases

Sponsored by CDD VAULT

Whitney Smith, Ph.D., Director, Business Development, Collaborative Drug Discovery (CDD), Inc.

Collaborative innovation is uniquely able to realize the economics of well-integrated specialization required for chemical biology and drug discovery. Particularly in the neglected infectious disease areas lacking a profit motive, better collaborative tools are fundamentally important to catalyze faster progress. Layering unique collaborative capabilities upon requisite drug discovery database functionality unlocks and amplifies synergy between biologists and chemists. Researchers need to have tools that balance individual needs for robust, intuitive registration and bioactivity analyses while at the same time facilitating collaborations with secure data partitioning, communication, and group engagement.

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

Sponsored by SYGNATURE discovery

DESIGN AND DEVELOPMENT OF NOVEL ALLOSTERIC MODULATORS

2:15 Chairperson's Remarks

Ravi G. Kurumbail, Ph.D., Research Fellow and Structural Biology Laboratory Head, Pfizer

2:20 Allosteric Activators of AMP-Activated Protein Kinase for the Treatment of Diabetic Nephropathy

Ravi G. Kurumbail, Ph.D., Research Fellow and Structural Biology Laboratory Head, Pfizer

Starting from a high-throughput screening hit, we have developed a clinical candidate for diabetic nephropathy through optimization of physico-chemical properties and by computational methods. Furthermore, structural, biophysical and kinetic studies have provided additional insights into the molecular mode of action of our allosteric AMPK activators. I will describe the discovery of our clinical candidate along with *in vitro* and *in vivo* data that support its utility for renal diseases.

2:50 Dynamics-Based Allostery in Protein Kinases

Phillip Aoto, Ph.D., Research Scientist, Department of Pharmacology, University of California, San Diego

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

3:20 Germinal-Center Kinase-Like Kinase Co-Crystal Structure Reveals a Swapped Activation Loop and C-Terminal Extension

Laura Silvian, Ph.D., Principal Scientist and Head, Physical Biochemistry, Biogen

We describe here the crystal structure of an activation loop mutant of GLK kinase domain bound to an inhibitor. The structure reveals a weakly associated, activation loop swapped dimer with more than 20 amino acids of ordered density at the carboxy-terminus. This C-terminal PEST region binds intermolecularly to the hydrophobic groove of the N-terminal domain of a neighboring molecule. Although the GLK activation loop mutant crystallized demonstrates reduced kinase activity, its structure demonstrates all the hallmarks of an "active" kinase.

3:50 Refreshment Break

4:20 Structure-Based Design, Synthesis, and Dermal Application of Novel Tyrosine Kinase 2 (TYK2) Inhibitors

Takatoshi Yogo, Ph.D., Principal Scientist, Research, Immunology Unit, Takeda Pharmaceutical Company Limited

We present a discovery and optimization of 3-amino-1,5-dihydro-4H-pyrazolopyridin-4-one derivatives as a novel chemical series of TYK2 inhibitor. This chemical series was discovered through a unique design strategy, including a hypothesis that an initial lead compound bound to TYK2 with flipped binding mode, as well as structure-based design supported by X-ray crystal structures. Our preclinical candidate exhibited selectivity for IL-23 signaling inhibition against GM-CSF in human PBMC assay, demonstrating the unique cytokine selectivity and the potential of fewer JAK2 related adverse effects.

4:50 Designing Selective Kinase Inhibitors with Quantum Molecular Design

Shahar Keinan, Ph.D., CSO, R&D, Cloud Pharmaceuticals

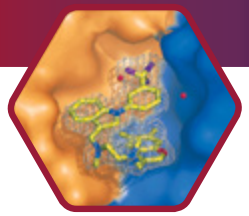
We report here using QM/MM calculation combined with artificial intelligence (AI) searches and cloud computing to design novel and selective JAK3 inhibitors. The measured activity of our designed molecules for JAK1, JAK2, JAK3 and Tyk2 correlates well with the calculations. Using the multi-object optimization tools in Quantum Molecular Design allows further hit-to-lead optimization, either for percutaneous absorption targeting allergic dermatitis or oral formulation targeting Rheumatoid arthritis.

5:20 Discovery and Pharmacological Characterization of Novel Quinazoline-Based PI3K Delta-Selective Inhibitors

Nicolas Soldermann, Ph.D., Senior Investigator and Group Leader, Global Discovery Chemistry, Novartis Institutes for BioMedical Research

Using a scaffold deconstruction–reconstruction strategy, we identified 4-aryl quinazolines that were optimized into potent PI3Kδ isoform selective analogues with good pharmacokinetic properties. With compound 11, we illustrate that biochemical PI3Kδ inhibition translates into modulation of isoform-dependent immune cell function (human, rat, and mouse). After oral administration of compound 11 to rats, proximal PD markers are inhibited, and dose-dependent efficacy in a mechanistic plaque forming cell assay could be demonstrated.

5:50 Close of Conference



Inaugural

Protein-Protein Interactions, Part 2

Targeting Protein-Protein Interactions of Epigenetic Readers and the Ubiquitin Proteasome System

TUESDAY, APRIL 25

12:30 pm Registration

NEXT-GENERATION BET BROMODOMAIN INHIBITORS

1:30 Chairperson's Remarks
Huawei (Ray) Chen, Ph.D., Principal Scientist II, Oncology iMed, AstraZeneca

1:40 Clinical Candidate AZD5153 Is a Novel Bivalent Inhibitor of BET Bromodomains
Huawei (Ray) Chen, Ph.D., Principal Scientist II, Oncology iMed, AstraZeneca
Here we describe the discovery and characterization of the bivalent BET probe biBET and AZD5153, an orally bioavailable clinical candidate. The avidity afforded through bivalent binding translates into increased cellular and antitumor activity in preclinical tumor models. Our work illustrates a novel concept in ligand design – simultaneous targeting of two separate domains with a drug-like small molecule – providing precedent for a potentially more effective paradigm for developing ligands for other multi-domain proteins.

2:10 Development of Dual-Activity Small Molecules that Target BRD4 and Dopamine Receptor D2
Jeffrey W. Strovel, Ph.D., President and CEO, ConverGene
Our compounds showed high activity in a binding test against BRD4, exhibited long half-lives and 100% bioavailability upon oral administration, profoundly suppressed MYC expression both *in vitro* and *in vivo*, and strongly inhibited growth of AML cells in a mouse xenograft model. Importantly, a lead candidate has been developed from a subclass of our BET inhibitors that showed additional activity against dopamine receptor D2 (DRD2). In addition to being a therapeutic target for psychiatric diseases, DRD2 is emerging as a therapeutic target for cancer/leukemia stem cells.

2:40 Selective BET-BD1 Inhibition Results in Strong Anti-Inflammatory Activity in Animal Models of Autoimmune Disease
Thomas Franch, Ph.D., CSO, Nuevolution AS
Inhibition of BET proteins is relevant for both oncology and inflammatory diseases. As most BET inhibitors reported in the literature are pan-BET inhibitors, the contribution of individual BDs to the biological activity of BET proteins is currently unclear, and domain-specific inhibition (intra- and/or inter-BET) remains largely unexplored. NUE7770 has high potency and pronounced selectivity towards the first BD (BD1) of the BET family. We will present the results of *in vivo* efficacy studies conducted with NUE7770 in several mouse models of inflammatory and autoimmune disease.

3:10 Sponsored Presentation *(Opportunity Available)*

Sponsored by
CHIRAL TECHNOLOGIES INC
DAICEL GROUP

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

4:30 Fragment-Based, Structure-Enabled Approach to the Discovery of Novel Inhibitors of the BET Family of Proteins: ABBV-075 and Others
Le Wang, Ph.D., Principal Research Scientist, Oncology Discovery, Chemistry, AbbVie, Inc.
Phenotypic cell-based screening assays combined with affinity chromatography and mass-spectrometry identified the BET family of bromodomains as a potential target for blocking proliferation in a variety of cancer cell lines. A 2-dimensional NMR fragment screen was conducted in order to search for novel scaffolds. Protein X-ray co-crystal structures of five NMR fragment screen hits were solved. This is a successful medicinal chemistry story starting from a weak NMR screen fragment to ABBV-075, our clinical candidate.

5:00 A Platform for Development of Combinatorial Inhibitory Chemotypes: A Potent Inhibitor of PI3K, BRD4 and CDK4/6 (SRX-3177) in One Small Molecule
Donald Durden, M.D., Professor, Department of Pediatrics, University of California, San Diego
A novel thienopyranone molecular scaffold has been discovered and modeled *in silico* to develop chemotypes which selectively inhibit PI3 kinase, the bromodomain protein BRD4 and CDK4/6. Molecular modeling studies and a robust PI-3K, CDK6 and BRD4 BD1 homology model 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.

5:30 Breakout Discussions

6:15 Close of Day

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

WEDNESDAY, APRIL 26

8:00 am Plenary Breakfast Presentation *(Sponsorship Opportunity Available)*

8:30 PLENARY KEYNOTE PRESENTATION
Drug Discovery and Pan-Assay Interference Compounds (PAINS)
Jonathan B. Baell, Ph.D., Faculty of Pharmacy and Pharmaceutical Sciences, Monash University
I will discuss issues around the PAINS filter that we published in 2010 and since then has generated much discussion in the industry. The PAINS filter helped explain the difficulties with certain compounds that many hit-to-lead medicinal chemists around the world, principally in academia and small biotechs but to some extent in big pharma also, were encountering. However, because some known drugs contain PAINS, there is the fear that such filters may be too stringent.

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

HISTONE METHYLTRANSFERASE COMPLEX INHIBITORS

10:30 Chairperson's Remarks
Masoud Vedadi, Ph.D., Principal Investigator, Molecular Biophysics, Structural Genomics Consortium; Assistant Professor, Department of Pharmacology and Toxicology, University of Toronto

10:45 Targeting WD40-Repeat Containing Proteins
Masoud Vedadi, Ph.D., Principal Investigator, Molecular Biophysics, Structural Genomics Consortium; Assistant Professor, Department of Pharmacology and Toxicology, University of Toronto
WD40-repeat containing proteins exist as part of various protein complexes. There are more than 340 predicted WD40-repeat containing proteins encoded in the human genome. Examples of such proteins are WDR5 and EED which are part of MLL1/SET1 family and PRC2 complexes, respectively. Disrupting the proper interaction of these subunits with catalytic domain of the protein often affect their activity and have been shown to be a reliable approach in discovery of potent, selective and cell active inhibitors for these complexes.

11:15 Fragment-Based Discovery of WDR5-MLL1 Disruptors

Shaun Stauffer, Ph.D., Research Assistant Professor, Pharmacology; Associate Director, Medicinal Chemistry, Vanderbilt University

Fragment-based screening methods coupled with X-ray crystallography offer the potential for rapid optimization of high-affinity ligands for target protein. We have utilized this approach to afford small molecule disruptors of the WDR5-MLL1 complex with subnanomolar affinity.

11:45 Sponsored Presentation *(Opportunity Available)*

12:00 pm FEATURED PRESENTATION: Targeting the PRC2 Complex through a Novel Protein-Protein Interaction Inhibitor of EED

Chaohong Sun, Ph.D., Senior Principal Research Scientist; Head, Fragment Based Drug Discovery, and Global Protein Sciences-Small Molecule, AbbVie

In this talk, we will present our discovery of A-395, a first-in-class antagonist of PRC2 protein-protein interactions (PPI). A-395 binds potently to EED, thereby allosterically inhibiting activity of PRC2 complex. It showed potent cellular activity and comparable *in vivo* activities to known EZH2 enzymatic inhibitors and furthermore, retained potent activity against cell lines resistant to the catalytic inhibitors, suggesting potential clinical benefits of this novel mechanism of targeting PRC2 complex.

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

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

Sponsored by SYGNATURE discovery

TARGETED PROTEIN DEGRADATION

2:15 Chairperson's Remarks

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

2:20 Targeted Protein Degradation by Small Molecules

Alessio Ciulli, Ph.D., Associate 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.

2:50 Targeting BET Protein Degradation for New Cancer Therapeutics

Shaomeng Wang, Ph.D., 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.

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

3:20 A New Paradigm in Drug Action: Differentiated Gain of Function among IMiD Structural Analogues Binding the E3 Ubiquitin Ligase, CRL4CRBN

Brian Cathers, Ph.D., Executive Director, Co-Leader & Head, Drug Discovery, Protein Homeostasis Thematic Center of Excellence, Celgene

Solution of the ligand-bound CRBN target complex provides a rationale for distinguishing "gain of function" targeting of key substrates, including the transcription factors aiolos (IKZ3) and ikaros (IKZ1) or the protein kinase CK1alpha. Is it possible to harness the action of a single E3 ligase and direct its actions toward new and different substrates? The presentation will explain distinctions among existing drugs, address guiding concepts applicable to determining new therapeutic applications, and point to the therapeutic power of harnessing protein homeostatic mechanisms.

3:50 Refreshment Break

4:20 De-Risking E3 Ligases with Novel Strategies and Technologies

Alexander Statsyuk, Ph.D., Assistant Professor, Department of Pharmacological and Pharmaceutical Sciences, University of Houston

E3 ligase enzyme mechanisms are still being uncovered, preventing the design of the mechanism-based inhibitors. Second, in contrast to protein kinases and methyl transferases, the assays to screen for inhibitors of E3s are complicated and require E1, E2, E3 enzymes, Ub, ATP and additional reagents to quantify a mixture of the reaction products. In this lecture, we will outline general approaches to design E3 ligase inhibitors. We will also outline our progress toward discovery and design of selective inhibitors of E3 ligases using the novel E3 ligase probe UbFluor that we have developed.

4:50 Discovery of Novel Spiro[3H-Indole-3,2'-Pyrrolidin]-2(1H)-One Compounds as Chemically Stable and Orally Active Inhibitors of the MDM2–p53 Interaction

Andreas Gollner, Ph.D., Laboratory Head, Medicinal Chemistry, Boehringer Ingelheim

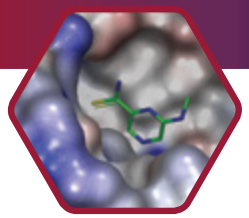
Scaffold modification based on Wang's pioneering MDM2–p53 inhibitors led to novel, chemically stable spiro-oxindole compounds bearing a spiro[3H-indole-3,2'-pyrrolidin]-2(1H)-one scaffold that are not prone to epimerization as observed for the initial spiro[3H-indole-3,3'-pyrrolidin]-2(1H)-one scaffold. Further structure-based optimization inspired by natural product architectures led to a complex fused ring system ideally suited to bind to the MDM2 protein and to interrupt its protein-protein interaction (PPI) with TP53.

5:20 Inhibition of an E2/E3 Protein-Protein Interaction as a Novel Strategy to Interfere with E3 Ligase Activity

Jara Brenke, Ph.D., Research Scientist, Assay Development and Screening Platform, HelmholtzZentrum München

This lecture will give insights into the discovery of a novel E2/E3 protein-protein interaction small molecule inhibitor that we were able to validate and characterize in a variety of biochemical as well as cell-based assays including primary mouse and human cells. More importantly, we can show that this first-in-class inhibitor is effective in preclinical autoimmune mouse models for psoriasis as well as rheumatoid arthritis.

5:50 Close of Conference



Twelfth Annual

Fragment-Based Drug Discovery

From Hits to Leads and Lessons Learned

TUESDAY, APRIL 25

12:30 pm Registration

FRAGMENTS TO LEADS AND CANDIDATES

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

1:40 LTA4H Case Study: Parallel Core and Substituent FBDD to Clinical Compounds
Matthew R. Netherton, Ph.D., Senior Principal Scientist, Small Molecule Discovery Research, Medicinal Chemistry, Boehringer Ingelheim Pharmaceuticals, Inc.
Factors enabling the rapid discovery of the clinical Leukotriene A4 Hydrolase inhibitor BI 691751 will be discussed. These include rapid screening in orthogonal assays and enablement of high-throughput crystallography for hit generation, as well as independent, parallel optimization of both fragment core and pendant groups.

2:10 Advancing a Clinical Candidate Targeting IRAK4 from a Fragment Lead
Seungil Han, Ph.D., Associate Research Fellow, Structural Biology & Biophysics, WorldWide Research & Development, Pfizer, Inc.
Small molecule inhibitors of interleukin-1 receptor-associated kinase 4 (IRAK4) are being developed for the treatment of SLE and RA. An integrated approach that included structural, biochemical, computational and medicinal chemistry disciplines has enabled us to develop a first-in-class, highly ligand efficient and kinome-selective IRAK4 clinical compound starting from a weak fragment.

2:40 Targeting Inducible Nitric Oxide Synthase (iNOS)
Fredrik Edfeldt, Ph.D., Associate Principal Scientist, Biophysics, Discovery Sciences, AstraZeneca R&D, Sweden
In this case study we describe the discovery of two novel series of iNOS inhibitors. Initial NMR screening yielded a set of fairly potent starting points. We established a soakable crystal system that allowed us to determine X-ray structures with 10 fragment hits. In subsequent chemistry efforts we made rapid progress: for the two series only six key crystal structures were determined and only ~50 compounds synthesized in order to reach low nanomolar cell potency.

3:10 Presentation to be Announced

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forteBIO
A Division of Pall Life Sciences

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DAICEL GROUP

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

FBDD FOR BROMODOMAIN EPIGENETIC TARGETS

4:30 Fragment-Based, Structure-Enabled Approach to the Discovery of Novel Inhibitors of the BET Family of Proteins: ABBV-075 and Others
Le Wang, Ph.D., Principal Research Scientist, Oncology Discovery, Chemistry, AbbVie
Phenotypic cell-based screening assays combined with affinity chromatography and mass-spectrometry identified the BET family of bromodomains as a potential target for blocking proliferation in a variety of cancer cell lines. A 2-dimensional NMR fragment screen was conducted in order to search for novel scaffolds. Protein X-ray co-crystal structures of five NMR fragment screen hits were solved. This is a successful medicinal chemistry story starting from a weak NMR screen fragment to ABBV-075, our clinical candidate.

5:00 A Platform for Development of Combinatorial Inhibitory Chemotypes: A Potent Inhibitor of PI3K, BRD4 and CDK4/6 (SRX-3177) in One Small Molecule
Donald Durden, M.D., Professor, Department of Pediatrics, UCSD
A novel thienopyranone molecular scaffold has been discovered and modeled *in silico* to develop chemotypes which selectively inhibit PI3 kinase, the bromodomain protein BRD4 and CDK4/6. Molecular modeling studies and a robust PI-3K, CDK6 and BRD4 BD1 homology model 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.

5:30 Breakout Discussions

6:15 Close of Day

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

WEDNESDAY, APRIL 26

8:00 am Plenary Breakfast Presentation *(Sponsorship Opportunity Available)*

8:30 PLENARY KEYNOTE PRESENTATION
Drug Discovery and Pan-Assay Interference Compounds (PAINS)
Jonathan B. Baell, Ph.D., Faculty of Pharmacy and Pharmaceutical Sciences, Monash University
I will discuss issues around the PAINS filter that we published in 2010 and since then has generated much discussion in the industry. The PAINS filter helped explain the difficulties with certain compounds that many hit-to-lead medicinal chemists around the world, principally in academia and small biotechs but to some extent in big pharma also, were encountering. However, because some known drugs contain PAINS, there is the fear that such filters may be too stringent.

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

> "Attending this conference has inspired me to inspire others – thank you, CHI!"
>
> *- Bob H., Professor of Chemistry, St. Olaf College*

BEST PRACTICES FOR FRAGMENT-BASED DRUG DESIGN (FBDD)

10:30 Chairperson's Remarks
Mary Harner, Ph.D., Research Investigator II, Leads Discovery & Optimization, Bristol-Myers Squibb

10:45 FBDD: Part of an Integrated Drug Discovery Platform
Derek Cole, Ph.D., Director, Medicinal Chemistry, Takeda

11:15 Fragment-Based Screening Using X-ray Crystallography: Challenges and Practical Considerations
Dominic Tisi, Ph.D., Associate Director, Molecular Science, Astex
This presentation will focus on the key challenges associated with successful prosecution of a fragment screen. I will discuss the practical hurdles associated with protein characterisation and crystallographic fragment screening and how biophysical methods can be synergistically employed during a screen. Case studies will be given which highlight the challenges and rewards of using crystallography as a primary screening method for fragment based lead generation.

11:45 Sponsored Presentation *(Opportunity Available)*

12:00 pm Discovering Drug Seeds by Practical NMR Strategies
Steven LaPlante, Ph.D., Professor, Innovative Drug Discovery, University of Quebec
This presentation will describe the critical role NMR is playing for discovering the seeds for new drugs. Central to these efforts is the creation of a new curated fragment library, the development of consensus NMR screening methods, the design of new NMR software, and the application of follow-up NMR experiments. As a result, quality hits are prioritized which significantly benefits medicinal chemistry efforts.

Sponsored by
ZoBio

12:30 Luncheon Presentation to be Announced

Sponsored by
SYGNATURE discovery

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

CHEMICAL SPACE

2:15 Chairperson's Remarks
Seth Cohen, Ph.D., Professor, Department of Chemistry and Biochemistry, University of California, San Diego

2:20 Important Aspects of Fragment Screening Collection Design
Ashley Adams, Ph.D., Senior Scientist, Discovery Chemistry and Technology, AbbVie, Inc.
Recently, AbbVie embarked on an initiative to completely revamp our fragment screening collection. Our initial fragment deck predated Ro3 dogma with little attention paid to the physicochemical properties of the collection and thus contained a significant number of intractable starting points for fragment optimization campaigns. This presentation highlights the important design criteria and analyses that formed the basis of this important exercise.

2:50 Natural Products: Promising Starting Points for Fragment-Based Screening
Tim Schuhmann, Ph.D., Investigator III, Natural Products Unit, Novartis Pharma AG
We generated a library of natural-product inspired fragments largely by chemical degradation of complex natural products. As shown by computational analysis, the resulting set is nicely complementing classical fragment screening sets by adding spherical motives and shows promising biological activities in the screens performed so far. In the talk, our strategy, the generation and implementation of the set as well as preliminary biological data and follow-up approaches will be presented.

3:20 Retrospective Analysis of Validated Fragment Hits Bound to Their Targets
Fabrizio Giordanetto, Ph.D., Head, Medicinal Chemistry, D. E. Shaw Research LLC
This is a first of its kind retrospective analysis of a large set of validated fragment hits bound to their corresponding targets to reveal preferred molecular properties, topologies and interacting motifs at a fragment level across a large variety of protein targets. It will inspire expert medicinal and computational chemists, as well as provide an important fragment evaluation primer to non-experts.

3:50 Refreshment Break

NEW TARGETS AND NEW APPROACHES

4:20 FEATURED PRESENTATION: Probing GPCR and Bacterial Targets with Fragment Based Discovery
Rod Hubbard, Ph.D., Professor, University of York and Senior Fellow, Vernalis Research
I will summarize two current research projects: (1) Screening of the molecular machine that is the bacterial replisome, identifying fragments that disrupt DNA replication and beginning to identify which targets/interfaces are effected; (2) In collaboration with groups in Zurich and Melbourne, NMR fragment screening of stabilized GPCRs by Vernalis with some cellular activity readouts. These projects illustrate the power of fragments in chemical biology – using chemical tools to explore biological systems.

4:50 FBDD for Metalloenzyme Inhibition – A Bioinorganic Perspective
Seth Cohen, Ph.D., Professor, Department of Chemistry and Biochemistry, University of California, San Diego
This presentation will discuss a bioinorganic approach to fragment-based drug discovery (FBDD) that will focus on the use of this method for developing metalloenzyme inhibitors. FBDD is found to be a very effective and advantageous strategy for drugging metalloenzymes and this presentation will highlight some case studies spanning anti-cancer, viral, and bacterial targets. Some fundamental studies, including structural investigation of fragments and studies to address the selectivity of metalloenzyme inhibitors, will be discussed.

5:20 Fragment Docking Identifies Inhibitors for Jumonji Histone Demethylases 4 Subfamily
Magdalena Korczynska, Ph.D., Associate Specialist, Brian Shoichet Lab, Department of Pharmaceutical Chemistry, University of California San Francisco
Using crystal structures of the KDM4 subfamily we have performed virtual screening of a purchasable *in silico* fragment library. This screen identified 7 inhibitors with IC50 values between 18μM and 176μM (ligand efficiencies of >0.3). Molecules containing the 5-aminosalicylate core were selected as candidates for further optimization. After several rounds of iterative target-specific compound docking, hybrid molecule design, compound synthesis, *in vitro* characterization, and crystallization, we have developed a 43nM inhibitor of KDM4C.

5:50 Close of Conference

Fifth Annual

Macrocyclics & Constrained Peptides

Bigger, Better and Still Oral Small Molecules

TUESDAY, APRIL 25

12:30 pm Registration

DESIGNING FOR CELL-PERMEABILITY AND OTHER Ro5 FEATURES

1:30 Chairperson's Remarks
Jan Kihlberg, Ph.D., Professor, Organic Chemistry, Uppsala University

1:40 FEATURED PRESENTATION: Macrocyclic Secondary Structure: Permeability and Chemical Biology
Spiros Liras, Ph.D., Director, Cardiovascular Metabolic Department, Pfizer

Emerging themes regarding permeability of macrocycles displayed in defined secondary structures will be discussed, specifically for alpha helices. In addition, the impact of macrocycles secondary structure on pharmacology in the context of the GLP-1 receptor will be discussed.

2:10 Decoding Rules of Passive Membrane Permeability in Cyclic Peptides: Lessons from Natural Products and Beyond
Scott Lokey, Ph.D., Professor, Chemistry and Biochemistry, University of California, Santa Cruz

The best known cyclic peptide with drug-like membrane permeability is cyclosporine A, but a survey of natural products suggests that there may be many others. These compounds offer a treasure trove of structural motifs that can be mimicked in non-natural cyclic peptides to bias them toward passive membrane permeability. I will present our efforts to capitalize on our understanding of the factors that govern passive permeability in cyclic peptides inspired by natural products.

2:40 Permeability of Semi-Peptidic Macrocycles
Eric Marsault, Ph.D., Professor, Medicinal Chemistry and Pharmacology, University of Sherbrooke

Macrocycles have recently attracted a high level of interest for their unique potential ability to combine large surface areas and suitable druglike properties. While macrocyclic peptides have been thoroughly analyzed to define permeability rules, there is no systematic study on semi-peptidic macrocycles, which constitute a rapidly increasing subclass among clinical candidates. We will discuss recent data on the structure-permeability relationship of macrocycles composed of a tripeptide tethered with a nonpeptidic linker.

3:10 Conformational Sampling of Macrocycles: Recent Progress
Sponsored by OpenEye Scientific
Paul Hawkins, Ph.D., Head, Scientific Solutions, OpenEye Scientific Software

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

3:40 Refreshment Break in the Exhibit Hall with Poster Viewing
Sponsored by CHIRAL TECHNOLOGIES INC DAICEL GROUP

4:30 Selected Poster Presentation(s)
One to three poster presenters whose work fits themes of the meeting and either represents topics that need more coverage on our agenda or represents work of significant potential impact will be chosen to give short summaries of their posters.

4:45 PANEL DISCUSSION: Reaching Consensus on New Chemical Rules for Macrocycles
Sponsored by ASINEX
Moderator: Mark Parisi, MS, Executive Director, Chemistry, Asinex
Panelists: Adrian Whitty, Ph.D., Professor, Biochemistry, Boston University
Contest Winner - this could be YOU!

There has been much discussion, speculation, and general commentary on New Rules for Macrocycles and an academic-industrial group (Asinex-Boston University-Pharma) has come together to explicitly address this topic. This panel will gather input from the macrocyclic community with the goal of arriving at a definitive new set of rules for macrocycles submitted for publication for the benefit of researchers in the Macrocyclic Drug Discovery community. Given the focus on group involvement, we are inviting attendees to submit their ideas as we will choose one applicant to be on the panel; please access information on how to enter the panelist competition via the following link : DrugDiscoveryChemistry.com/Asinex-Panel

5:30 Breakout Discussions

6:15 Close of Day

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

WEDNESDAY, APRIL 26

8:00 Plenary Breakfast Presentation *(Sponsorship Opportunity Available)*

8:30 PLENARY KEYNOTE PRESENTATION
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9:30 Coffee Break in the Exhibit Hall with Poster Viewing

STRATEGIES FOR CONSTRAINING PEPTIDES

10:30 Chairperson's Remarks
Scott Lokey, Ph.D., Professor, Chemistry and Biochemistry, University of California, Santa Cruz

10:45 Cyclic Peptides as Specific Immunomodulators
Dehau Pei, Ph.D., Professor, Department of Chemistry and Biochemistry, The Ohio State University

I will present our work on developing cyclic peptide inhibitors against the interactions between calcineurin-NFAT, NEMO-IKK, and/or TNFa-TNFR.

11:15 Tether-Functionalized Stapled Peptides for the Estrogen Receptor/Coactivator Interaction

Terry Moore, Ph.D., Assistant Professor, Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago

Stapled peptides are often designed so that the staple replaces two non-interacting residues, although there are now several examples where the staple can replace interacting, hydrophobic residues. We have developed novel stapling amino acids that can mimic hydrophobic amino acids, and we have incorporated these into sequences derived from steroid receptor coactivator. These peptides inhibit the interaction of coactivator with both wild-type and recently described somatic mutant estrogen receptors.

11:45 Sponsored Presentation *(Opportunity Available)*

12:00 pm Development of Drug-Like Cotransins: Structure-Activity and Structure-Pharmacokinetic Studies of Cyclic Depsipeptide Modulators of Sec61

Phillip Patrick Sharp, Ph.D., Postdoctoral Scholar, Laboratory of Jack Taunton, Cellular and Molecular Pharmacology, University of California, San Francisco

Cotransins, cyclic heptadepsipeptide allosteric modulators of Sec61, are potentially powerful compounds for targeting canonically 'undruggable' therapeutic targets. However, developing cotransins that have high substrate selectivity and good pharmacokinetic profiles is challenging. This presentation will disclose novel synthetic modifications of cotransin structure that augment both their substrate selectivity and pharmacokinetics.

12:30 Luncheon Presentation to be Announced

Sponsored by SCHRÖDINGER

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

Sponsored by SYGNATURE discovery

COMPOUNDS WITH THERAPEUTIC PROMISE

2:15 Chairperson's Remarks

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

2:20 Discovery & Development of PTG-100, an Oral Peptide Antagonist of α4β7 Integrin, for the Treatment of Inflammatory Bowel Disease

Ashok Bhandari, Ph.D., Vice President, Chemistry, Protagonist Therapeutics

We discuss the discovery of PTG-100, a potential first-in-class oral peptide antagonist of α4β7 integrin in clinical trials for the treatment of patients with ulcerative colitis and Crohn's disease. PTG-100 alters trafficking of gut homing T cells in animal models of colitis and was discovered by our oral peptide technology platform. Target engagement was assessed in the peripheral blood of colitis and healthy mice, and translated to the demonstration of pharmacodynamic proof-of-concept in a Phase I trial with normal healthy volunteers.

2:50 Discovery of Potent Cyclophilin Inhibitors Based on Structural Simplification of Sanglifehrin A

Vicky Steadman, Ph.D., Director of Drug Discovery, Discovery, Cypralis

Sanglifehrin, a complex macrocyclic natural product (MW>1000, 17 chiral centers), is a potent inhibitor of cyclophilins, a target for HCV. Through a structure guided medicinal chemistry approach, potent, simplified and drug like macrocyclic inhibitors of cyclophilin were identified (MW~500 and 4 chiral centers). The design, synthesis and biological activity of these partially peptidic macrocycles will be discussed.

3:20 Novel Cyclic Antibiotic Drug Leads Inferred from a Bacterial Toxin

Brice Felden, Ph.D., Research Head, Rennes University, Inserm

Staphylococcus aureus is a commensal bacterium and pathogen that causes community-acquired, healthcare-related, and nosocomial infections in humans. We previously discovered a linear peptide toxin that induces deaths to competing bacteria (both Gram-positive and negative), but also to host human cells. We present our work around synthesizing a series of 20 compounds; our most promising derivatives are small cyclic pseudopeptides with inconsequential toxicity to human cells and mice, enhanced stability in human sera, and sharp antibacterial activity on infected mice.

3:50 Refreshment Break

4:20 Side Chain Cyclized Aromatic Amino Acids: Great Tools as Local Constraints in Opioid Peptide and Peptidomimetic Design

Steven Ballet, Ph.D., Associate Professor, Departments of Chemistry and Bio-Engineering Sciences, Vrije Universiteit Brussel

Constraining the conformation of flexible peptides is a proven strategy to increase potency, selectivity, and metabolic stability. In this presentation, we focus on cyclic aromatic amino acids in which the side chain is connected to the peptide backbone to provide control of x1- and x2-space (as opposed to the usual focus of constraining the backbone dihedral angles). The manifold applications for cyclized analogues of the aromatic amino acids within peptide medicinal chemistry are showcased with examples of enzyme inhibitors and ligands for G protein-coupled receptors.

4:50 Design of Technology-Compatible Cyclic Peptide Scaffolds with Oral Bioavailability

Lauren Monovich, Ph.D., Senior Investigator, Global Discovery Chemistry, Novartis

Traditionally, permeable macrocyclic peptides have been identified by discrete synthesis and careful side chain variation of privileged, natural product scaffolds. More recently, the basic principles governing passive permeability were applied to the prospective design of macrocyclic peptide scaffolds with oral bioavailability. However, there remains the broad challenge of chemical diversity sufficient to enable regular identification of novel protein ligands. Herein, we present macrocyclic peptide scaffolds with ribosomal library-compatible amino acids and experimentally validated oral bioavailability.

5:20 Novel Routes for the Synthesis of Medium and Large Fused Ring Systems as Chemical Navigators for Phenotypic Screening

Taleb Al Tel, Ph.D., Director, Sharjah Institute for Medical Research, University of Sharjah, UAE

I will be describing our efforts directed towards designing unprecedented and diverse macrocyclic compounds collections (medium and large sized ring systems) possessing privileged architectures that represent the basic core of many biologically significant compounds. Furthermore, anticancer and antimalarial activities of these compounds will also be presented.

5:50 Close of Conference

> "Well organized meeting with a good selection of speakers across targets and industry."
>
> *- Vijay P., Research Investigator, Aurigene Discovery Technologies*

Small Molecules for Cancer Immunotherapy

Discovery and Development of Immune-Modulatory Small Molecules

THURSDAY, APRIL 27

7:25 am Registration and Morning Coffee

PD-1/PD-L1 SMALL MOLECULE INHIBITORS

7:55 Chairperson's Opening Remarks
Rogier C. Buijsman, Ph.D., Head, Chemistry, Netherlands Translational Research Center B.V. (NTRC)

8:00 FEATURED PRESENTATION: Small Molecule Antagonists Targeting PD-1/PD-L1 and Other Immune Checkpoint Pathways
Murali Ramachandra, Ph.D., CSO, Aurigene Discovery Technologies Limited
We are therefore 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.

8:30 A Novel Small Molecule to Target PD-1/PD-4 and MUC 16 and MUC 4 in Cancer Immunotherapy
Krishna Menon, Ph.D., Scientific Advisor, Research & Development, AR Biosystems
AR Biosystems has developed NCEs to treat cancer and other related conditions affecting PD-1, PD-4, MUC 4 and MUC 16.

9:00 Coffee Break

IDO AND TDO INHIBITORS

9:30 FEATURED PRESENTATION: Inventing INCB24360 (epacadostat), an Indoleamine-2,3-Dioxygenase-1 (IDO1) Inhibitor for Immuno-Oncology
Andrew P. Combs, Ph.D., Vice President, Medicinal Chemistry, Incyte Corporation

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10:00 Selective Small Molecule Inhibitors of IDO1 and TDO for Cancer Immunotherapy
Rogier C. Buijsman, Ph.D., Head, Chemistry, Netherlands Translational Research Center B.V. (NTRC)
To enable high-throughput, low-volume miniaturized screening, we developed the NFK GreenScreen™ assay technology, which enables the quantitative determination of small molecule compound activity against either IDO1 or TDO by measuring the conversion of tryptophan into N-formyl kynurenine. During this presentation, I will provide an update of our IDO1/TDO lead optimization project and a side-by-side comparison with clinical and preclinical reference inhibitors.

10:30 Discovery of Novel Selective IDO1 Inhibitors
Lijun Sun, Ph.D., Associate Professor, Center for Drug Discovery, Beth Israel Deaconess Medical Center, Harvard Medical School
We conducted *in silico* screening of a unique conformer library composed of 20 million entries. Using the IDO1 and TDO2 enzymatic assays, we identified 2 novel scaffolds IDO1 inhibitors. We will discuss the *in silico* process, the *in vitro* activity and ADME characterizations, and the optimizations of the inhibitors.

11:00 Sponsored Presentation *(Opportunity Available)*

11:15 Enjoy Lunch on Your Own

TARGETING THE STING PATHWAY, A2A RECEPTORS AND TREGS

1:00 pm Chairperson's Remarks
R.P. (Kris) Iyer, Ph.D., Co-Founder & CSO, Spring Bank Pharmaceuticals

1:05 Development of SB 11285, a Highly Potent STING Agonist for Application in Immune-Oncology
R.P. (Kris) Iyer, Ph.D., Co-Founder & CSO, Spring Bank Pharmaceuticals
STING is an intracellular adapter protein that activates IFN and NF-KB pathways to induce potent innate and adaptive response against cancer. We have discovered the cyclic dinucleotide SB 11285 as a highly potent STING agonist for immuno-oncology applications for a variety of cancers. This talk will focus on the key aspects of development of this next-generation anticancer agent.

1:35 A2A Receptor Agonists
Michail Sitkovsky, Ph.D., Professor, Eleanor W. Black Chair and Director of New England Inflammation and Tissue Protection Institute, Northeastern University
During this presentation, I will provide the instructive overview of our discovery of cAMP elevating A2a adenosine receptor, a new paradigm in toxicology studies, and discuss why A2b is not as important as A2a receptor.

2:05 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.

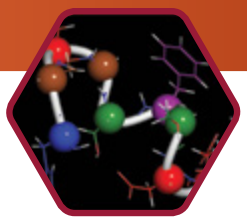
3:05 Refreshment Break

3:35 Small Molecules as Frontline Therapy for Immune Oncology: Experience from Ubiquitin Pathway Targets
Tauseef Butt, Ph.D., President and CEO, Progenra, Inc.
This presentation will describe de-ubiquitylase USP7 and ubiquitin ligases that promote tumor evasion by immune system. We will show data that certain tumor cells are dependent on these targets for growth and metastasis. Small molecules inhibitors that target ubiquitin pathway enzymes have dual effects, unleashing anti-tumor immune response as well as direct anti-tumor activity. We believe that small molecules that have dual properties can replace biologicals as frontline therapy for cancer.

4:05 Inhibition of Kinase-Mediated Signaling in Myeloid Cells Suppresses Peritumoral Immune Suppression in Pancreas Cancer
Michael Burnet, Ph.D., Managing Director, Oncology Discovery, Synovo GmbH
We have identified small molecule kinase inhibitors that act on myeloid cells infiltrating tumors. These compounds promote the tumor-specific local secretion of interferon gamma leading to activation of CD8+ and NK cells. Tumor specificity appears to be due to a reliance on tumor co-signalling for target pathways to be expressed. The agents have safety margins in the range of 15-30x and are effective in very low doses in mice in the order of 3 to 5 mg/kg/day. The compounds synergize both cytotoxic agents and checkpoint antibodies.

4:35 Targeting HDAC3 for Cancer Immunotherapy and Combinations
Edward Holson, Ph.D., CSO, KDAc Therapeutics

5:05 Close of Symposium



Biophysical Approaches for Drug Discovery

Advances and New Applications in SPR, NMR, cryoEM and More

THURSDAY, APRIL 27

7:25 am Registration and Morning Coffee

INTEGRATING BIOPHYSICAL APPROACHES

7:55 Chairperson's Opening Remarks
Derek Cole, Ph.D., Director, Medicinal Chemistry, Takeda

8:00 FEATURED PRESENTATION: Combining Biophysical Techniques for Difficult Targets: Case Vignettes
Kevin Lumb, Ph.D., Scientific Director, Discovery Sciences, Janssen R&D

8:30 Applications of the Thermal Shift Assay: More than Melts the Eye
Mary Harner, Ph.D., Research Investigator II, Leads Discovery & Optimization, Bristol-Myers Squibb
The thermal shift assay (TSA) is a commonly employed biophysical method for characterization of molecular properties and molecular interactions. However, TSA has taken a back seat to novel and rising biophysical technologies that are deemed more information-rich than a simple protein melting curve. This talk will highlight applications of TSA including fragment screening, SAR support orthogonal to biochemical assay formats, X-ray crystallography surrogate identification, binding selectivity panels, binding mechanism, target destabilization, and metal contamination studies.

9:00 Coffee Break

9:30 Kinetic and Thermodynamic Profiling in Drug Discovery: Are We There Yet?
Ying Wang, Ph.D., Principal Research Scientist, Department of Chemistry and Technology, AbbVie
Extensive kinetic and thermodynamic data were collected and analyzed via SPR and ITC throughout the hit to tool/lead and high throughput screening campaigns for the identification of allosteric inhibitor of the PRC2 complex through EED binding. Correlations with biochemical data and structural information will be presented as well as our perspectives on where we are at on harnessing the power of thermodynamic and kinetic profiling in drug discovery.

10:00 Combining X-Ray Crystallography, SPR and ITC to Understand the Structure-Binding Kinetic Relationships of a Type I CDK Inhibitor
Pelin Ayaz, Ph.D., Postdoctoral Researcher, Chemistry, Biology, and Drug Discovery, D.E. Shaw Research
Roniciclib is a type I pan-CDK (cyclin dependent kinase) inhibitor that displays prolonged residence times on CDK2 and CDK9, whereas residence times on other CDKs are transient, thus giving rise to a kinetic selectivity of Roniciclib. This work is one of the few known examples of an SKR (structure – binding kinetics relationships) study in a pharma development pipeline.

10:30 Affinity Selection Mass Spectrometry for Target Validation and Hit Triage
Jeff Messer, Director, NCE Molecular Discovery, GSK
Biophysics in Hit ID is deployed to screen and/or qualify hits from biochemical screens. GSK's Encoded Library Technology selects small molecule binders from large combinatorial mixtures (>1E9) then deconvolutes structure by DNA barcode. We will share semi-quantitative methods that we have developed to qualify primary hits from combinatorial mixture or crude compound re-prep that uses DNA or mass encoding respectively.

11:00 Sponsored Presentation *(Opportunity Available)*

11:15 Enjoy Lunch on Your Own

SPECIFIC BIOPHYSICAL TECHNIQUES

1:00 pm Chairperson's Remarks
Samantha J. Allen, Ph. D., Senior Scientist, Lead Discovery-Screening, Janssen Research & Development

1:05 NMR Molecular Replacement, NMR2
Julien Orts, Ph.D., Assistant Professor, Physical Chemistry, ETH Zurich
Here, we present NMR2, a MR-like approach in NMR to determine the structures of the binding pockets of ligands at atomic resolution. The NMR2 method uses a high throughput structure calculation protocol, rather than a docking- scoring simulation. It is fast and is a completely new method. It extends the very successful Molecular Replacement method from X-ray crystallography to the NMR field.

1:35 Interpreting Fragment-Target X-Ray Crystals
Anthony Bradley, Ph.D., Postdoctoral Researcher, Structural Genomics Consortium, University of Oxford
X-Chem is a union of high-throughput X-Ray screening, analysis tools and chemistry to enable rapid fragment-based chemical probe development. Making use of bespoke tools, we are able to develop and analyse 1,000s of datasets in a semi-automated manner and determine the binding modes of weakly bound fragments. From this, in-house analysis tools aid chemists to make informed decisions regarding which compounds to design next.

2:05 Cryo-EM as a Tool for Discovery and Development of Viral Vaccines
Erin Tran, Ph.D., Staff Scientist, Laboratory of Cell Biology, Biophysics Section, National Cancer Institute, Center for Cancer Research, National Institutes of Health

3:05 Refreshment Break

BIOPHYSICAL APPROACHES FOR MEMBRANE PROTEINS

3:35 Fragments and SPR for GPCRs
Shuo Wang, Ph.D., Principal Scientist, Biophysical Chemistry, Takeda California
As a label free, real-time and high throughput methodology, SPR is one of the most powerful biophysical approaches for fragment library screening. An advanced application is fragment screening using SPR on membrane protein targets, such as GPCRs. This talk focuses on the technical aspects of fragment screening by SPR on solubilized wild type receptors.

4:05 A Bio-Electronic Sensor for Cell-Free, Label-Free Study of GPCR-Ligand Interactions on Native Cell Membranes
Jaime Arenas, Ph.D., Director, Assay Development, Sensor Technology, Nanotech Biomachines, Inc.
The ability to characterize the kinetic binding of drug candidates to native GPCR and other integral membrane protein targets is a critical unmet need in the lead generation process for these targets. I will discuss capabilities of our graphene-based electronic sensor for cell-free and label-free measurement of kinetic binding to integral membrane protein targets in their native conformation in grafted cell membranes.

4:35 M2 Proton Channel of Influenza Studied by NMR Spectroscopy
Yibing Wu, Ph.D., Specialist, Department of Pharmaceutical Chemistry, University of California, San Francisco
The M2 protein is a highly proton selective channel that is essential for the virus life cycle. We used solution NMR to investigate the channel opening/closing and drug inhibition mechanisms. This structure is the first high-resolution M2 mutant structure and will aid our structure-guided drug development efforts.

5:05 Close of Symposium

Hotel & Travel Information

CONFERENCE HOTEL:

Sheraton San Diego Hotel & Marina
1380 Harbor Island Drive
San Diego, CA 92101
Phone: 619-291-2900

Discounted Room Rate: $215 s/d
Discounted Cut-off Date: March 28, 2017

RESERVATIONS AND ADDITIONAL TRAVEL INFORMATION:

Go to the travel page of **DrugDiscoveryChemistry.com**

San Diego Highlights:

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

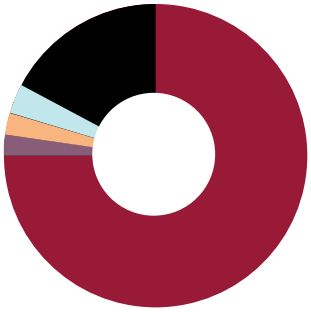
PRESENT A POSTER AND SAVE $50!

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 **March 10, 2017**. There will be dedicated poster sessions for Conference and Symposia programs. See website for details.

Reasons you should present your research poster at this conference:

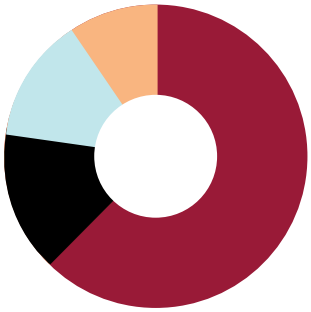
- Your poster will be seen by our international delegation, representing leaders from top pharmaceutical, biotech, academic and government institutions
- Receive $50 off your registration
- Your poster will be automatically entered into the main conference poster competition
- Your poster abstract will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

2016 Attendee Demographics



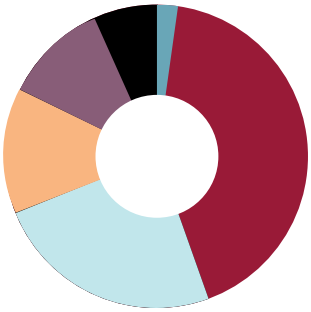
Company Type

Commercial (Biotech + Pharma)	75%
Academic + Government	18%
Financial + Services	3%
Other	2%
Healthcare	2%



Geographic Location

USA	66%
West Coast	47%
East Coast	36%
Midwest	17%
Europe	17%
Asia	11%
Rest of World	6%



Delegate Title

Scientist/Technologist	42%
Executive + Director	30%
Sales & Marketing	11%
Professor	9%
Manager	6%
Other	2%

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PODIUM PRESENTATIONS – WITHIN THE MAIN AGENDA!

Showcase your solutions to a guaranteed, targeted audience through a 15- or 30-minute presentation during a specific conference program, breakfast, or lunch. Package includes exhibit space, on-site branding, and access to cooperative marketing efforts by CHI. For the luncheon option, lunches are delivered to attendees who are already seated in the main session room. Presentations will sell out quickly, so sign on early to secure your talk!

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

INVITATION-ONLY VIP DINNER/HOSPITALITY SUITE

Sponsors will select their top prospects from the conference pre-registration list for an evening of networking at the hotel or at a choice local venue. CHI will extend invitations and deliver prospects, helping you to make the most out of this invaluable opportunity. Evening will be customized according to sponsor's objectives. (i.e.: Purely social, Focus group, Reception style, Plated dinner with specific conversation focus)

Additional branding & promotional opportunities include:

- Conference Tote Bags
- Literature Distribution (Tote Bag Insert or Chair Drop)
- ~~Badge Lanyards~~ - SOLD!
- Padfolios
- ~~Poster Awards~~ - SOLD!
- Program Guide Advertisement

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Exhibitors will enjoy facilitated networking opportunities with 700+ qualified delegates, making it the perfect platform to launch a new product, collect feedback, and generate new leads. Exhibit space sells out quickly, so reserve yours today!

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

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For additional information, please contact:

Carolyn Benton
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CONFERENCE PRICING

PREMIUM CONFERENCE PRICING - BEST VALUE (Includes access to two conferences, two short courses, and one symposium)	Commercial	Academic, Government, Hospital-affiliated
Early Rate Until January 27	$2999	$1999
Advance Rate Until March 10	$3199	$2099
Registrations after March 10	$3299	$2199
STANDARD CONFERENCE PRICING (Includes access to two conferences, excludes short courses and symposia)		
Early Rate Until January 27	$2299	$1099
Advance Rate Until March 10	$2449	$1199
Registrations after March 10	$2649	$1299
BASIC CONFERENCE PRICING (Includes access to one conference, excludes short courses and symposia)		
Early Rate Until January 27	$1749	$899
Advance Rate Until March 10	$1849	$999
Registrations after March 10	$1949	$1099

SHORT COURSE PRICING (APRIL 23 & 25)

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

SYMPOSIA PRICING (APRIL 27)

1 Symposium	$999	$599

Afternoon Short Courses (April 23)

SC1: Trends in Physical Properties of Drugs

SC2: GPCR Structure-Based Drug Discovery

SC3: Designing Peptide Therapeutics for Specific PPIs

SC4: RNA as a Small Molecule Drug Target

Dinner Short Courses (April 23)

SC5: Immunology Basics for Chemists

SC6: Introduction to Allosteric Modulators and Biased Ligands of GPCRs

SC7: Ligand-Receptor Molecular Interactions and Drug Design

SC8: Drug Metabolism and Its Impact on Decisions in Lead Discovery

Concurrent Conferences (April 24-25)	Concurrent Conferences (April 25-26)	Concurrent Symposia (April 27)
T1: Inflammation Inhibitors	T5: Kinase Inhibitor Chemistry	S1: Small Molecules for Cancer Immunotherapy
T2: Protein-Protein Interactions Part I	T6: Protein-Protein Interactions Part II	S2: Biophysical Approaches for Drug Discovery
T3: GPCR-Targeted Drug Design	T7: Fragment-Based Drug Discovery	
T4: Blood-Brain Penetrant Inhibitors	T8: Macrocyclics and Constrained Peptides	

Dinner Short Courses (April 25)

SC9: Impact of Convergence of Immunotherapy and Epigenetics on Drug Discovery

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

SC11: Advancing Tools and Technology for Fragment-Based Design

SC12: Introduction to Targeted Covalent Inhibitors

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.

CONFERENCE DISCOUNTS

Poster Submission - Discount ($50 Off): Poster abstracts are due by March 10, 2017. 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.

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Group Discounts: Discounts are available for multiple attendees from the same organization. For more information on group rates contact Bill Mote at +1-781-972-5479.

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.

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Please use keycode **DCH F** when registering!

Please refer to the Registration Code below:

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