FINAL DAYS to Register

Cambridge Healthtech Institute's 14th Annual

APRIL 8-12, 2019 | SAN DIEGO, CA
SAN DIEGO CONVENTION CENTER

Drug Discovery Chemistry

Optimizing Small Molecules for Tomorrow's Therapeutics

CONFERENCE PROGRAMS

APRIL 9-10

- Protein-Protein Interactions
- Small Molecules for Cancer Immunotherapy
- Kinase Inhibitor Chemistry
- Fragment-Based Drug Discovery
- Directed Evolution-Based Drug Discovery

APRIL 10-11

- Modulating the Ubiquitin-Proteasome System
- Inflammation Inhibitors
- Macrocyclics & Constrained Peptides
- GPCRs & Membrane Proteins

APRIL 12 SYMPOSIA

- AI for Early Drug Discovery
- Lead Optimization for Drug Metabolism
- Blood-Brain Barrier & CNS Drug Discovery
- Biophysical Approaches

Plenary Keynotes:

Chemical Biology of Proteostasis
Jack Taunton, PhD, Professor, Department of Cellular and Molecular Pharmacology, University of California San Francisco

New Ways of Targeting K-Ras
Frank McCormick, PhD, Professor, HDF Comprehensive Cancer Center, University of California San Francisco

Organized by:
Cambridge HEALTHTECH Institute

DrugDiscoveryChemistry.com

Premier Sponsors: eurofins DISCOVERY | HARKER BIO | OpenEye SCIENTIFIC

CONFERENCE AT-A-GLANCE

Monday APRIL 8	Tuesday APRIL 9	Wednesday APRIL 10	Thursday APRIL 11	Friday APRIL 12
Location: San Diego Convention Center				**Location:** Hard Rock Hotel
PRE-CONFERENCE SHORT COURSES*	PROTEIN-PROTEIN INTERACTIONS	DINNER SHORT COURSES*	MODULATING THE UBIQUITIN-PROTEASOME SYSTEM	ARTIFICIAL INTELLIGENCE FOR EARLY DRUG DISCOVERY
	SMALL MOLECULES FOR CANCER IMMUNOTHERAPY		INFLAMMATION INHIBITORS	LEAD OPTIMIZATION FOR DRUG METABOLISM & SAFETY
	KINASE INHIBITOR CHEMISTRY		MACROCYCLICS & CONSTRAINED PEPTIDES	BLOOD-BRAIN BARRIER AND CNS DRUG DISCOVERY
	FRAGMENT-BASED DRUG DISCOVERY		GPCRS & MEMBRANE PROTEINS	BIOPHYSICAL APPROACHES FOR DRUG DISCOVERY
	DIRECTED EVOLUTION-BASED DRUG DISCOVERY		TRAINING SEMINAR: DRUG METABOLISM	

*Separate registration is required

PLENARY KEYNOTES

TUESDAY, APRIL 9TH | 4:30-6:00PM

Chemical Biology of Proteostasis

Jack Taunton, PhD, Professor, Department of Cellular and Molecular Pharmacology, University of California San Francisco

Dr. Taunton's research at UCSF focuses on structure-based design of reversible and irreversible covalent inhibitors, as well as mechanistic studies of cyclic peptide natural products. Taunton is a co-founder of Principia BioPharma, Global Blood Therapeutics, Kezar Life Sciences, and Cedilla Therapeutics. Taunton earned his graduate degree in the laboratory of Stuart Schreiber at Harvard University and completed postdoctoral studies in the laboratory of Tim Mitchison at Harvard Medical School. He has been on the faculty at UCSF since 2000 and was a Howard Hughes Medical Investigator from 2008-2015.

THURSDAY, APRIL 11TH | 8:45-9:45AM

New Ways of Targeting K-Ras

Frank McCormick, PhD, Professor, HDF Comprehensive Cancer Center, University of California San Francisco

Prior to joining the UCSF faculty, Dr. McCormick pursued cancer-related work with several Bay Area biotechnology firms: Cetus Corporation Director of Molecular Biology, 1981-1990; Vice President of Research, 1990-1991 and Chiron Corporation, Vice President of Research 1991-1992. In 1992 he founded Onyx Pharmaceuticals and served as its Chief Scientific Officer until 1996. At Onyx, he initiated and led drug discovery efforts that led to the approval of Sorafenib in 2005 for treatment of renal cell cancer, and for liver cancer in 2007. Sorafenib is being tested in multiple indications worldwide. McCormick is the author of over 285 scientific publications and holds 20 issued patents. He also served as President, 2012-2013 for the American Association for Cancer Research (AACR). Since 2013, he has lead the National Cancer Institute's (NCI) sponsored Ras Initiative at the Frederick National Laboratories for Cancer Research, overseeing the NCI's national effort to develop therapies against Ras-driven cancers.

Short Courses*

*Separate registration required

Morning Short Courses

MONDAY, APRIL 8, 10:00 AM – 1:00 PM

SC1: Covalent Fragments: Applications in Target-Based and Phenotypic Screens

Topics include: design principles of covalent fragment libraries; target-based and phenotypic screens using covalent fragments; strategies to grow fragments into drug leads; case studies of coupling covalent fragment growth with selectivity profiling in cells.

Instructor:

Alexander Statsyuk, PhD, Assistant Professor, Department of Pharmacological and Pharmaceutical Sciences, University of Houston

SC2: Trends in Physical Properties of Drugs

Topics include: Properties that impact drug efficacy, development, delivery and formulation; including pKa, tautomerism, crystal structure interpretation among others. Use of computational tools.

Instructors:

Terry Stouch, PhD, President, R&D, Science for Solutions, LLC
Robert Fraczkiewicz, PhD, Team Leader, Simulations Plus, Inc.
Max Totrov, PhD, Principal Scientist, MolSoft, LLC

SC3: Introduction to GPCR-Based Drug Discovery

Topics include: GPCR pharmacology, including allosteric modulation; biased signaling, persistent signaling, and accessory proteins; emerging GPCR screening methods, including cellular redistribution assays; affinity mass spectrometry and biosensors.

Instructor:

Annette Gilchrist, PhD, Professor, Department of Pharmacology, Midwestern University

Afternoon Short Courses

MONDAY, APRIL 8, 2:00 – 5:00 PM

SC5: Ligand-Receptor Molecular Interactions and Drug Design

Topics include: medicinal chemistry drug design principles illustrated via case studies such as interpretation of atomic-level protein X-ray and modeled structures of binding model; understanding the relative amounts of potency gain from different interactions; and case studies to illustrate all the design strategies.

Instructor:

Maricel Torrent, PhD, Principal Research Scientist, Molecular Modeling, AbbVie

SC6: Methodologies for Optimizing Drug Clearance and Drug-Drug Interactions

Topics include: drug metabolism; CYP regulation; the role of bioactivation and how each affects lead optimization; and common assays and methodologies for predicting clearance and drug-drug interactions.

Instructors:

Zhengyin Yan, PhD, Principal Scientist, Department of Drug Metabolism and Pharmacokinetics, Genentech, Inc.
Donglu Zhang, PhD, Principal Scientist, Department of Drug Metabolism and Pharmacokinetics, Genentech, Inc.

SC7: Emerging Targets for Cancer Immunotherapy

Topics include: recently published data on immunology (STING, RIG- 1), epigenetic (HDAC, HAT), ubiquitin (DUBs, ligases) and autophagy targets; resulting strategies for development of new standalone or combination therapies for many types of cancers.

Instructors:

Wayne W. Hancock, MD, PhD, Professor of Pathology and Chief of Transplant Immunology, Children's Hospital of Philadelphia and University of Pennsylvania
Aditya Murthy, PhD, Scientist, Cancer Immunology, Genentech, Inc.
Arvin Iracheta-Vellve, PhD, Research Scientist II, TIDE and Cancer Program, Broad Institute of MIT & Harvard

Dinner Short Courses

MONDAY, APRIL 8, 6:00 – 9:00 PM

SC9: Advancing Tools and Technologies for Fragment-Based Design

Topics include: pros and cons of fragment-based approaches; what makes a good fragment; properties of a good fragment library; finding, validating and characterizing low affinity ligands; the importance of using orthogonal screening methods; and what to do with a fragment – growing, linking, and more.

Instructors:

Daniel A. Erlanson, PhD, Co-Founder, Carmot Therapeutics, Inc.
Ben Davis, PhD, Research Fellow, Biology, Vernalis Research

SC10: Diversity-Oriented Platforms for Ligand Discovery: Focusing on DNA-Encoded Libraries

Topics Include: Pros and cons of using DNA-encoded libraries (DEL), Overview of different DEL formats, "Split and pool" DNA recorded library synthesis strategy, Purpose of different encoding steps in the DEL process, Designing toward hits with the desired affinity, selectivity, and mechanism of action, Data analysis and the decision-making for which chemotypes to prosecute

Instructors:Svetlana Belyanskaya, PhD, Encoded Library Technologies, R&D Platform Technology & Science, GSK Boston
Ghotas Evindar, PhD, Head, Post-Selection Chemistry Group, Encoded Library Technologies, R&D Platform Technology & Science, GSK

SC11: Targeted Protein Degradation Using PROTACs and Molecular Glues

Topics include: basic understanding of proteolysis-targeting chimeric molecules (PROTACs); applying PROTACS to target and degrade specific proteins of interest; case studies from instructors' research.

Instructors:

Lara Gechijian, PhD, Scientist/Project Lead, Jnana Therapeutics; Former Graduate Student, Laboratory of Drs. James Bradner/Nathanael Gray, Harvard Medical School
Eric Fischer, PhD, Assistant Professor, Cancer Biology, Dana-Farber Cancer Institute/Harvard Medical School
Alexander Statsyuk, PhD, Assistant Professor, Department of Pharmacological and Pharmaceutical Sciences, University of Houston

Dinner Short Courses

WEDNESDAY, APRIL 10, 6:30 – 9:00 PM

SC13: Biochemistry and Pharmacology of the Ubiquitin-Proteasome System

Topics include: basic mechanistic biochemistry and pharmacology of the ubiquitin proteasome system, including E1, E2, E3, and deubiquitinating enzymes; signaling pathways regulated by UPS; the effect of small molecules on UPS-regulated pathways; assays and technologies for discovering enzyme inhibitors of the UPS system.

Instructor:

Alexander Statsyuk, PhD, Assistant Professor, Department of Pharmacological and Pharmaceutical Sciences, University of Houston

SC14: Immunology Basics for Chemists

Topics include: review of the immune system's cellular players; review of the inflammatory process; autoimmune and inflammation-related diseases; current treatment landscape; promising drug targets; and principles in immuno-oncology (e.g., checkpoint blockade).

Instructors:

Songqing Na, PhD, Senior Scientist, Biotechnology & Autoimmunity Res-AME, Eli Lilly and Company
Gavin Lewis, PhD, Scientist, Immunobiology Research Team, Janssen R&D

SC15: Macrocyclic Compounds for Drug Discovery: Opportunities, Challenges and Strategies

Topics include: unique characteristics of macrocycles; factors affecting cell permeability and PK/ADME properties; synthetic strategies for macrocyclic compound libraries and macrocyclization challenges; and drug discovery and development examples.

Instructors:

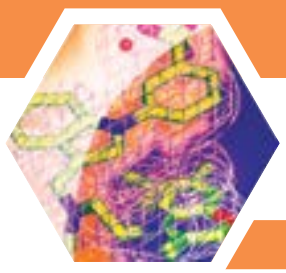
Eric Marsault, PhD, Professor, Medicinal Chemistry and Pharmacology, University of Sherbrooke
Mark Peterson, PhD, COO, Cyclenium Pharma, Inc.

SC16: GPCR Structure-Based Drug Discovery

Topics include: methodologies for the characterization and crystallization of GPCRs; a review of X-ray crystallographic and cryoEM GPCR structures and their lessons; biophysical tools (NMR, fluorescence spectroscopy, EPR, SPR and computational approaches) for observing function-related conformational dynamics of GPCRs; implications of structural knowledge on drug discovery especially related to allosteric modulation by small molecules, ions, and engineered partner proteins.

Instructors:

Matthew Eddy, PhD, Assistant Professor, Chemistry, University of Florida
Nicolas Villanueva, PhD, Project Scientist, Laboratory of Roger Sunahara, Pharmacology, University of California, San Diego



12TH ANNUAL

Protein-Protein Interactions

Targeting PPIs and Nucleic Acid Complexes for Therapeutic Interventions

April 9-10, 2019 | San Diego Convention Center | San Diego, CA

TUESDAY, APRIL 9

7:00 am Registration Open and Morning Coffee

TARGETING MCL-1 AND BCL-2 COMPLEXES

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

8:05 Chairperson's Opening Remarks
Roderick E. Hubbard, PhD, Professor, University of York and Senior Fellow, Vernalis

8:10 Enabling Fragment and Structure-Based Discovery for Mcl-1 and Bcl-2
Roderick E. Hubbard, PhD, Professor, University of York and Senior Fellow, Vernalis

Preventing sequestration of pro-apoptotic peptides by Mcl-1 or Bcl-2 induces apoptosis. However, the large hydrophobic cleft and flexibility of structure is a challenge for small molecule discovery. I will describe our work (protein production, fragment screening, biophysical methods) to establish structure and fragment based drug discovery that identified hit series of compounds, some of which were subsequently optimized to clinical candidates for cancer therapy.

8:40 Discovery of AZD5991, a Potent and Selective Macrocyclic Mcl-1 Inhibitor for Treatment of Cancer
Scott Mlynarski, PhD, Senior Scientist, Oncology Chemistry, IMED Biotech Unit, AstraZeneca

9:10 Sponsored Presentation *(Opportunity Available)*

9:40 Networking Coffee Break

10:05 AMG176, a Selective MCL-1 Targeted Drug Candidate
Paul E. Hughes, PhD, Principal Scientist, Oncology Research, Amgen

We will describe the discovery and development of AMG 176 a potent and selective MCL1 inhibitor. We rigorously applied small-molecule conformational restriction to optimize chemical matter culminating in the discovery of AMG 176. MCL1 inhibition rapidly induces apoptosis in subsets of hematological cancer cell lines, tumor xenografts, and primary patient samples. The combination of AMG 176 with venetoclax and standard of care agents is synergistic in multiple model systems highlighting the therapeutic promise of AMG 176 as a single agent and in combination.

10:35 Structure-Based Discovery of Selective and Potent Inhibitors of the BCL2 Family
Andras Kotschy, PhD, Director, Oncology, Servier Research Institute

MCL1 sequesters pro-apoptotic BH3 domain containing members of the BCL2 family, which is exploited by cancer cells to evade cell death and develop resistance. The presentation describes how using a fragment-based approach we developed the clinical candidate S64315 (also named MIK665) that Inhibits these protein-protein interactions. Major hurdles were establishing structural support and understanding its limitations, choosing the appropriate pharmacological tools, and addressing the drug-likeness of our potential candidates.

11:05 Prospective Discovery of Small Molecule Enhancers of Specific E3 ligase-Substrate Interactions
Kyle Simonetta, Ph.D., Senior Scientist, Lead Discovery, Nurix Therapeutics, Inc.

11:35 LUNCHEON PRESENTATION: Evolution of Contract Research Organizations to Contract Innovation Organizations?

Sponsored by eurofins | DISCOVERY

Vicky Steadman, PhD, Business Line Leader, Integrated Drug Discovery, Eurofins Discovery (formerly Eurofins Pharma Discovery Services)

CROs were employed by their customer to carry out certain pre-designated tasks. However, CROs evolved to provide solutions to customer's challenges and are evolving further to provide innovation in the form of project ideas. Collaborative partnerships on integrated drug discovery projects are now common in the drug discovery landscape. Eurofins, an integrated drug discovery provider, will present a successful case history which led to pre-clinical candidates for a pharma partner on a challenging PPI target.

12:20 pm Session Break

PROTEIN-NUCLEIC ACID COMPLEXES AS DRUG TARGETS

1:15 Chairperson's Remarks
Marianne Sadar, PhD, Professor, Pathology and Genome Sciences, University of British Columbia/BC Cancer Agency

1:20 Targeting RNA: Discovery of Risdiplam; a Selective SMN2 Gene Splicing Modulator for the Treatment of Spinal Muscular Atrophy
Hasane Ratni, PhD, Expert Scientist, Medicinal Chemistry, F. Hoffmann-La Roche, Basel, Switzerland

RNA splice modifiers are a new class of small molecule therapeutics. We have been developing orally available small molecules to increase levels of SMN protein via the alternative splicing of the survival motor neuron 2 (SMN2) pre-mRNA for the treatment of spinal muscular atrophy. We will present the discovery of risdiplam, and its full profile. This compound is currently completing pivotal clinical trials in all type SMA patients.

1:50 Gene Signature Screen (GSS) to Identify Novel Modulators of a Transcriptional Factor
Seong Joo Koo, PhD, Senior Scientist, Lead Discovery, Janssen Pharmaceutica NV

Gene Signature Screening (GSS) is an emerging multiparametric approach to identify disease-associated pathway modulators. We evaluated the potential of GSS to identify novel small molecule inhibitors of a transcription factor by screening 57,000 compounds using a 22-gene signature. Our results show that GSS can identify novel and known inhibitors, demonstrating that GSS can be used to discover inhibitors of transcription factors that are traditionally considered as "undruggable targets."

2:20 Small-Molecule Covalent TEAD•Yap Antagonists
Samy Meroueh, PhD, Associate Professor, Department of Biochemistry and Molecular Biology, Indiana University School of Medicine

Hippo signaling controls tissue homeostasis and organ growth by regulating Yap co-activation of TEA domain (TEAD) transcription factors. We report small-molecule TEAD•Yap inhibitors that selectively form a covalent bond with a conserved cysteine in the palmitate pocket of TEADs. In mammalian cells, the compounds formed a covalent complex with TEAD4, inhibited its binding to Yap1, blocked its transcriptional activity, suppressed expression of CTGF, and inhibited cell viability of glioblastoma spheroids.

2:50 Novel PPI Inhibitors Targeting the Centrosome to Fight Cancer
Kamyar Hadian, PhD, Group Leader, Helmholtz Zentrum Muenchen

Centrosome amplification is a hallmark of human cancers that can trigger cancer cell invasion. To survive, cancer cells cluster amplified

extra centrosomes and achieve pseudo-bipolar division. Here, we set out to prevent clustering of extra centrosomes by identifying novel small molecules that target the Tubulin-CPAP protein-protein-interaction. Biochemical, cell-based and *in vivo* validation demonstrate a global approach to target various cancers including drug-resistant cancers exhibiting high incidence of centrosome amplification.

3:20 NEW: Allosteric Inhibitor of β-catenin Selectively Targets Oncogenic Wnt Signaling in Colon Cancer

Elmar Nurmemmedov, PhD, Principal Investigator & Director of Drug Discovery, John Wayne Cancer Institute at Providence St. John's Health

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

Sponsored by SYGNATURE DISCOVERY

4:30 Welcome Remarks from Lead Conference Director

Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

4:35 Plenary Technology Spotlight: Molecular Modelling for the Masses: Orion

Sponsored by OpenEye SCIENTIFIC

Paul Hawkins, Head, Scientific Solutions, OpenEye Scientific

The advent of cloud computing has been transformative for many fields that utilize computation, including drug discovery. The cloud offers robust, elastic, and scalable compute resources through a browser, decreased IT overhead, costs, and time to obtain actionable results. In this presentation I illustrate how the cloud, and in particular OpenEye's web-based platform Orion, is democratizing molecular modelling by providing easy to use access to cutting-edge molecular design tools coupled with essentially unlimited compute resources.

5:05 Plenary Keynote Introduction

Vicky Steadman, PhD, Business Line Leader, Integrated Drug Discovery, Eurofins Discovery (formerly Eurofins Pharma Discovery Services)

5:10 PLENARY KEYNOTE:

Chemical Biology of Proteostasis

Jack Taunton, PhD, Professor, Department of Cellular and Molecular Pharmacology, University of California San Francisco

We have recently discovered several macrocyclic compounds that potently and selectively modulate protein homeostasis. I will discuss our recent efforts to unravel their molecular mechanisms.

6:00 Welcome Reception in the Exhibit Hall with Poster Viewing

7:00 Close of Day

WEDNESDAY, APRIL 10

7:30 am Continental Breakfast Breakout Discussions

See website for details.

INNOVATIONS FOR TARGETING OF PPIs

8:30 Chairperson's Remarks

Samantha J. Allen, PhD, Principal Scientist, Screening, Janssen R&D LLC

8:35 Cereblon Neosubstrate Degradation in Efficacy and Teratogenecity

Philip Chamberlain, DPhil, Senior Director, Structural and Chemical Biology, Celgene

Cereblon modulators are a class of small molecules, including the approved drugs lenalidomide and pomalidomide, that are capable of inducing degradation of target proteins. Cereblon modulators function by scaffolding a protein-protein interaction between cereblon and target proteins resulting in their ubiquitination and proteasomal degradation. A structural understanding has provided a rationale for the mechanism of action, and is enabling the discovery of new substrates and therapeutic mechanisms.

9:05 Discovery and Clinical Development of Drugs Targeting the Intrinsically Disordered Region of Androgen Receptor

Marianne Sadar, PhD, Professor, Pathology and Genome Sciences, University of British Columbia/BC Cancer

Androgen receptor (AR) is a transcription factor and validated therapeutic target for prostate cancer. Resistance to therapies targeting AR is mediated by expression of constitutively active splice variants of AR that lack its ligand-binding domain. Thus targeting the intrinsically disordered N-terminal domain of AR is of interest. We report our approach to the discovery and clinical development of small molecule inhibitors of this drug target previously considered to be "un-druggable."

9:35 Coffee Break in the Exhibit Hall with Poster Awards Announced

Poster Awards Sponsored by Domainex

FRAGMENT-BASED LIGAND DISCOVERY AND PPIs

10:30 FEATURED PRESENTATION: Molecular Glues for Protein-Protein Interactions: A Fragment-Based Approach to Stabilize 14-3-3/Client Complexes

Michelle Arkin, PhD, Professor, Department of Pharmaceutical Chemistry, University of California San Francisco

Many proteins have multiple binding partners, potentially inducing different biological effects. Stabilizing such protein-protein interactions offers an opportunity to dial in specificity for both partners, and can be inhibitory, activating, or synthetic. Our team is developing specific stabilizers of 14-3-3/client proteins to evaluate the scope and limitations of these effects. This talk will describe our initial foray in the 14-3-3 stabilization using fragment-based drug discovery approaches.

11:00 Biophysics and Structural Biology Offer a Direct Path to Allosteric Drugs

Gregg Siegal, CEO, ZoBio

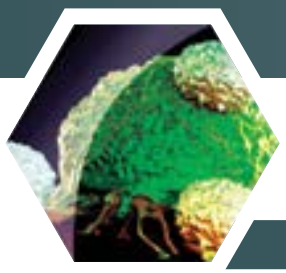
Allosteric drugs offer exciting new opportunities. ZoBio's platform of biophysics and structural biology allows us to design campaigns that directly seek allosteric modulators of pharmaceutical targets. I will illustrate this capability using HSP70 as an example. HSP70 is a validated target in both oncology and neurodegeneration and yet, has proven challenging to drug. The process used to develop compounds that are selective for the ADP-bound form and inhibit ATPase activity will be described.

11:30 Fragment Philosophy Used in the Identification of eFT508, an Oral, Potent and Highly Selective Inhibitor of Mitogen-Activated Protein Kinase Interacting Kinase (MNK) 1 and 2

Paul Sprengeler, PhD, Research Fellow, Medicinal Chemistry, eFFECTOR Therapeutics, Inc.

Starting from a handful of fragments and fragment-like molecules, the crystal structure-guided approach, leveraging stereoelectronic interactions, to eFT508, an exquisitely selective, potent dual MNK1/2 inhibitor, will be presented. eFT508 was designed to assess the potential for control of oncogene signaling at the level of mRNA translation and has shown potent *in vivo* anti-tumor activity in models of DLBCL and solid tumors. It is currently being evaluated in Phase 2 clinical trials in solid tumors and lymphoma.

12:00 pm Close of Conference



3RD ANNUAL

Small Molecules for Cancer Immunotherapy

Design of New Molecules and Combinations for Immuno-Oncology Targets

April 9-10, 2019 | San Diego Convention Center | San Diego, CA

TUESDAY, APRIL 9

7:00 am Registration Open and Morning Coffee

NEW COMPOUNDS FOR SINGLE AND COMBINATION IO THERAPY

8:00 Welcome Remarks

Tanuja Koppal, PhD, Conference Director, Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks

Donald Durden, MD, Professor, Pediatrics, University of California, San Diego; Director of Operations, SignalRx Pharmaceuticals

8:10 Modulation of Immune Response with Porcupine Inhibitor RXC004 in Preclinical Cancer Models

Inder Bhamra, PhD, Research Fellow, Medicinal Chemistry, Redx Pharma

RXC004 is a potent and selective Porcupine inhibitor currently undergoing Phase I clinical evaluation in cancer patients. Porcupine is a membrane bound O-acyltransferase responsible for post-translational modification of all Wnt ligands. Porcupine inhibitors are efficacious in preclinical models of Wnt ligand driven cancers. Preclinical models demonstrate that RXC004 has an anti-tumour effect via immuno-stimulatory mechanisms, both as a single agent or in combination with anti-PD1 antibodies.

8:40 Toll-Like Receptor (TLR) 7 and 8 Agonists with Direct Inflammasome Activation

David Ferguson, PhD, Professor, Medicinal Chemistry, University of Minnesota

TLR 7 and 8 agonists are potent modulators of proinflammatory cytokine induction but may also induce regulatory cytokines leading to the upregulation of PD-L1 and activation of MDSCs and Tregs. The benefits of combining sunitinib with and without an anti-PD-L1 antibody and a TLR-based nanovaccine evaluated using *in vitro* and *in vivo* models show reductions in MDSCs and Tregs can be afforded through co-administration of sunitinib with vaccination. Gains in antigen specific CD8 T cell responses were also noted by addition of anti-PD-L1 antibodies resulting in improved anti-tumor response of the TLR-based vaccine *in vivo*.

9:10 Tankyrase Inhibitors: Evidence for Therapeutic Potential in Immuno-Oncology

Sponsored by

Luc Van Hijfte, PhD, Senior Vice President, Medicinal Chemistry, Mercachem

WNT/β-catenin signaling regulates key cellular functions including proliferation, differentiation, migration, apoptosis, stem cell renewal and immune system modulation. Abberrant WNT/ β-catenin signaling is found in multiple cancers. In particular, the recently described role of the WNT/β-catenin pathway in regulating immune cell infiltration in the tumor micro-environment suggests an impact of the pathway on immunotherapy. Hence, WNT-directed therapeutic intervention represents an area of significant developmental focus. The Poly-ADP-ribosylases tankyrase 1 and 2 are central biotargets in the WNT/β-catenin signaling pathway, regulating the turnover of the protein complex that controls β-catenin stability and in adition impacting the hippo signaling pathway. Several small molecules have been identified that inhibit tankyrases 1 and 2, and we have earlier shown efficacy of tankyrase inhibitors in WNT dependent adenoma and tumor models. The successful discovery of novel, selective tankyrase inhibitors from a hit stage to an advanced lead stage, and *in vivo* data that these compounds demonstrate a promising new approach in immuno-oncology in combination with check-point

9:40 Networking Coffee Break

10:05 *In silico* Design of a "First-in-Class" Novel Dual Syk/PI3K Inhibitor to Block the Immunosuppressive Tumor Microenvironment

Donald Durden, MD, Professor, Pediatrics, University of California, San Diego; Director of Operations, SignalRx Pharmaceuticals

Macrophages (MQs) play a critical role in tumor growth, immunosuppression and inhibition of adaptive immune responses in cancer. Hence, targeting signaling pathways in MQs that promote tumor immunosuppression will provide therapeutic benefit. PI3Kg has been recently established by our group and others as a novel immuno-oncology target. Herein, we report that a macrophage Syk-PI3K axis drives polarization of immunosuppressive macrophages which establish an immunosuppressive tumor microenvironment in *in vivo*syngeneic tumor models. Genetic or pharmacological inhibition of Syk and/or PI3Kg in MQs promotes a pro-inflammatory MQ phenotype, restores CD8+ T cell activity, destabilizes HIF under hypoxia, and stimulates antitumor immune response. Moreover, we have developed *in silico* the "first in class" dual Syk/PI3K inhibitor, SRX3207, for the combinatorial inhibition of Syk and PI3K in one small molecule. This chemotype demonstrates efficacy in multiple tumor models and represents a novel combinatorial approach to activate antitumor immunity.

10:35 Small-Molecule Therapeutics Targeting Immunosuppressive TIGIT and Adenosine Signaling Pathways

Murali Ramachandra, PhD, CSO, Aurigene Discovery Technologies Limited

Potential advantages of small molecule agents include oral dosing, greater response rate due to better tumor distribution, potential for simultaneously targeting closely related checkpoint proteins, and possibility of better management of adverse events. After succeeding in identifying agents targeting PD-L1, VISTA, TIM3 and CD47, which are at different stages of development (most advanced CA-170 in Phase II clinical trial), we have now focused our attention in discovering agents targeting newer checkpoint protein such as TIGIT and immunosuppressive adenosine signaling. The talk will cover our approaches and status of these programs.

11:05 SELECTED POSTER PRESENTATION: 3PO - Small Molecule PFKFB3 Inhibitor Induce Apoptosis and Cell Cycle Arrest in A375 Human Melanoma Cell Line with Endogenous BRAFV600E Mutation

Krzysztof Kotowski, Medical Student, Faculty of Medicine, Wroclaw Medical University

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

12:20 pm Session Break

MODULATING THE TUMOR MICROENVIRONMENT

1:15 Chairperson's Remarks

David Ferguson, PhD, Professor, Medicinal Chemistry, University of Minnesota

1:20 Targeting the Tumor Microenvironment with TGFβ Inhibitors

Rikke B. Holmgaard, PhD, Principal Research Scientist, Oncology Research, Eli Lilly and Company

Inhibiting the immune suppressive effects of TGFβ is an emerging strategy as a way to increase benefit of cancer immunotherapy. We explored the impact of the clinical stage TGFβ pathway inhibitor, galunisertib on anti-tumor immunity at clinically relevant doses. Our data show strong dose-dependent anti-tumor activity with immunological memory in preclinical mouse models with established tumors; as well as combinatorial activity with anti-PD-L1 resulting in tumor regressions associated with enhanced

T-cell activation. A second generation, more potent and selective TGFβRI inhibitor, LY3200882, is currently in Phase I.

1:50 Targeting the CBP/P300 Bromodomain for Immuno-Oncology

Karen Gascoigne, PhD, Scientist, Discovery Oncology, Genentech, Inc.

The histone acetyl-transferases CBP/P300 are critical regulators of gene expression in both tumor and immune cells. We describe a novel CBP/P300 bromodomain inhibitor, and its use to probe the role of the bromodomain in CBP/P300 activity at chromatin and in tumor & immune cell function. CBP/P300 bromodomain inhibition impacts the function of MDSC and Treg cells, and directly impairs tumor growth *in vitro* and *in vivo*.

2:20 "It Takes Guts to Rev Up CARs": Harnessing the Power of Gut Microbiome to Modulate Responses of Novel Cancer Therapies

Muhammad Bilal Abid, MD, MRCP, Clinician-Scientist, Medical College of Wisconsin

Preclinical and human studies establishing a clear relationship between antigen presentation machinery, gut microbiome diversity, and certain microbial taxa, coupled with preclinical studies highlighting the suppressive role of Tregs on CAR T-cells, postulate that modulating gut microbiota may very well impact responses to CAR T-cells.

2:50 GCN2 Mediates Response to Stress Caused by Amino Acid Deprivation Influencing both Immunological Function and Cell Growth in the Tumor Microenvironment

David Wustrow, PhD, Vice President, Drug Discovery, FLX Bio

GCN2 plays a key role in the regulation of T cell anergy and apoptosis caused by amino acid depletion in the tumor microenvironment. Inhibition of GCN2 abrogates immune suppression by increasing proliferation and effector function of T cells and via reversal of the suppressive function of MDSCs. GCN2 inhibitors have also been shown to potentiate the anti-tumor effects of the amino acid depleting agent asparaginase. Efforts to discover and assess novel GCN2 inhibitors will be described.

3:20 CETSA® Enabled Drug Discovery

Sponsored by PELAGO BIOSCIENCE

Michael Dabrowski, PhD, CEO, Pelago Bioscience

CETSA allows quantification of target engagement under relevant physiological conditions, which is prerequisite for achieving the intended efficacy. Over the last 8 years CETSA has been applied in hundreds of studies from early target validation to analysis of clinical samples. In his talk Michael will explore examples of applications and also discuss future perspectives in enabling drug discovery using the CETSA method.

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

Sponsored by SYGNATURE DISCOVERY

4:30 Welcome Remarks from Lead Conference Director

Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

4:35 Plenary Technology Spotlight: Molecular Modelling for the Masses: Orion

Sponsored by OpenEye SCIENTIFIC

Paul Hawkins, Head, Scientific Solutions, OpenEye Scientific

The advent of cloud computing has been transformative for many fields that utilize computation, including drug discovery. The cloud offers robust, elastic, and scalable compute resources through a browser, decreased IT overhead, costs, and time to obtain actionable results. In this presentation I illustrate how the cloud, and in particular OpenEye's web-based platform Orion, is democratizing molecular modelling by providing easy to use access to cutting-edge molecular design tools coupled with essentially unlimited compute resources.

5:05 Plenary Keynote Introduction

Vicky Steadman, PhD, Business Line Leader, Integrated Drug Discovery, Eurofins Discovery (formerly Eurofins Pharma Discovery Services)

5:10 PLENARY KEYNOTE:

Chemical Biology of Proteostasis

Jack Taunton, PhD, Professor, Department of Cellular and Molecular Pharmacology, University of California San Francisco

We have recently discovered several macrocyclic compounds that potently and selectively modulate protein homeostasis. I will discuss our recent efforts to unravel their molecular mechanisms.

6:00 Welcome Reception in the Exhibit Hall with Poster Viewing

7:00 Close of Day

WEDNESDAY, APRIL 10

7:30 am Continental Breakfast Breakout Discussions

See website for details.

EMERGING ROLE OF PROTACs IN ONCOLOGY

8:30 Chairperson's Remarks

Markus Queisser, PhD, Scientific Leader, Protein Degradation DPU, R&D Future Pipelines Discovery, GlaxoSmithKline

8:35 Proteolysis Targeting Chimeric Molecules (PROTACs) as Small Molecule Modality in Immuno-Oncology

Markus Queisser, PhD, Scientific Leader, Protein Degradation DPU, R&D Future Pipelines Discovery, GlaxoSmithKline

Targeted protein degradation using bifunctional small molecules known as proteolysis targeting chimeric molecules (PROTACs) is emerging as a novel modality. PROTACs redirect ubiquitin-ligases to target specific proteins for degradation. The advantages of the PROTAC technology lie in its modular, rationally designed molecules, capable of producing a cellular protein knock-down as demonstrated in both cellular and *in vivo* with the ligase ligand and targeting warhead combine to exert a synergistic effect in oncology.

9:05 FEATURED PRESENTATION: Empirical & Structure-Based PROTAC Design: Lessons Learned with VHL-Based PROTACs

Peter Ettmayer, PhD, Scientific Director, Cancer Research, Boehringer Ingelheim RCV GmbH & Co KG

Current PROTAC design is driven by screening exit vectors and linkers until a suitable degrader is identified. We will present an alternative rational PROTAC optimization based on high-resolution ternary complex crystal structures and cooperativity considerations. The case study will exemplify a successful structure driven campaign to degrade targets previously considered undruggable and pave the way towards new therapeutics for the treatment of genetically-defined tumors.

9:35 Coffee Break in the Exhibit Hall with Poster Awards Announced

Poster Awards Sponsored by Domainex

10:30 TIP60 Inhibition and Cancer Therapy

Wayne W. Hancock, MD, PhD, Professor, Pathology and Chief of Transplant Immunology, Children's Hospital of Philadelphia and University of Pennsylvania

Foxp3+ Tregs predominate in the microenvironment of many "hot" tumors where they impair antitumor immunity. There are currently no approved strategies that specifically focus on targeting intratumoral Foxp3+ Tregs. We have found that newly developed conventional and PROTAC forms of Tip60 inhibitors (Tip60i) can impair Treg function and boost anti-tumor immunity in syngeneic lung tumor models. Given that mouse Tip60 shares 99.6% identity (511 of 513 amino acids) with human Tip60, the relevance of our mechanistic studies in murine models to human disease appears compelling.

11:00 Targeted Protein Degradation for Treatment of Cancer

Michael Plewe, PhD, Vice President, Medicinal Chemistry, Cullgen, Inc.

Targeted protein degradation using bifunctional molecules to remove specific proteins by hijacking the ubiquitin proteasome system has emerged as a novel drug discovery approach. These bifunctional degrader molecules consist of a ligand that binds to the protein targeted for degradation, a linker and a ligand for recruitment of an E3 ligase. We will present case studies for developing degraders for oncology targets such as anaplastic lymphoma kinase (ALK) that could lead to novel therapeutics with minimal toxicity.

11:30 Dual Role of USP7 Inhibitors in Treatment of Malignant Diseases

Tauseef Butt, PhD, CEO, Progenra

USP7 is a multifaceted DUB that mediates immune evasion by promoting aggressive Treg functions in tumor tissue as well as direct tumor growth. Progenra's USP7 inhibitors eradicate experimental tumors in syngeneic models by suppressing regulatory T cells to unleash Teffector anti-tumor responses as well as direct anti-tumor action. USP7 inhibitors have been reported by other pharma companies. However, these molecules have poor therapeutic efficacy as compared to Progenra molecules. Molecular mechanisms that differentiate USP7 inhibitors will be discussed.

12:00 pm Close of Conference

Kinase Inhibitor Chemistry

Emerging Targets, Tools, Opportunities and New Strategies

April 9-10, 2019 | San Diego Convention Center | San Diego, CA

TUESDAY, APRIL 9

7:00 am Registration Open and Morning Coffee

PROTACs, RESEARCH UPDATES & NEXT GENERATION OF KINASES

8:00 Welcome Remarks

Nandini Kashyap, Conference Director, Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks

Erik Schaefer, President & CSO, Research & Development, AssayQuant Technologies

8:10 Development of Selective CDK Inhibitors and Degraders

Nicholas Kwiatkowski, PhD, Lead Scientist, Nathanael Gray Lab, Cancer Biology, Dana-Farber Cancer Institute

Cyclin-dependent kinases (CDKs) regulate key pathways that are frequently misregulated in cancer, making them attractive drug targets. However, the high sequence and structural conservation shared by CDK family members make the development of CDK-specific pharmacological agents difficult. We have employed several orthogonal strategies to permit the selective inhibition of distinct CDK family members and interrogation of their biological function in normal and disease states.

8:40 FEATURED PRESENTATION: Targeted Degradation of Bruton's Tyrosine Kinase (BTK)

Matthew Calabrese, PhD, Senior Principal Scientist and Structural Biology Lab Head, Structural and Molecular Sciences, Pfizer, Inc.

Proteolysis targeting chimeras present an exciting opportunity to modulate proteins in a manner that is independent of enzymatic or signaling activity. Despite this interest, fundamental questions remain regarding the parameters most critical for achieving potency and selectivity. We have employed a series of biochemical and cellular techniques to investigate requirements for efficient knockdown of Bruton's tyrosine kinase (BTK) and will share the results of this case-study and the lessons learned.

9:10 Structure-Based Predictions of CYP Selectivity, Reactivity, and Regioselectivity

Sponsored by Chemical Computing Group

Alain Ajamian, Director, Business Development, Chemical Computing Group

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

9:40 Networking Coffee Break

10:05 Large Scale Proteomics Approaches to Accelerate Degrader Development for Kinases and Other Challenging Targets in Cancer

Eric S. Fischer, PhD, Assistant Professor, Cancer Biology/Biological Chemistry and Molecular Pharmacology, Dana-Farber Cancer Institute/Harvard Medical School

This presentation will discuss the use of large scale chemical-proteomics approaches to accelerate the development of small molecule degraders as chemical probes and lead candidates. Small molecules capable of inducing protein degradation through recruitment of ubiquitin E3 ligases to target proteins, often referred to as degraders or PROTACs, are a new and promising drug modality. We will discuss general approaches to significantly accelerate the development of novel chemical probes for kinases and other targets in cancer.

ARTIFICIAL INTELLIGENCE IN KINASE INHIBITOR DISCOVERY

10:35 Artificial Intelligence in Kinase Inhibitor Discovery

Istvan J. Enyedy, PhD, Principal Scientist, Biogen

Machine learning in combination with automated inhibitor optimization and statistical analysis may be used to accelerate kinase inhibitor discovery. The performance of a prototype artificial intelligence protocol will be presented.

11:05 Defining the Protein Kinase Conformational Space with Machine Learning

Avner Schlessinger, PhD, Assistant Professor, Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai

We have developed a machine-learning algorithm to classify kinase conformations based on structural features of the kinase domain. Our classification scheme captures known kinase conformations and defines an additional conformational state. Next, we present KinaMetrix, a comprehensive publicly accessible web-resource for studying kinase pharmacology and drug discovery. KinaMetrix enables researchers to investigate and visualize the kinase conformational space as well as small molecule substructures that exhibit conformational specificity.

11:35 Luncheon Presentation: Sensors for Continuous Monitoring of Protein Kinase & Phosphatase Activity

Sponsored by AssayQuant®

Erik Schaefer, President & CSO, Research & Development, AssayQuant Technologies

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

12:20 pm Session Break

NEW TARGETS & PROMISING CANDIDATES

1:15 Chairperson's Remarks

Lenka Munoz, PhD, Associate Professor, School of Medical Sciences, Discipline of Pathology, The University of Sydney

1:20 Reversing the Paradigm: Protein Kinase C as a Tumor Suppressor

Tim Baffi, Graduate Student, Alexandra Newton's Lab, Department of Pharmacology, University of California San Diego

Protein kinase C (PKC) has historically been considered an oncoprotein. However, our analysis of >100 somatic mutations identified in human cancers reveals that most mutations are loss-of-function and none are activating; in contrast, germline mutations that enhance activity are associated with degenerative diseases. Our results reveal that therapeutic strategies should focus on restoring, rather than inhibiting, PKC activity in cancer.

1:50 Discovery of Soft panJAK Inhibitors for Topical Treatment of Inflammatory Skin Diseases

Daniel R. Greve, PhD, Senior Manager, Head of MedChem II, LEO Pharma A/S

The presentation covers our efforts aiming for selective, pan-JAK inhibitor molecules having a pharmacokinetic profile that allows for high local exposure combined with low systemic exposure, driven by high hepatic clearance. The lead compounds are efficacious in our mouse xenograft model of plaque psoriasis, while having promising profile in safety/tox studies.

2:20 Targeting the Nuclear Translocation of MAPKs as a Novel Anti-Inflammatory and Anti-Cancer Therapy

Galia Maik-Rachline, PhD, Associate Staff Scientist, Biological Regulation, The Weizmann Institute of Science

We have identified two novel, distinct, regulated nuclear translocation mechanisms for ERK1/2 and JNK/p38, of which we made use of as a promising therapeutic approach. We developed a myristoylated, NTS-derived phosphomimetic peptide (EPE peptide), which blocked ERK1/2 nuclear translocation by inhibiting its interaction with importin7 (Imp7). We also developed additional p38-derived myristoylated peptide, termed PERY peptide that prevented JNK1/2 and p38α/β nuclear translocation by interfering with their binding to either Imp7 or Imp9. Our results in several cancer and inflammatory models support the use of nuclear translocation of MAPKs as a novel drug target for signaling related diseases.

2:50 Non-Kinase Targets of Protein Kinase Inhibitors

Lenka Munoz, PhD, Associate Professor, School of Medical Sciences, Discipline of Pathology, The University of Sydney

Non-kinase targets of kinase inhibitors can contribute to desired activity, side effects or act as silent bystanders. As the correct understanding of drug's mechanism of action is critical for the interpretation and success of preclinical as well as clinical drug development, these discoveries highlight the importance of expanding the pharmacology of kinase inhibitors beyond the kinome. I will present kinase inhibitors for which other than kinase targets have been identified and discuss molecular pharmacology guidelines when using kinase inhibitors.

3:20 Selected Poster Presentation: Computational Evaluation of Potential Inhibitors for Protein Kinase CK2

Doga Ozsen, Graduate Student, Department of Chemical Engineering, Yeditepe University, Turkey

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

Sponsored by SYGNATURE DISCOVERY

4:30 Welcome Remarks from Lead Conference Director

Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

4:35 Plenary Technology Spotlight: Molecular Modelling for the Masses: Orion

Sponsored by OpenEye Scientific

Paul Hawkins, Head, Scientific Solutions, OpenEye Scientific

The advent of cloud computing has been transformative for many fields that utilize computation, including drug discovery. The cloud offers robust, elastic, and scalable compute resources through a browser, decreased IT overhead, costs, and time to obtain actionable results. In this presentation I illustrate how the cloud, and in particular OpenEye's web-based platform Orion, is democratizing molecular modelling by providing easy to use access to cutting-edge molecular design tools coupled with essentially unlimited compute resources.

5:05 Plenary Keynote Introduction *(Sponsorship Opportunity Available)*

5:10 Plenary Keynote:

Chemical Biology of Proteostasis

Jack Taunton, PhD, Professor, Department of Cellular and Molecular Pharmacology, University of California San Francisco

We have recently discovered several macrocyclic compounds that potently and selectively modulate protein homeostasis. I will discuss our recent efforts to unravel their molecular mechanisms.

6:00 Welcome Reception in the Exhibit Hall with Poster Viewing

7:00 Close of Day

WEDNESDAY, APRIL 10

7:30 am Continental Breakfast Breakout Discussions

See website for details.

ALLOSTERIC MODULATORS, KINETICS, TARGET OPTIMIZATION FOR KINASES AND PHOSPHATASES

8:30 Chairperson's Remarks

Alexis Denis, Head of Discovery Division, Oncodesign

8:35 Make it Cyclic: A Paradigm for the Discovery of Selective Kinases Inhibitors "Nanocyclix"

Sponsored by Oncodesign

Alexis Denis, Head of Discovery Division, Oncodesign

Cyclization in drug discovery is a growing paradigm. We have developed an Integrated Drug Discovery platform Nanocyclix to synthesize small libraries of macrocycles and design specific molecules through SBDD to identify new kinases inhibitor. Nanocyclix molecule are in the drug-like space and display nM potencies and good selectivity across the kinome. Nanocyclix paradigm will be exemplified at the level of H2L and beyond in Oncology and Immuno-inflammation to illustrate the potential of the cyclization approach.

9:05 FEATURED PRESENTATION: Exploring the Hidden World of Non-Canonical Protein Phosphorylations

Tony Hunter, PhD, American Cancer Society Professor, Molecular and Cell Biology Laboratory, The Salk Institute for Biological Studies

Phosphorylation of histidine, lysine and arginine, the so-called "hidden phosphoproteome", is poorly characterized. To address this void, we developed monoclonal antibodies (mAbs) that selectively recognize the 1- and 3-isoforms of phosphohistidine (pHis) in proteins in a sequence-independent manner. We have used these mAbs in proteomic studies to identify pHis-containing proteins in cancer cell lines, and developed new protocols for enriching pHis-containing tryptic peptides and identifying sites of His phosphorylation. We have also used these mAbs for immunoblotting and immunostaining to detect and localize pHis proteins in normal and tumor tissues. Studies with these mAbs have allowed us to define a role for elevated His phosphorylation in liver cancer.

9:35 Coffee Break in the Exhibit Hall with Poster Awards Announced

Poster Awards Sponsored by Domainex

10:30 Using Fragment-Based Lead Discovery (FBLD) for Kinase Inhibitor Development

Marc O'Reilly, PhD, Senior Director of Molecular Sciences, Astex Pharmaceuticals

In this talk, I will provide examples of how Astex is exploiting high throughput protein crystallography and fragment-based lead discovery (FBLD) for kinase inhibitor development.

10:50 Selected Poster Presentation: Target Identification Using Theoretical Active Site Models

Belkıs Akbulut, Graduate Student, Department of Chemical Engineering, Yeditepe University, Turkey

11:10 Novel Design Paradigms for Protein Kinases and Phosphatases – Binding Kinetics and Allosteric Mechanisms

Gerhard Mueller, PhD, CSO, Gotham Therapeutics

We will demonstrate that a thorough understanding of the precise pharmacophoric requirements on the target's binding site is essential to pre-engineer the desired slow off-rates into new, thus literature-unprecedented scaffolds that qualify as privileged structures for the target family of kinases.

11:30 Recent Experiences with Fragments for Kinases

Roderick Hubbard, DPhil, Professor and Senior Fellow, University of York and Vernalis

Fragments provide valuable tools for probing kinase biology and starting points for lead molecules. I will discuss results from three recently disclosed kinase collaborative projects: DYRK1A, PAK1, LRRK2. For DYRK1A, potent, *in vivo* active, selective inhibitors probed target biology; for PAK1, design of protein constructs allowed rapid progress to be made in identifying selective leads; for LRRK2 surrogate kinase enabled structure-based design of highly selective, potent, brain penetrant inhibitors.

12:00 pm Close of Conference

Fragment-Based Drug Discovery

From Hits to Leads and Lessons Learned

April 9-10, 2019 | San Diego Convention Center | San Diego, CA

TUESDAY, APRIL 9

7:00 am Registration Open and Morning Coffee

FBDD SUCCESS STORIES

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

8:05 Chairperson's Opening Remarks
Dan Erlanson, PhD, Co-Founder, Carmot Therapeutics

8:10 Application of Fragment-Based Drug Discovery in the Identification of Novel FXIa Inhibitors for Thrombosis Prevention
Santhosh F. Neelamkavil, PhD, Director, Discovery Chemistry, Merck Research Laboratories

Fragment-based drug design has the potential to deliver hits to lead optimization with improved properties and aims to reduce compound-related attrition in clinic. We have been interested in the mechanism of FXIa inhibition, as this target has the potential for anti-coagulative activity with reduced bleeding liability. Here we will describe our efforts to identify a novel fragment hit, which was then elaborated to identify a series of potent FXIa inhibitors.

8:40 An Alternate Inhibition Mechanism for the Deubiquitinase USP7 and its Consequences for Ubiquitin Chain Linkage Selectivity
Till Maurer, PhD, Director, NMR-Lead, Analytical Enabling Technologies, Merck; formerly: Senior Scientist, Structural Biology, Genentech Inc.

USP7 inhibition is a bona fide P53 stabilization mechanism. Using a fragment based lead discovery approach we found small molecule ligands with a non-active site mechanism to inhibiting USP7. Binders to an acidic patch in the USP7 catalytic domain interfere with the binding of Ubiquitin and Ubiquitin chains. This finding allowed us to delineate how different Ubiquitin chain linkages are recognized and determine that specific interactions are responsible.

9:10 Development of gamma-Secretase Modulators for the Treatment of Alzheimer's Disease
Sponsored by amri
R. Jason Herr, PhD, Research Fellow, Medicinal Chemistry Department, AMRI

Alzheimer's Disease is characterized medically by an accumulation of plaques in the brain composed primarily of a 42-amino acid protein called amyloid β (Aβ42). One therapeutic approach currently being tested in the clinic is to use small molecule drugs to interfere with the function of the enzyme gamma-secretase. This enzyme has several important biological roles, but in the disease state its task is to produce the toxic protein Aβ42. This talk will describe a program designed to develop drugs to disrupt the ability of gamma-secretase to produce Aβ42, but still allow it to carry out its positive functions. One such gamma-secretase modulator (GSM) has moved forward into preclinical testing.

9:25 High-Throughput Fragment Screening by Weak Affinity Chromatography (WAC)
Sponsored by WAC™
Björn Walse, CEO, SARomics Biostructures/Red Glead Discovery

The advantages of WAC™ for FBS are the detection of weak binders by screening fragments at low concentrations (<5 μM) and its immediate ranking of hits. Here we present a USP7 WAC™ screen and its use for rapid establishment of SAR by analogue screening and downstream validation by biophysical techniques.

9:40 Networking Coffee Break

10:05 The Discovery of Novel Allosteric MEK1 Binders by Fragment-Based Approaches
Paolo Di Fruscia, PhD, Senior Scientist, Structure Biophysics & FBLD, Discovery Sciences, IMED Biotech Unit, AstraZeneca UK

MEK1 has been pursued as a target in AZ for the treatment of COPD. To develop structurally novel MEK1 inhibitors, suitable for inhalation strategies, a combination of virtual, biophysical and X-ray fragment screening technologies were explored. The fragment campaign returned several efficient hits co-binding with ATP in a well-established binding site. A few series were progressed and one elaborated into completely novel sub-μM equity.

10:35 Fragment-Based Drug Discovery Campaigns with Protein Complexes that Mediate Protein-Protein Interactions
Charles Wartchow, PhD, Senior Investigator, Novartis Institutes for Biomedical Research

We performed FBS campaigns with protein complexes from several disease areas and proteins involved in protein degradation. These campaigns present unique challenges; hit validation requires important counter screens to identify binding location and data interpretation can be more challenging than for monomeric targets. Methods used in successful campaigns include combinations of SPR, NMR, DSF, XRC and Biodesy's second-harmonic generation (SHG) platform. These methods identify and validate the binding of fragments to key functional regions of proteins and in unexpected locations.

11:05 Busted! Recognizing False Positives and False Negatives: Learnings from Comparative Analysis of Fragment Binding using X-Ray Crystallography and NMR
Engi Hassan, MSc, PhD Fellow, Laboratory of Gerhard Klebe, Pharmaceutical Chemistry, Philipps University in Marburg, Germany

X-ray crystallography provides structural information that is crucial for fragment optimization, however there are several criteria that must be met for a successful fragment screening including the production of soakable and well-diffracting crystals. Frequently, reliable cascades of screening methods are applied as pre-screens prior to labor-intensive X-ray crystallography which appears on first sight a beneficial strategy. We have done follow-up studies to investigate whether different screening methods will reveal similar collections of putative binders. The detailed comparative analysis of the findings obtained by the different methods, including which method is less likely to produce false negatives and false positives, will be presented in the talk.

11:35 Luncheon Presentation: Emerging Topics in Protein Production for Biotechnology: Challenges, Opportunities
Sponsored by FORMA
Tara Davis, PhD, Senior Scientist, X-Ray Crystallography, FORMA Therapeutics

Quality protein production, whether implemented internally or externally, is critical for successful drug discovery. Current trends in biotechnology towards study of difficult protein classes, PPI and allosteric targets, intrinsically disordered regions, biologics, and multi-protein complexes present unique challenges for early discovery protein sciences teams. Addressing these challenges will likely combine innovative modification of existing technologies, thoughtful integration of CRO expertise, and new approaches to pipeline strategy, e.g. utilizing AI/machine learning algorithms to overcome pipeline roadblocks. A broad overview of these topics will be discussed, with the hope of encouraging further discussion throughout the conference.

12:20 pm Session Break

NEW FBDD APPROACHES

1:15 Chairperson's Remarks
Maricel Torrent, PhD, Principal Research Scientist, Molecular Modeling, AbbVie

1:20 Pushing the Envelope for Fragment-Based Drug Discovery (FBDD) with 'MiniFrags'
Marc O'Reilly, DPhil, Senior Director, Molecular Sciences, Astex Pharmaceuticals
This talk will describe how Astex is employing protein crystallography and ultra high concentration, aqueous, MiniFrag ligand soaking to inform early stage drug discovery.

1:50 Fragment Library Design; Quantitative Analysis of Molecular Shape and Functionality
Sponsored by
Paul Colbon, PhD, CEO, UK Headquarters, Liverpool ChiroChem, Ltd.
This presentation introduces the development of a new parameter that guides considerations of vector space within the fragment library design process. This quantitative parameter measures the vector space coverage of the key functionalities (e.g., HBD's, HBA's, lipophilic groups) within a fragment library. Optimally designed libraries achieve the broadest coverage of vector space from the smallest number of compounds.

2:20 Solvation Energy-Driven Docking in Library Design: Applications to Fragment-Based and Fragment-Assisted Approaches
Pawel Sledz, PhD, Senior Scientist, Department of Biochemistry, University of Zurich
Fragment screening libraries suffer from low hit rates, in particular against difficult targets like PPI or proteins interacting with nucleic acids. For the design and assembly of target-focused libraries we developed a very efficient computational screening approach based on evaluation of solvation energies of fragments. By several examples I will illustrate how our approach allows for more efficient exploration of vast chemical space and significantly reduces the costs of early screening efforts, by enriching libraries in potential hits.

2:50 Playing with Water: from Weak Binders to Potent Inhibitors of the Oncogenic Transcription Factor BCL6
Sven Hoelder, PhD, Professor, Medicinal Chemistry and New Drug Design, Institute of Cancer Research
BCL6 is an oncogenic transcriptional repressor that contributes to the pathology of blood cancers, particularly lymphomas and acute leukaemias. Its oncogenic activity relies on the ability to recruit transcriptional co-repressors through its BTB domain. Inhibition of this protein-protein interaction is an attractive therapeutic approach. In this talk, we will present the discovery of nanomolar inhibitors starting from weak binders and particularly highlight the crucial role of water molecules in the binding site.

3:20 The Goldilocks Zone for Research Informatics - Next Generation Tools That Support Discovery Organizations of All Sizes
Sponsored by
Whitney Smith, PhD, Director, Business Development, Collaborative Drug Discovery, Inc.
Unlike traditional informatics that force you to choose between "complete, complicated, and expensive" vs "cheap, easy, and mostly-useless", CDD's Vault and BioAssayExpress affordably deliver comprehensive, secure, easy-to-use, and performant SaaS informatics for discovery teams. We'll discuss how this works and why it's necessary in today's fast-moving and collaboration-heavy research environment.

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

4:30 Welcome Remarks from Lead Conference Director
Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

4:35 Plenary Technology Spotlight: Molecular Modelling for the Masses: Orion
Sponsored by
Paul Hawkins, Head, Scientific Solutions, OpenEye Scientific
The advent of cloud computing has been transformative for many fields that utilize computation, including drug discovery. The cloud offers robust, elastic, and scalable compute resources through a browser, decreased IT overhead, costs, and time to obtain actionable results. In this presentation I illustrate how the cloud, and in particular OpenEye's web-based platform Orion, is democratizing molecular modelling by providing easy to use access to cutting-edge molecular design tools coupled with essentially unlimited compute resources.

5:05 Plenary Keynote Introduction
Vicky Steadman, PhD, Business Line Leader, Integrated Drug Discovery, Eurofins Discovery (formerly Eurofins Pharma Discovery Services)

5:10 Plenary Keynote:

Chemical Biology of Proteostasis
Jack Taunton, PhD, Professor, Department of Cellular and Molecular Pharmacology, University of California San Francisco
We have recently discovered several macrocyclic compounds that potently and selectively modulate protein homeostasis. I will discuss our recent efforts to unravel their molecular mechanisms.

6:00 Welcome Reception in the Exhibit Hall with Poster Viewing

7:00 Close of Day

WEDNESDAY, APRIL 10

7:30 am Continental Breakfast Breakout Discussions
See website for details.

FRAGMENT-DERIVED DRUG CANDIDATES PROGRESSING IN THE CLINIC

8:30 Chairperson's Remarks
Robert D. Mazzola, PhD, Director, Chemical Research, Merck Research Labs

8:35 FEATURED PRESENTATION: Discovery of ABL001, an Allosteric Inhibitor of Bcr-Abl Kinase

Wolfgang Jahnke, PhD, Director and Leading Scientist, Chemical Biology and Therapeutics, Novartis Institutes for Biomedical Research
The team effort that led to the discovery and early development of ABL001 will be described. Discovery of ABL001 started with a fragment-based screen using NMR spectroscopy and X-ray crystallography. An NMR-based conformational assay was needed to understand the requirements for functional inhibition of fragments. Structure-based design and medicinal chemistry finally resulted in the clinical candidate ABL001, which is currently in phase III trials of chronic myelogenous leukemia.

9:05 BACE Inhibitor Drug Discovery - From Fragment-Based Hits to Clinical Candidates

Erik J. Hembre, PhD, Research Fellow, Discovery Chemistry Research, Eli Lilly & Co.

Fragment based drug discovery is a powerful technique to identify starting points for difficult to drug targets. A case in point is BACE1, a key enzyme involved in the production of amyloid-beta peptides and the amyloid plaques associated with Alzheimer's disease. Enabled by a fragment-based approach, we identified a weak but efficient amino-thiazine hit structure that ultimately led to the delivery of three BACE1 clinical candidates, LY2811376, LY2886721, and LY3202626.

9:35 Coffee Break in the Exhibit Hall with Poster Awards Announced

Poster Awards Sponsored by Domainex

FRAGMENTS AND PPIs

10:30 FEATURED PRESENTATION: Molecular Glues for Protein-Protein Interactions: A Fragment-Based Approach to Stabilize 14-3-3/Client Complexes

Michelle Arkin, PhD, Professor, Department of Pharmaceutical Chemistry, University of California San Francisco

Many proteins have multiple binding partners, potentially inducing different biological effects. Stabilizing such protein-protein interactions offers an opportunity to dial in specificity for both partners, and can be inhibitory, activating, or synthetic. Our team is developing specific stabilizers of 14-3-3/client proteins to evaluate the scope and limitations of these effects. This talk will describe our initial foray in the 14-3-3 stabilization using fragment-based drug discovery approaches.

11:00 Biophysics and Structural Biology offer a Direct Path to Allosteric Drugs

Gregg Siegal, CEO, ZoBio

Allosteric drugs offer exciting new opportunities. ZoBio's platform of biophysics and structural biology allows us to design campaigns that directly seek allosteric modulators of pharmaceutical targets. I will illustrate this capability using HSP70 as an example. HSP70 is a validated target in both oncology and neurodegeneration and yet, has proven challenging to drug. The process used to develop compounds that are selective for the ADP-bound form and inhibit ATPase activity will be described.

11:30 Fragment Philosophy Used in the Identification of eFT508, an Oral, Potent and Highly Selective Inhibitor of Mitogen-Activated Protein Kinase Interacting Kinase (MNK) 1 and 2

Paul Sprengeler, PhD, Research Fellow, Medicinal Chemistry, eFFECTOR Therapeutics, Inc.

Starting from a handful of fragments and fragment-like molecules, the crystal structure-guided approach, leveraging stereoelectronic interactions, to eFT508, an exquisitely selective, potent dual MNK1/2 inhibitor, will be presented. eFT508 was designed to assess the potential for control of oncogene signaling at the level of mRNA translation and has shown potent *in vivo* anti-tumor activity in models of DLBCL and solid tumors. It is currently being evaluated in Phase 2 clinical trials in solid tumors and lymphoma.

12:00 pm Close of Conference

INAUGURAL

Directed Evolution-Based Drug Discovery

DNA Encoded Libraries and Other Diversity Oriented Platforms

April 9-10, 2019 | San Diego Convention Center | San Diego, CA

TUESDAY, APRIL 9

7:00 am Registration Open and Morning Coffee

DIVERSITY-ORIENTED PLATFORMS

8:00 Welcome Remarks

Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks

Sepideh Afshar, PhD, Principal Research Scientist, Department of Protein Engineering, Eli Lilly and Company

---

8:10 FEATURED PRESENTATION: One Bead One Compound Introduction and Innovations: Library against Library Screening

Kit S. Lam, MD, PhD, Distinguished Professor and Chair, Department of Biochemistry and Molecule Medicine, University of California Davis

I start with an overview of the one-bead-one-compound (OBOC) platform which enables rapid creation of chemically encoded high diversity combinatorial synthetic peptide, peptidomimetic, macrocyclic or small molecule libraries on micro-beads. Such libraries can then be efficiently screened for binding against molecular targets such as soluble proteins, phages, bacteria, and live cells. Screening can also be achieved with cell-based assays for cellular functions and signaling. I end by describing a method to greatly increase the diversity of molecular interactions, by using a phage-display protein domain library derived from cancer cells as probes to screen encoded OBOC small molecule libraries.

9:10 Unleashing DNA-Encoded Library Technology: Drug Discovery and Beyond

Sponsored by 药明康德 WuXi AppTec

Letian Kuai, PhD, Senior Director, Head of Biology & Informatics, WuXi AppTec

DNA Encoded Library (DEL) technology offers an unprecedented capability for researchers to synthesize and analyze numerically large chemical libraries to identify hits rapidly with very low cost. The natural strength of this technology to discover affinity molecules with SAR could lead to a wide range of potential applications.

9:40 Networking Coffee Break

10:05 Challenges and Emerging Approaches in Peptide Phage Display and its Application in Targeting Stem Cell Receptors

Rami Hannoush, Principal Scientist & Group Leader, Early Discovery Biochemistry, Genentech Inc.

10:35 FEATURED PRESENTATION: Unnatural Amino Acids for Exotic Macrocyclic Peptides and Targeting IL6R as a Case Study

Hiroaki Suga, PhD, Professor, Department of Chemistry, School of Science, The University of Tokyo

This talk discusses recent advances in the discovery of bioactive macrocyclic pseudo-natural peptides containing exotic amino acids using a discovery platform, the RaPID system. This system enables for extremely "rapid" affinity-based screening of pseudo-natural peptides against proteins of interest from a library consisting of a trillion different short sequences, usually less than 15 residues. Yet the discovered molecules exhibit remarkable bioactivity, often single digit nM or sub nM of dissociation constants.

11:35 Luncheon Presentation: Synthetic Biology and the Vital Role of Intellectual Property

Sponsored by patsnap

Christopher Bustos, Solutions Consultant, PatSnap

12:20 pm Session Break

DNA-ENCODED LIBRARIES (DEL)

1:15 Chairperson's Remarks

Svetlana Belyanskaya, PhD, Encoded Library Technologies, R&D Platform Technology & Science, GSK Boston

1:20 Discovery and Optimization of Potent and Selective TYK2 Pseudokinase Inhibitors through DNA-Encoded Library Technology

Ghotas Evindar, PhD, Head, Drug Design and Selection, Medicinal Science & Technology, GlaxoSmithKline

DNA-encoded chemical library screening is an established platform for identifying hits for therapeutic targets. At GSK the platform is utilized broadly to screen a wide range of therapeutic targets than any other screening methods including HTS. Herein, I will provide an overview of the ELT platform followed by a case study application of the platform to the discovery of a potent and selective class of TYK2 pseudokinase inhibitors. The talk will also describe hit to lead optimization of the chemical series through use of both ELT selection data and an obtained X-ray crystal structure of an early lead molecule.

1:50 Activity-Based DNA-Encoded Libraries Screening Technology

Brian Paegel, PhD, Associate Professor, Department of Chemistry, Department of Molecular Medicine, Scripps Research

Combinatorial DNA-encoded library (DEL) technology surveys vastly larger and more diverse chemical spaces than standard HTS collections, but relies on affinity selection to identify hits. We have developed solid-phase DEL synthesis protocols and engineered microfluidic screening technology for conducting activity-based screens using these DELs. I will describe screening results against several common target enzyme classes as well as *in vitro* translation as a stepping stone toward cellular screening.

2:20 Employing Photoredox Catalysis for the Synthesis of DNA-Encoded Libraries

Dominik Koelmel, PhD, Senior Scientist, DNA-Encoded Libraries, Pfizer

The development of photoredox catalysis has had a profound impact on the synthetic chemistry community, allowing for the facile preparation of complex compounds from rather simple and readily available starting materials. However, photoredox catalysis has hitherto not been used in the context of DNA-encoded chemistries. Our first proof-of-concept studies have now demonstrated that photoredox catalysis can be a valuable reaction platform for the preparation of DNA-encoded libraries (DELs).

2:50 Panel Discussion: 25 Years of DNA Encoded Libraries: Where are We?

Sponsored by HITGEN

Moderator: Barry Morgan, PhD, CSO, HitGen

Panelists:

Dean G. Brown, PhD, Director, External Chemistry, Hit Discovery, Discovery Sciences, IMED Biotech Unit, AstraZeneca

Ghotas Evindar, PhD, Head, Drug Design and Selection, Medicinal Science & Technology, GlaxoSmithKline

Brian Paegel, PhD, Associate Professor, Department of Chemistry, Department of Molecular Medicine, Scripps Research

Hiroaki Suga, PhD, Professor, Department of Chemistry, School of Science, The University of Tokyo

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

Sponsored by SYGNATURE DISCOVERY

4:30 Welcome Remarks from Lead Conference Director
Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

4:35 Plenary Technology Spotlight: Molecular Modelling for the Masses: Orion

Sponsored by OpenEye SCIENTIFIC

Paul Hawkins, Head, Scientific Solutions, OpenEye Scientific
The advent of cloud computing has been transformative for many fields that utilize computation, including drug discovery. The cloud offers robust, elastic, and scalable compute resources through a browser, decreased IT overhead, costs, and time to obtain actionable results. In this presentation I illustrate how the cloud, and in particular OpenEye's web-based platform Orion, is democratizing molecular modelling by providing easy to use access to cutting-edge molecular design tools coupled with essentially unlimited compute resources.

5:05 Plenary Keynote Introduction
Vicky Steadman, PhD, Business Line Leader, Integrated Drug Discovery, Eurofins Discovery (formerly Eurofins Pharma Discovery Services)

5:10 PLENARY KEYNOTE:

Chemical Biology of Proteostasis
Jack Taunton, PhD, Professor, Department of Cellular and Molecular Pharmacology, University of California San Francisco
We have recently discovered several macrocyclic compounds that potently and selectively modulate protein homeostasis. I will discuss our recent efforts to unravel their molecular mechanisms.

6:00 Welcome Reception in the Exhibit Hall with Poster Viewing

7:00 Close of Day

WEDNESDAY, APRIL 10

7:30 am Continental Breakfast Breakout Discussions
See website for details.

ENCODED LIBRARY APPROACHES

8:30 Chairperson's Remarks
Brian Paegel, PhD, Associate Professor, Department of Chemistry, Department of Molecular Medicine, Scripps Research

8:35 Finding the Right Fit: An *in vitro* Selection Approach for Optimizing Peptide Scaffolds for the Discovery of Peptide Leads
Matt Hartman, PhD, Associate Professor, Chemistry, Masey Cancer Center, Virginia Commonwealth University
Diverse libraries of macrocyclic peptides are a potential storehouse for therapeutic reagents against many different PPI targets. But it is often challenging to predict what the best macrocyclic scaffold would be for a particular target. Using mRNA display, we have generated trillions of cyclic and bicyclic peptides encompassing a variety of topologies. We have then used these libraries to select protein binders. The hits exhibit interesting and unique scaffold preferences.

9:05 Characterization of Specific Naa50 Inhibitors Identified using a DNA Encoded Library: a Lead-Finding Case Study for a Challenging Target
Pei-Pei Kung, PhD, Associate Research Fellow, Medicinal Chemistry, Pfizer San Diego
The catalytic site of Naa50 enzyme is considered difficult to drug because of its large binding site and lower hydrophobicity compared to typical druggable targets. We screened a 22 billion-member DNA-encoded library to identify novel Naa50 inhibitors. This provided several hits that were confirmed to be specific Naa50 binders/inhibitors. Crystal structures of these hits in complex with the Naa50 protein were obtained that helped explain their mechanism of action.

9:35 Coffee Break in the Exhibit Hall with Poster Awards Announced
Poster Awards Sponsored by Domainex

ENCODED LIBRARY APPLICATIONS

10:30 Design and Evolution of Macrocyclic Peptide Inhibitors of the Hedgehog Signaling Pathway
Rudi Fasan, PhD, Professor, Department of Chemistry, University of Rochester
The Hedgehog signaling pathway plays a central role during embryonic development and its aberrant activation has been implicated in the development and progression of several human cancers. This talk will describe the design and evolution of macrocyclic peptides capable of inhibiting the Hedgehog pathway by targeting and disrupting the Hedgehog protein/Patched interaction, the most upstream event in the ligand-induced activation of this cell signaling pathway.

11:00 NEW: Engineered TrpB Biocatalysts for the Modular Synthesis of Noncanonical Amino Acids
David K. Romney, PhD, Postdoctoral Fellow, Laboratory of Frances Arnold, Division of Chemistry and Chemical Engineering, California Institute of Technology
Noncanonical amino acids (ncAAs) are widely used as pharmaceutical precursors and biological probes. However, they often require multi-step synthetic routes that involve expensive transition-metal catalysts and hazardous reaction conditions. Consequently, many ncAAs are not commercially available or are prohibitively expensive. By using protein engineering techniques such as directed evolution, we developed a suite of biocatalysts based on the tryptophan synthase β-subunit (TrpB). These catalysts provide direct access to almost 100 ncAAs from readily available materials.

11:30 DEL for Membrane Proteins: Case Study of a GPCR
Dean G. Brown, PhD, Director, External Chemistry, Hit Discovery, Discovery Sciences, IMED Biotech Unit, AstraZeneca
This talk compares a DNA-encoded library screen to identify antagonists at protease activated receptor (PAR2) with a fragment screen using a stabilized PAR2 GPCR receptor. From these efforts, we identified two lead series of compounds, each of which bind to distinct and previously unknown allosteric sites. These results illustrate the power of integrating stabilized GPCR technologies into established screening paradigms.

12:00 pm Close of Conference

2ND ANNUAL

Modulating the Ubiquitin-Proteasome System

Novel Tools and Compounds to Target DUBs, Ligases and Other Proteins

April 10-11, 2019 | San Diego Convention Center | San Diego, CA

WEDNESDAY, APRIL 10

12:30 pm Registration Open

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

EXPLOITING THE UPS FOR TARGETED PROTEIN DEGRADATION

1:30 Welcome Remarks
Tanuja Koppal, PhD, Conference Director

1:35 Chairperson's Opening Remarks
Eric Fischer, PhD, Assistant Professor, Cancer Biology, Dana-Farber Cancer Institute/Harvard Medical School

1:40 Principles of Small Molecule Mediated Ubiquitin Ligase Targeting
Eric Fischer, PhD, Assistant Professor, Cancer Biology, Dana-Farber Cancer Institute/Harvard Medical School

Small molecules that induce protein degradation through ligase-mediated ubiquitination have shown considerable promise as a new pharmacological modality. Thalidomide and related IMiDs provided the clinical proof of concept, while significant progress has recently been made towards chemically induced targeted protein degradation using heterobifunctional small molecule ligands. I will present recent work towards a better understanding of the molecular principles that govern neo-substrate recruitment and its application to the development of small molecule degraders.

2:10 New Screening Technologies and Chemical Probes Targeting the Ubiquitin System: Inhibitors, Activators, and Degraders
Alexander Statsyuk, PhD, Assistant Professor, Department of Pharmacological and Pharmaceutical Sciences, University of Houston

Two major principles of targeting the ubiquitin system have emerged: direct targeting of the enzymes that control protein ubiquitination and hijacking E3 ligases to induce protein degradation. In this lecture, I will outline novel screening tools and technologies to discover small molecule inhibitors/activators and hijackers for RBR/HECT E3 ligases. I will show how UbFluor technology can be used to identify nanomolar inhibitors of HECT E3 ligases, thus validating UbFluor technology as a tool to discover HECT E3 ligase inhibitors.

2:40 Expanding the Druggable Target Space - Degrading a Multi-Functional Transcriptional Regulator
Lara Gechijian, PhD, Scientist/Project Lead, Jnana Therapeutics; Former Graduate Student, Laboratory of Drs. James Bradner/Nathanael Gray, Harvard Medical School

There has been limited success targeting transcription with small organic molecules because many transcriptional regulators are not amenable to conventional therapeutic approaches, as their ligandable domain may not be functionally relevant in disease. Because potent ligands of the bromodomain of TRIM24 are ineffectual in contexts of TRIM24 genetic dependence, we repurposed the potent ligands of the TRIM24 bromodomain as the TRIM24 targeting-ligand component of heterobifunctional degraders to orchestrate the recruitment of TRIM24 to the E3 ubiquitin ligase machinery.

3:10 Solving a 60-Year Mystery: SALL4 Mediates Teratogenicity as a Thalidomide-Dependent Substrate of Cereblon
Mary Matyskiela, PhD, Principal Scientist, Structural and Chemical Biology, Celgene

Targeted protein degradation through small molecule modulation of cereblon offers vast potential for new therapeutics, but cereblon-binding molecules carry the safety risks of thalidomide, which caused an epidemic of severe birth defects in the 1950s. We identify SALL4 as a thalidomide-dependent cereblon substrate whose degradation phenocopies genetic embryopathies caused by SALL4 mutation. This work expands the scope of cereblon neosubstrates and offers a path towards safer therapeutics through understanding the molecular basis of thalidomide-induced teratogenicity.

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

4:30 SPOTLIGHT PRESENTATIONS: Development of Small Molecule Protein Degraders as New Therapeutic Modalities

Applying Enzymology Concepts to the Optimization of Targeted Protein Degraders
Stewart Fisher, PhD, CSO, C4 Therapeutics

Targeted Degradation of IRAK4 Protein Via Heterobifunctional Small Molecules for Treatment of MYD88 Mutant Lymphoma
Nan Ji, PhD, Executive Director, Head of Chemistry, Kymera Therapeutics

Protein Degradation Beyond Bi-functional Degraders
Michal Walczak, PhD, CSO, Captor Therapeutics

5:30 Breakout Discussions
See website for details.

6:15 Close of Day

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

THURSDAY, APRIL 11

8:00 am Breakfast Presentation *(Sponsorship Opportunity Available)* **or Morning Coffee**

8:45 Welcome Remarks from Lead Conference Director
Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

8:50 Plenary Keynote Introduction
Timothy Craig, PhD, HarkerBio

Sponsored by

8:55 PLENARY KEYNOTE:

New Ways of Targeting K-Ras
Frank McCormick, PhD, Professor, HDF Comprehensive Cancer Center, University of California San Francisco

Efforts to find drugs that bind K-Ras directly have increased recently, enabled by NMR-based fragment screening, di-sulfide tethering, *in silico* drug design and biophysical methods such as Second Harmonic Generation (SHG). We will report progress on attacking two sites in the K-Ras protein; cysteine-185 (the site of prenylation), and histidine-95, a residue unique to K-Ras, to develop covalent K-Ras inhibitors, as well as compounds identified by SHG and other methods.

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

UNDERSTANDING AND OPTIMIZING THE USE OF PROTACs

10:40 Chairperson's Remarks
Peter Dragovich, PhD, Staff Scientist, Discovery Chemistry, Genentech

10:45 FEATURED PRESENTATION: Small Molecule-Induced Protein Degradation with Proteolysis Targeting Chimeric Molecules (PROTACs)

Markus Queisser, PhD, Scientific Leader, Protein Degradation DPU, R&D Future Pipelines Discovery, GlaxoSmithKline

The advantages of the PROTAC technology lie in its modular, rationally designed molecules, capable of producing potent, selective and reversible cellular protein knock-down as

demonstrated in both cellular and *in vivo*. The removal of a disease-causing protein is an attractive therapeutic option. This presentation aims to highlight the potential of PROTACs in drug discovery with a focus on their challenges from our perspective.

11:15 Lessons from Viral Hijacking of Ubiquitin-Mediated Protein Degradation

Yue Xiong, PhD, William R. Kenan Professor of the Biochemistry and Biophysics, University of North Carolina; Co-Founder, Cullgen

Virus has learned the use of ubiquitin-proteasome system to overcome the host cellular defense, which provides us insight into the small molecule design to induce target protein degradation for drug discovery. Understanding ternary structure of viral/E3 complex will enhance the success rate of degraders. Protein-protein interaction between viral protein and E3 ligases may also lead us to the discovery of new E3 ligand.

11:45 Targeting Deubiquitylases (DUBs): Opportunities for Collaborative Drug Discovery

Sponsored by UBIQUIGENT

Jason Brown, PhD, Scientific and Business Development Director, Ubiquigent Ltd.

We will discuss Ubiquigent's deubiquitylase (DUB) enzyme targeting small molecule hit-to-lead platform featuring: Our in-house DUB-targeting computational and medicinal chemistry capability and a comprehensive small molecule assay workflow featuring our widely accessed DUBprofiler™ and REDOXprofiler™ service platforms.The company also has significant capabilities to target other ubiquitin system proteins – including E3 ligases – and is developing a platform to provide PROTAC hit-to-lead SAR support. Commercial access models: Ubiquigent is providing access to its comprehensive capabilities to execute early stage hit-to-lead projects via our Collaborative Drug Discovery programme. Individual services may also be accessed via Fee For Service (FFS) or FTE routes.

12:00 pm Antibody-Mediated Delivery of Protein Degraders

Peter Dragovich, PhD, Staff Scientist, Discovery Chemistry, Genentech

Chimeric Chemical Inducers of DEgradation (CIDEs) which effect intracellular degradation of target proteins via E3 ligase-mediated ubiquitination are currently of high interest in medicinal chemistry. However, these entities are relatively large compounds that often possess molecular characteristics which may compromise oral bioavailability, solubility, and/or *in vivo* pharmacokinetic properties. Accordingly, we explored whether conjugation of CIDEs to monoclonal antibodies using technologies originally developed for cytotoxic payloads might provide alternate delivery options for these novel agents.

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

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

Poster Awards Sponsored by Domainex

TARGETING DUBs AND LIGASES

2:15 Chairperson's Remarks

Domagoj Vucic, PhD, Principal Scientist, Early Discovery Biochemistry, Genentech

2:20 Multiple Therapeutic Actions of USP7 Inhibitors: Impairment of FOXP3+ Treg Function and Direct Effects on Tumor Cell Metabolism and DNA Damage Responses

Wayne W. Hancock, MD, PhD, Professor, Pathology and Chief of Transplant Immunology, Children's Hospital of Philadelphia and University of Pennsylvania

With relevance to a critical unmet need in immune-oncology, we have shown that USP7 is a key target for therapeutic regulation of Foxp3+ Treg cells through its regulation of Tip60 expression. We now provide evidence of direct effects of Tip60 inhibitors (Tip60i) and USP7 inhibitors (USP7i) on tumor cells, including modulation of tumor cell metabolism and impairment of the DNA damage response (DDR). These dual mechanisms of action provide a compelling rationale for USP7i use in oncology.

2:50 Pharmacological Assessment of Potent, Selective, and Orally Bioavailable USP7 Inhibitors

Dennis Hu, PhD, Senior Scientist, FLX Bio

USP7 is a deubiquitinase (DUB) that has been reported to regulate the levels of multiple proteins with roles in cancer progression and immune response, including MDM2 and FOXP3. Using a structure-based drug design strategy, we have identified reversible USP7 inhibitors that are highly potent in biochemical and cellular assays and are >10,000 fold selective for USP7 over other DUBs. Potent and selective USP7 inhibitors with excellent oral pharmacokinetic properties were used to assess the pharmacologic effects of USP7 inhibition *in vitro* and *in vivo*.

3:20 Structures of the Substrate-engaged Proteasome

Andres Hernandez, PhD, Research Fellow, The Scripps Institute

As the primary eukaryotic proteolytic machine, the 26S proteasome is responsible for ubiquitin-mediated degradation of misfolded, damaged, or obsolete proteins. We determined several structures of the proteasome as it actively translocated substrate. These structures reveal the mechano-chemical coupling of ATP hydrolysis to substrate translocation. Additionally, these structures suggest a co-translocational deubiquitination mechanism that positions ubiquitin and its isopeptide scissile bond in the Rpn11 deubiquitinase.

3:50 Networking Refreshment Break

EMERGING UBIQUITIN TARGETS FOR THERAPEUTIC INTERVENTION

4:20 Engineered Ubiquitin Variants for Inhibition and Activation of the Ubiquitin Proteasome System

Sachdev Sidhu, PhD, Professor, Donnelly Centre and Department of Molecular Genetics, University of Toronto

Despite the central importance of the ubiquitin proteasome system in virtually every biological process, inhibitors for the hundreds of component enzymes are severely limited. We have devised a general strategy for using engineered ubiquitin variants to rapidly develop tight and specific binders for virtually any protein that associates with ubiquitin. This approach has yielded numerous inhibitors, and in some cases activators, for deubiquitinases, E2 enzymes, E3 ligases, and non-catalytic docking modules. These tools have proven valuable for cell biology, structural studies, and drug target validation.

4:50 Conformation, Complexation, and Catalysis in the AAA+ ATPase p97/VCP

Michelle Arkin, PhD, Professor, Department of Pharmaceutical Chemistry, University of California San Francisco

Valosin Containing Protein (VCP, p97) is an AAA+ ATPase involved in several aspects of protein homeostasis, including ER-associated degradation, segregation of proteins from complexes, and membrane remodeling. This spectrum of activities is governed by protein-protein interactions between p97, adaptor proteins, and ubiquitin-processing enzymes. p97 function is furthermore modulated by ATPase activity and conformational changes throughout the protein's barrel structure. We will compare inhibitors of p97 that act through different mechanisms and consequently modulate different aspects of p97 function.

5:20 Targeting Ubiquitin Ligases in Inflammatory Diseases

Domagoj Vucic, PhD, Principal Scientist, Early Discovery Biochemistry, Genentech

Disbalance in cellular signaling and cell death lead to unregulated cell death and cytokine production and contribute to numerous inflammatory diseases. RIP2 ubiquitination is critically associated with NOD2 signaling and production of pro-inflammatory cytokines. Selective targeting of RIP2 E3 ligase XIAP or RIP2 kinase inhibition can efficiently block NOD2 signaling and cytokine production. Collectively, our studies define major events regulating cell death and inflammatory signaling and contribute to development of anti-inflammatory and tissue protective treatments.

5:50 Close of Conference

Inflammation Inhibitors

Medicinal Chemistry for Oral-Based Autoimmune and Inflammation Related Therapeutics

April 10-11, 2019 | San Diego Convention Center | San Diego, CA

WEDNESDAY, APRIL 10

12:30 pm Registration Open

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

INTRACELLULAR KINASE INHIBITORS (AND MORE) FOR INFLAMMATION AND AUTOIMMUNITY

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

1:35 Chairperson's Opening Remarks
Phillip Schwartz, PhD, Associate Principal Scientist, Pharmacology, Merck Research Laboratories

---

1:40 FEATURED PRESENTATION: Discovery of a Cross-Species Potent and Selective Inhibitor of Receptor-Interacting Protein Kinase (RIPK1) Providing Protection in a Number of Immunological Models

Snahel Patel, PhD, Scientist, Discovery Chemistry, Genentech, Inc.
Regulation of cell death signaling is critical for the maintenance of homeostasis and prevention of disease. Necroptosis, a caspase-independent regulated form of cellular death, is emerging as an important mediator of a number of human pathologies. Activation of necroptotic signaling through TNF signaling or organ injury activates RIPK1 and RIPK3 leading to inflammatory cell death. We present the development of a cross-species potent and selective small molecule inhibitor of RIPK1 to explore the prevention of cell death in a number of disease models of inflammation.

2:10 Considerations in the Generation of Covalent BTK Inhibitors
Noel S. Wilson, MSc, Senior Scientist III, Discovery Chemistry and Technology, AbbVie
Bruton tyrosine kinase (BTK) plays a central role in signaling from the B-cell receptor, which has prompted the development of small-molecule BTK inhibitors for the treatment of autoimmune conditions. The design strategy of irreversible kinase inhibitors, as well as the extensive modeling and crystallographic support which allowed rapid progress of the program into the clinic, will be disclosed. The culmination of these strategies identified ABBV-105, a selective, covalent inhibitor that is efficacious in a preclinical model for RA.

2:40 Protein Binding Pockets Design Strategy to Enable Prospective Lead Discovery
Gerard Rosse, PhD, President, Arrival Discovery LLC
The presentation will focus on exploiting 3D protein surface information of multiple protein families such as GPCRs, Kinases, PDEs and PPIs to generate a prospective small molecule collection. This pocketome approach is combined with advanced automation technologies for chemistry, purification and compound management to expedite lead finding and maximize drug discovery. The value of an industrial approach to interrogate allosteric and orthosteric protein binding sites for intelligent design of small molecules and the changing landscape of automated chemistry and Super Critical Fluid chromatography within modern medicinal chemistry to reduce costs and increase prodcutivity, will be examplified with case studies of exploratory phase programs.

3:10 Targeting Inflammation with RIPK1 Inhibition
Allison Beal, PhD, Manager and Associate Fellow, Innate Immunity RU, GlaxoSmithKline

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

4:30 Inhibition of Autoimmune Pathways with Dual Inhibition of JAK1 and TYK2: Discovery of PF-06700841
Andrew Fensome, PhD, Associate Research Fellow, Medicines Design, Pfizer
The Janus (JAK) kinases are a family of four non-receptor tyrosine kinases that modulate cytokine signaling through the Signal and Transduction of Transcription (STAT) pathways. The JAK kinases (JAK1, JAK2, JAK3 and TYK2) are important in a variety of cell types in the innate and adaptive immune system. I describe a series of selective JAK1/ TYK2 inhibitors for a range of inflammatory disorders such as inflammatory bowel disease, systemic lupus erythematosus and psoriasis. An important part of our program has been our understanding of PK:PD developed from our extensive experience with tofacitinib (Xeljanz ™) in the clinic and in preclinical animal models. The lead is a well behaved molecule with excellent in-vitro potency and a superior off-target poly-pharmacology profile. PF-06700841 is currently in Phase 2 clinical study.

5:00 Oral Integrin-Specific Peptide Antagonists for Ulcerative Colitis
Larry Mattheakis, PhD, Vice President, Biology, Protagonist Therapeutics

5:30 Breakout Discussions
See website for details.

6:15 Close of Day

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

THURSDAY, APRIL 11

8:00 am Breakfast Presentation *(Sponsorship Opportunity Available)* **or Morning Coffee**

8:45 Welcome Remarks from Lead Conference Director
Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

8:50 Plenary Keynote Introduction

Sponsored by

8:55 PLENARY KEYNOTE:

New Ways of Targeting K-Ras
Frank McCormick, PhD, Professor, HDF Comprehensive Cancer Center, University of California San Francisco
Efforts to find drugs that bind K-Ras directly have increased recently, enabled by NMR-based fragment screening, di-sulfide tethering, *in silico* drug design and biophysical methods such as Second Harmonic Generation (SHG). We will report progress on attacking two sites in the K-Ras protein; cysteine-185 (the site of prenylation), and histidine-95, a residue unique to K-Ras, to develop covalent K-Ras inhibitors, as well as compounds identified by SHG and other methods.

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

NEW INFLAMMATION TARGETS FOR SMALL MOLECULES

10:40 Chairperson's Remarks
Snahel Patel, PhD, Scientist, Discovery Chemistry, Genentech, Inc.

10:45 Pharmacological Regulation of the Keap1-NRF2 System Unveils Mitochondrial Targeting in Inflammation
Michelangelo Campanella, PhD, PharmD, Professor and Unit Head, Mitochondrial Cell Biology and Pharmacology, Research Group RVC and

University College London Consortium for Mitochondrial Research

My talk will report upon Nrf2 inducers as pharmacological tolls in mitochondrial quality control operated by targeted autophagy. It will also dwell on their targeting of mitochondrial pathways which define autoimmunity and inflammation. The presentation will therefore elaborate on the prominent in cell activity of the non-covalent Keap1-Nrf2 protein-protein interaction (PPI) inhibitor PMI, structurally distinct from the covalent Keap1 modifiers (e.g., sulforaphane) and highlight promising ligands targeting mitochondrial pathways involved in the inflammatory response.

11:15 Novel Small Molecule E3 Ligase Activators as Anti-Inflammatory Agents

Kumar Suresh, PhD, Senior Director, R&D Biology, Progenra, Inc.

In this talk, I will present for the first time discovery and characterization of novel E3 ligase activators that suppress TH2 and TH17 differentiation and exhibit robust anti-inflammatory properties. Nedd4-family E3 ligases, including Itch, negatively regulate inflammatory immune responses by suppressing TH2 and TH17 differentiation and cytokine production. Genetic disruption of Itch leads to the development of multi-system immune disorders and lung inflammation.

11:45 CETSA® Enabled Drug Discovery

Sponsored by PELAGO BIOSCIENCE

Michael Dabrowski, PhD, CEO, Pelago Bioscience

CETSA allows quantification of target engagement under relevant physiological conditions, which is prerequisite for achieving the intended efficacy. Over the last 8 years CETSA has been applied in hundreds of studies from early target validation to analysis of clinical samples. In his talk Michael will explore examples of applications and also discuss future perspectives in enabling drug discovery using the CETSA method.

12:00 pm Targeting TRAF6 E3 Ligase Activity with Small Molecules Combats Chronic Inflammation and Autoimmunity

Kamyar Hadian, PhD, Group Leader, Helmholtz Zentrum München

Constitutive NF-κB signaling represents a hallmark of chronic inflammation and autoimmune diseases. The E3 ligase TRAF6 acts as a key regulator bridging innate immunity, pro-inflammatory cytokines, and antigen receptors to the NF-κB pathway. Here, we present an inhibitor of TRAF6-Ubc13 interaction that reduces TRAF6 activity *in vitro* and in cells. Importantly, this inhibitor ameliorated inflammation and improved disease outcomes of autoimmune psoriasis and rheumatoid arthritis in preclinical mouse models.

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

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

Poster Awards Sponsored by Domainex

TARGETING THE INNATE IMMUNE SYSTEM

2:15 Chairperson's Remarks

Daniel Dairaghi, PhD, Senior Research Advisor, Medicinal Chemistry, Eli Lilly & Co.

2:20 Bacterial Mediated Chemical Transformations of Autoimmune Drug Metabolism

Jason Michael Crawford, PhD, Associate Professor, Departments of Chemistry and Microbial Pathogenesis, Yale University

Photorhabdus asymbiotica causes soft tissue infections of the skin. This bacterium produces the immunomodulator tapinarof during its pathogenic phase. Tapinarof is in phase 3 clinical trials to treat the skin disorders psoriasis and atopic dermatitis. We demonstrate that bacteria can transform tapinarof into other novel potent products that activate the pathways associated with clinical efficacy and kill inflammatory bacteria of the skin.

2:50 Discovery of Novel and Potent Spirocyclic RORγt Inhibitors

Chip Lugar, Senior Research Scientist, Discovery Chemistry Research, Eli Lilly and Company

RORγt is a ligand dependent transcription factor that serves as the master regulator of Th17 and other IL-17 producing immune cells. It has become an important target for the treatment of autoimmunity, especially conditions that respond to anti-IL-17 antibodies such as psoriasis. A screening effort yielded substituted 4',5'-dihydrospiro[piperidine-4,7'-thieno[2,3-c]pyran]-2'-carboxamides. We will present optimization of this novel spirocyclic scaffold from a weak screening hit to a potent RORγt inhibitor for use *in vivo* studies to define the level and duration of target engagement required for efficacy.

3:20 Targeting ROR and Other Nuclear Hormone Receptors: Chemistry Challenges and Beyond

Scott Thacher, PhD, CEO, Orphagen

This presentation will cover the chemistry challenges we've faced targeting nuclear hormone receptor for inflammation and cancer. A sub-theme will be "finding the right indication for druggable nuclear receptors." I will also discuss our second-in-line program for antagonists to steroidogenic factor-1 (NR5A1).

3:50 Networking Refreshment Break

4:20 NEW: Breakout Discussion Report-Outs

Daniel Dairaghi, PhD, Senior Research Advisor, Medicinal Chemistry, Eli Lilly & Co.
Derek Cole, PhD, Senior Director, GI Medicinal Chemistry, Gastroenterology Drug Discovery Unit, Takeda Pharmaceuticals

4:50 Targeting Soluble TNF to Eliminate Chronic Inflammation without Immunosuppression

RJ Tesi, MD, CEO/CMO, Inmune Bio

INB03 is a selective inhibitor of soluble TNF that is a potent anti-inflammatory agent that is not immunosuppressive. Current drug development leverages that important biology as part of therapy for cancer, neurodegenerative diseases and NASH. INB03 is significantly different from existing non-selective TNF inhibitors that block both soluble TNF (the BAD TNF) and trans-membrane TNF (the GOOD TNF). This difference makes all of the difference in safety, efficacy and therapeutic opportunity.

5:20 GSNOR Inhibitors for Inflammatory, Auto-Immune, and Oxidative Stress Based Diseases: RA, IBD, and NASH

Matthews O. Bradley, PhD, Chairman, President and Founder, SAJE Pharma, LLC

S-nitrosoglutathione Reductase (GSNOR) regulates nitrosylation signal transduction pathways and is over-expressed in many inflammatory human diseases. We identified, using X-ray crystallography and predictive *in vitro* assays, inhibitors of GSNOR that are potent, selective, orally bioavailable, and safe. The compounds inhibit oxidants, cytokines, chemokines, and inflammatory cells both *in vitro* and *in vivo*. The lead compound, SPL-891.1, is active in models of RA, IBD, and NASH among others.

5:50 Close of Conference

Macrocyclics & Constrained Peptides

Cell-Penetrating, Bigger Molecules for Oral-Based Therapeutics

April 10-11, 2019 | San Diego Convention Center | San Diego, CA

WEDNESDAY, APRIL 10

12:30 pm Registration Open

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

DESIGN CHALLENGES FOR MACROCYCLIC PEPTIDES

1:30 Welcome Remarks

Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

1:35 Chairperson's Opening Remarks

Scott Lokey, PhD, Professor, Chemistry and Biochemistry, University of California, Santa Cruz

1:40 FEATURED PRESENTATION: Molecular Chameleons: Oral Compounds at the Border of Druggable Chemical Space

Jan Kihlberg, PhD, Professor, Department of Organic Chemistry, Uppsala University

Our analyses of crystal and solution phase structures of compounds at the border of oral druggable space suggest that they must behave as molecular chameleons. Depending on the environment they populate, small and distinct sets of conformations allow them to combine aqueous solubility with cell permeability and potent target binding. Predicting the conformations and properties of molecular chameleons is difficult, but our studies allow us to speculate on what future breakthroughs might be.

2:10 Advances in the Synthesis and Applications of Macrocycles

Andrei K. Yudin, PhD, Professor, Department of Chemistry, University of Toronto

Synthetic tools that allow one not only to cyclize linear precursors but also to exercise control over conformation-driven cellular permeability are in high demand. This lecture will summarize our ongoing efforts in this area and will highlight key experimental findings obtained in the past few months.

2:40 The Permeability Landscape around Lariat Cyclic Peptides

Scott Lokey, PhD, Professor, Chemistry and Biochemistry, University of California, Santa Cruz

Heterodetic cyclic peptides (lariat peptides) differ from simple homodetic cyclic peptides by the addition of a tail extending from the cyclic portion. Although lariat peptides comprise a large portion of bioactive cyclic peptide natural products, exploration of permeability in this space has been limited. We recently discovered a simple lariat scaffold based on a natural product, Xentrivalpeptide A, composed entirely of non-N-methylated alpha amino acids. I describe the synthesis and properties of several passively permeable lariat peptides with six H-bond donors and molecular weights greater than 800.

3:10 Exploring Conformational Space of Macrocycles: From the Solid State to Solution

Sponsored by OpenEye Scientific

Paul Hawkins, Head, Scientific Solutions, OpenEye Scientific

Tools for conformational sampling of macrocycles are validated against conformations from the solid state. This approach, while straightforward, provides no performance data for the solution state, where most pharmaceutically-relevant data is obtained. Here we describe our approach to macrocycle conformation sampling, and compare it to other methods on conformations from the solid state. We show how this approach can incorporate structural data from solution and be used to solve NMR structures of macrocycles in solution.

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

4:30 Versatile Bio-Orthogonal Strategies for Synthetic Peptide and Protein Stabilization

Raymond E. Moellering, PhD, Assistant Professor, Department of Chemistry, Institute for Genomics and Systems Biology, University of Chicago

Numerous chemistries have been applied to stabilize specific peptide conformations. Many of these strategies, however, lack the general structural, chemical and environmental compatibility desirable for diverse applications in enforcing bioactive peptide and protein folds. In this talk I will present recent progress on the development and application of novel chemical strategies to stabilize secondary and tertiary peptide conformations for challenging pharmacologic targets.

5:00 A*STAR Peptide Engineering Platform (PEP): Targeting Macrocyclic Modalities for Protein-Protein Interactions

*Charlie Johannes, PhD, Principal Scientist II & Head Director, Organic Chemistry, A*STAR*

This talk will focus on how A*STAR has embraced the revitalization of peptide research and is evolving technologies to enable the discovery and development of new peptide modalities for protein-protein interactions. Examples targeting the p53 and translational initiation (EIF4F) pathways for oncology and multimodal biomarkers for immunology will highlight our recent advances in diversity, screening, design, chemistry and formulation.

5:30 Breakout Discussions

See website for details.

6:15 Close of Day

6:30 Dinner Short Courses*

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

THURSDAY, APRIL 11

8:00 am Breakfast Presentation *(Sponsorship Opportunity Available)* **or Morning Coffee**

8:45 Welcome Remarks from Lead Conference Director

Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

8:50 Plenary Keynote Introduction

Sponsored by

Timothy Craig, PhD, HarkerBio

8:55 PLENARY KEYNOTE:

New Ways of Targeting K-Ras

Frank McCormick, PhD, Professor, HDF Comprehensive Cancer Center, University of California San Francisco

Efforts to find drugs that bind K-Ras directly have increased recently, enabled by NMR-based fragment screening, disulfide tethering, *in silico* drug design and biophysical methods such as Second Harmonic Generation (SHG). We will report progress on attacking two sites in the K-Ras protein; cysteine-185 (the site of prenylation), and histidine-95, a residue unique to K-Ras, to develop covalent K-Ras inhibitors, as well as compounds identified by SHG and other methods.

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

MACROCYCLIC MODALITIES INTO THE CLINIC

10:40 Chairperson's Remarks

Adrian Whitty, PhD, Professor, Biochemistry, Boston University

10:45 Discovery of a Potent and Orally Bioavailable Cyclophilin Inhibitor Derived from the Sanglifehrin Macrocycle

Petr Jansa, PhD, Senior Research Scientist II, Medicinal Chemistry, Gilead Sciences

Our aim was to discover through total synthesis an orally bioavailable, non-immunosuppressive cyclophilin (Cyp) inhibitor with potent anti-hepatitis C virus (HCV) activity that could serve as part of an all oral antiviral combination therapy. An initial lead derived from the sanglifehrin A macrocycle was optimized using structure based design to produce a potent and orally bioavailable inhibitor. The macrocycle ring size was reduced by one atom, and an internal hydrogen bond drove improved permeability and drug-like properties.

11:15 FEATURED PRESENTATION: Third Wave of Macrocyclic Peptide Therapeutics: Benchmarking and Druggable Target Space

Tomi K. Sawyer, PhD, Distinguished Scientist, Peptide Drug Discovery & Innovative Technologies, Merck & Co., Inc.

There have been three major waves of peptide drug discovery –– the first for receptor and extracellular targets, the second for intracellular targets, and now a third that is converging super-diversity (e.g., 106-1012-membered libraries) with both structure-based design and expanding target space. This has inspired new peptide modalities and opportunities to expand druggable target space (e.g., intracellular protein-protein and protein-DNA/RNA interactions). This presentation will highlight progress in the development of new screening tools for peptide permeability for benchmarking macrocyclic α–helical peptide structure-permeability relationships to advance this peptide modality into the clinic.

11:45 FideltaMacro™: Macrolide Inspired Macrocycles as Promising Templates for Unmet Medical Needs

Sponsored by Fidelta

Tanja Poljak, PhD, Group Leader, Medicinal Chemistry, Fidelta Ltd.

This talk will present recent results on our macrolide inspired macrocyclic library prepared using FideltaMacroTM technology including *in vitro* screening, pharmacokinetic data as well as *in vivo* proof of concept data. Inhibition of IL17A/IL17R interaction will be presented as a case study of targeting protein-protein interactions. Other major achievements such as a novel macrocyclic compound that showed efficacy in the mouse bleomycin model and additional novel oral antibacterials with *in vivo* demonstrated Gram-negative activity data will be discussed.

12:00 pm Discovery to Approval: Medicinal Chemistry Retrospective of Lorlatinib, A Macrocyclic ALK Inhibitor for Metastatic and Resistance Non-Small Cell Lung Cancer

Ted. W. Johnson, PhD, Research Fellow, Design Chemistry, Pfizer Oncology

PF-06463922 (lorlatinib), a novel macrocyclic inhibitor of ALK/ROS1, recently received FDA approval for the treatment of ALK-refractory Non-Small Cell Lung Cancer. Lorlatinib exhibits low nanomolar, cell-based inhibitory activity against a panel of clinically-derived ALK kinase-domain mutations and overlapping CNS activity to treat brain metastases. A complete retrospective will be presented with focus on unique lab objective and safety challenges.

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

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

Poster Awards Sponsored by Domainex

TARGET MODULATION WITH MACROCYCLES

2:15 Chairperson's Remarks

Ted W. Johnson, PhD, Research Fellow, Design Chemistry, Pfizer Oncology

2:20 Macrocyclic Inhibitors of Pim1/2 Kinase

Liping H. Pettus, PhD, Principal Scientist, Chemistry Research & Discovery, Amgen

Pim-1/2 kinases have been pursued as therapeutic targets for the treatment of hematologic malignancies. Starting from a non-selective HTS hit, we developed a series of 13-membered macrocycles. Systemic exploration of the macrocyclic linker led to the identification of AM-0944 as a selective inhibitor of Pim-1/2 kinases that was potent *in vitro* (pBAD IC50 25 nM) and efficacious in KMS-12-BM mouse xenograft model (100% TGI at 100 mg/kg daily PO dose).

2:50 Macrocyclic Agonists of the Neurotensin Receptors: Tools to Modulate Receptor Selectivity and Undesired Effects

Eric Marsault, PhD, Professor, Medicinal Chemistry and Pharmacology, University of Sherbrooke

Neurotensin mediates opioid-independent analgesia via the NTS1 and NTS2 receptors. Careful exploration of optimal sites of cyclization on Neurotensin 8-13 led to two distinct series of macrocyclic pharmacological probes. Series 1 possesses low nM potency for both NTS1 and NTS2, while series 2 is associated with low nM potency for NTS2 and >1,000-fold selectivity vs NTS1. *In vivo*, these series allowed separation of the desired analgesia from the undesired hypotension and hypothermia.

3:20 Macrocycles Targeting Intracellular PPIs for Addressing Refractory Oncology Targets

David Spellmeyer, PhD, CSO, Circle Pharma

Circle Pharma deploys a structure–based design/synthetic chemistry platform for macrocycle therapeutic discovery that incorporates prediction of intrinsic cell permeability as a key step in the design workflow. While this platform is target-agnostic, Circle's internal pipeline is directed to intracellular protein-protein interactions that are key drivers in oncology pathways, including p53:MDM2/4, MCL1:BH3, cyclinA:cdk2 and beta-catenin:TCF4. Examples of Circle's development work will be presented.

3:50 Networking Refreshment Break

4:20 Macrocyclic Peptide Triazole Inhibitors as Irreversible HIV-1 Inactivators

Adel Ahmed, PhD, Research Assistant Professor, Biochemistry and Molecular Biology, Drexel University College of Medicine

Through a facile chemical synthesis pathway based on solid phase peptide synthesis, we have developed a class of small cyclic peptides (cPTs) that target the HIV-1 Env gp120 glycoproteins. cPTs have great lipophilicity/hydrophilicity balance and have good aqueous solubility, making them appealing to develop as an orally bioavailable therapeutic. cPTs also have promising pharmacokinetics (PK) in rats with an estimated half-life of > 3 hours. They resist proteolysis by model and serum proteases.

4:50 New Cyclic Peptidomimetics to Combat Bacterial Infections

Brice Felden, PhD, Professor, Bacterial Regulatory RNAs & Medicine, Rennes University

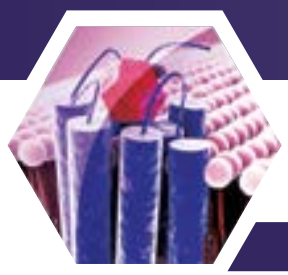
This presentation will describe novel therapies we are developing against Gram positive and negative bacteria. They are based on cyclic peptidomimetics. These new modalities do not trigger resistance *in vivo*.

5:20 Hydrocarbon-stapled Peptidomimetics Targeting Relaxin-3/RXFP3 Networks in Eating and CNS Disorders

Subhi Marwari, PhD, Postdoctoral Research Associate, Department of Medicine and Neuroscience, SUNY Upstate Medical University

The "helix-in-groove" mode of the neuropeptide relaxin-3 (H3)-RXFP3 receptor underlies a series of intracellular signalling events and provides a blueprint for molecular mimicry that can drive drug discovery. Investigating a series of stapling approaches and combining with intranasal delivery, we have demonstrated the potential of this system in eating and CNS disorders. A complete perspective from in-silico design to brain uptake capacities using novel multi-specific therapeutic modalities will be presented. This may be the first preclinical demonstration of a macrocyclic or hydrocarbon constrained peptide across the blood-brain barrier.

5:50 Close of Conference



3RD ANNUAL

GPCRs & Membrane Proteins

Designing Drugs Targeted at Proteins with Multiple Membrane-Spanning Domains

April 10-11, 2019 | San Diego Convention Center | San Diego, CA

WEDNESDAY, APRIL 10

12:30 pm Registration Open

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

STRUCTURAL ADVANCES FOR MEMBRANE PROTEINS

1:30 Welcome Remarks

Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

1:35 Chairperson's Opening Remarks

Vsevolod 'Seva' Katritch, PhD, Assistant Professor, The Bridge Institute, University of Southern California

1:40 Structure-Based Ligand Discovery for Class 'A' GPCRs: New Targets and Approaches

Vsevolod 'Seva' Katritch, PhD, Assistant Professor, The Bridge Institute, University of Southern California

With the rapid accumulation of high-resolution crystallographic and cryo-EM data for GPCRs, structure-based virtual ligand screening and rational design are quickly finding their prominent place as mainstream lead discovery and optimization tools. This talk will discuss several recently emerged structural targets for pain, addiction and immune disorders, as well as updates in virtual screening approaches we use to discover new chemotypes as probe compounds for these targets.

2:10 Nanobody-Stabilized Kappa Opioid Receptor Structure and Implications for Biased Opioid Ligand Design

Tao Che, PhD, Postdoctoral Fellow, Bryan Roth Lab, Department of Pharmacology, University of North Carolina Chapel Hill

This presentation will cover the design of biased ligands at the kappa-opioid receptor (KOR) using the crystal structure of KOR as a model.

2:40 CXC Chemokine Receptor 4: Structural Updates on a Druggable Target

Tony Ngo, PhD, Postdoctoral Fellow, Kufareva Lab, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California at San Diego

As a key driver of cancer cell migration and metastasis, the CXC chemokine receptor 4 is a target of several drug development programs. CXCR4 shares an endogenous chemokine CXCL12 with the atypical, intrinsically biased receptor ACKR3, but the structural principles of chemokine binding and receptor activation remain unknown. Our work reveals the basis for CXCL12 interaction and activation of CXCR4, and comparison with ACKR3, with potential implications for drug design.

3:10 Novel Kv7 Ion Channel Openers for the Treatment of Epilepsy

Sponsored by JBILANT BIOSYS

Takeshi Yura, PhD, Vice President, Medicinal Chemistry, Jubilant Biosys Ltd.

Neuronal voltage-gated potassium channels, Kv7s, are the molecular mediators of the M current and regulate membrane excitability in the central and peripheral neuronal systems. The identification of two distinct chemical series and their optimization towards novel small molecule Kv7 openers will be described. The results of *in vitro* and *in vivo* studies for selected compounds from these series will be presented, including data indicating their efficacy in seizure models.

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

4:30 Single-molecule FRET analysis of a Multimeric Membrane Protein

Matthieu Masureel, Ph.D., Postdoctoral Scholar, Kobilka Lab, Molecular and Cellular Physiology, Stanford University School of Medicine

I will discuss single-molecule FRET analysis of ligand efficacy in β2 adrenergic receptor - G protein activation. I will also briefly describe the application of this technology to membrane proteins in general.

5:00 First-in-Class Small Molecule Modulators of Adhesion GPCRs

Gregory Tall, PhD, Associate Professor, Pharmacology, University of Michigan

Adhesion GPCRs control many aspects of developmental transitions, tissue maintenance in adults, and a slew of regulatory functions in various tissues. There is a paucity of small molecule ligands to manipulate the receptor subclass. We recently demonstrated that adhesion GPCRs are activated by a tethered-peptide-agonist mechanism. With this understanding, we engineered receptors for high throughput screening of chemical libraries. We found the first adhesion GPCR small molecule antagonist and the first small molecule partial agonist.

5:30 Breakout Discussions

See website for details.

6:15 Close of Day

6:30 Dinner Short Courses*

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

THURSDAY, APRIL 11

8:00 am Breakfast Presentation *(Sponsorship Opportunity Available)* **or Morning Coffee**

8:45 Welcome Remarks from Lead Conference Director

Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

8:50 Plenary Keynote Introduction

Sponsored by

8:55 PLENARY KEYNOTE:

New Ways of Targeting K-Ras

Frank McCormick, PhD, Professor, HDF Comprehensive Cancer Center, University of California San Francisco

Efforts to find drugs that bind K-Ras directly have increased recently, enabled by NMR-based fragment screening, di-sulfide tethering, *in silico* drug design and biophysical methods such as Second Harmonic Generation (SHG). We will report progress on attacking two sites in the K-Ras protein; cysteine-185 (the site of prenylation), and histidine-95, a residue unique to K-Ras, to develop covalent K-Ras inhibitors, as well as compounds identified by SHG and other methods.

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

TRANSPORTERS AND ION CHANNELS

10:40 Chairperson's Remarks

Matthew Eddy, PhD, Assistant Professor, Chemistry, University of Florida

10:45 A New Era in Discovery of Solute Carrier (SLC) Transporter Modulators

Alan D. Wickenden, PhD, Scientific Director, Discovery Sciences, Janssen R&D

SLC transporters constitute the second largest family of membrane proteins in the human genome and a rich and relatively untapped source of therapeutic drug targets. Unfortunately, the identification of new SLC modulators has been

limited. This talk will review recent progress in understanding the structural and molecular basis of SLC transporter function and describe the opportunities these new insights may present for SLC transporter drug discovery.

11:15 Discovery of GLPG2451, a Novel Potentiator for the Treatment of Cystic Fibrosis

Steven Van der Plas, PhD, Group Leader, Medicinal Chemistry, Galapagos

Cystic Fibrosis is caused by mutations in the Cystic Fibrosis Transmembrane Regulator (CFTR) gene, resulting in loss of fuction of the CFTR ion channel. Potentiators are a class of CFTR modulators that allow the effective opening of the CFTR channel by increasing its open probability. I describe the discovery and optimisation of a novel series of potentiators. Additionally, the clinical compound GLPG2451 will be disclosed and its properties will be discussed.

11:45 Spotlight Presentation: Discovery and Pharmacodynamic studies of Potent Dual Norepinephrine and Dopamine Transport Inhibitors

Dean G. Brown, PhD, Director, External Chemistry, Hit Discovery, Discovery Sciences, IMED Biotech Unit, AstraZeneca

12:00 Small-Molecule Covalent TEAD•Yap Antagonists

Samy Meroueh, PhD, Associate Professor, Department of Biochemistry and Molecular Biology, Indiana University School of Medicine

Hippo signaling controls tissue homeostasis and organ growth by regulating Yap co-activation of TEA domain (TEAD) transcription factors. We report small-molecule TEAD•Yap inhibitors that selectively form a covalent bond with a conserved cysteine in the palmitate pocket of TEADs. In mammalian cells, the compounds formed a covalent complex with TEAD4, inhibited its binding to Yap1, blocked its transcriptional activity, suppressed expression of CTGF, and inhibited cell viability of glioblastoma spheroids.

12:30 LUNCHEON PRESENTATION: Stabilization of Native Membrane Protein Targets for Drug Discovery

Anass Jawhari, CSO, Management, CALIXAR

CALIXAR has developed an innovative detergent/surfactant-based approach for therapeutic membrane protein stabilization. GPCRs, ion channels, transporters can be stabilized without any single mutation, truncation or fusion. We will illustrate that using most recent case studies on targets of high medical relevance for which functional and structural integrities were preserved. This innovative approach represents a serious alternative to classical protein engineering approaches to enable drug discovery (SBDD, FBDD, Antibody Discovery & Vaccine).

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

Poster Awards Sponsored by Domainex

GPCR PHARMACOLOGY, KINETICS AND SIGNALING CHALLENGES FOR CHEMISTS

2:15 Chairperson's Remarks

Dean G. Brown, PhD, Director, External Chemistry, Hit Discovery, Discovery Sciences, IMED Biotech Unit, AstraZeneca

2:20 FEATURED PRESENTATION: One Receptor, Many Partners: How do GPCRs Stimulate Diverse Signaling Proteins?

Ron O. Dror, PhD, Associate Professor, Computer Science, Stanford University

The search for functionally selective or biased ligands that promote GPCR signaling through desired but not undesired pathways represents a major current focus of drug discovery efforts. To enable the rational design of such biased ligands, we are using atomic-level simulations, together with complementary experimental data, to determine how GPCRs cause various intracellular proteins—including arrestins, kinases, and G proteins—to activate and signal.

2:50 The Good, the Bad, and the Confusing: Binding Kinetics at GPCR Targets and Potential Effects on Lead Optimization and Translatability

Brian Murphy, PhD, Senior Principal Scientist, CV and Fibrosis Drug Discovery, Disease Sciences and Biologics, R&D, Bristol-Myers Squibb

Sam Hoare, PhD, Founder, Pharmechanics LLC

Small molecule binding kinetics likely plays an important role in determining both *in vitro* potency and *in vivo* efficacy of compounds. For example, compound off-rate may affect the duration of action of compounds *in vivo*. I will review literature data in support of, and in contradiction to the notion that residence time is a critical factor in compound efficacy *in vivo*. I will also show examples where *in vitro* measures of compound affinity and efficacy can be compromised without consideration of compound binding kinetics.

3:20 FEATURED PRESENTATION: GPCRs as Allosteric Sensors linking Hormone Binding to G Protein Activation to Modulation by Small Molecules and Cations

Roger K. Sunahara, PhD, Professor, Pharmacology, University of California San Diego

G protein-coupled receptors (GPCR) are critical conduits that sense and communicate extracellular stimuli. Their diversity and physiological importance thus make them superb therapeutic targets. Recent advances in the structural biology of GPCRs, along with support from pharmacological and biochemical studies, has helped in understanding the mechanism of GPCR activation and also has been informative for structure-based drug design. We will discuss our recent data on receptor allostery and structure-based drug design of subtype-specific GPCR ligands.

3:50 Networking Refreshment Break

TARGETING PAIN OR THE CNS: OPIOID ALTERNATIVES AND BEYOND

4:20 Chemistry and Pharmacology of Mitragyna Speciosa

Susruta Majumdar, PhD, Associate Professor of Pharmacology, Center for Clinical Pharmacology, St. Louis College of Pharmacy/Washington University

Mitragyna Speciosa, also known as Kratom, originates from the leaves of a tropical tree found in South-East Asia. It has been shown to have pain-relieving properties with less withdrawal effects compared to other opioids. I will discuss the chemistry and pharmacology of Mitragyna Speciosa and present evidence for the biased agonism of the compound.

4:50 Development of D3 Dopamine Receptor Selective Bitropic Ligands

Robert Luedtke, PhD, Professor, Department of Pharmacology and Neuroscience, University of North Texas Health Science Center

I will focus on the development of bitropic D3 dopamine receptor selective ligands for the treatment of cocaine abuse. Though D2 and D3 dopamine receptors have a high level of amino acid sequence homology, we have been able to identify compounds with high binding affinity at the D3 dopamine receptor subtype and that possess greater than 100 fold degree of D3 vs. D2 receptor binding selectivity. Our dopamine GPCR subtype selective ligands resulted from collaborations between medicinal chemists, computational chemists and behavioral pharmacologists.

5:20 Structure, Dynamics and Activation of the CGRP Receptor, a Medically Important Class B GPCR

Christopher Reynolds, PhD, Professor, Royal Society Industry Fellow, School of Biological Sciences, University of Essex

Calcitonin gene-related peptide (CGRP) is a widely expressed neuropeptide; antagonists can be used to treat migraine while agonists are cardioprotective. The CGRP receptor is a heterodimer of the calcitonin receptor-like receptor (CLR) class B G-protein-coupled receptor and the type 1 transmembrane domain protein, receptor activity modifying protein (RAMP) 1. I will present dynamics and activation of the CGRP receptor in complex with the CGRP peptide and the Gs-protein heterotrimer based on our recent 3.3 Å cryo-electron microscopy structure of the human CGRP receptor, photoaffinity labelling studies, and molecular dynamics simulations. Our results also provide novel insights into the role of RAMPs in the activation of the CGRP receptor.

5:50 Close of Conference

INAUGURAL

SYMPOSIUM

Artificial Intelligence for Early Drug Discovery

How to Best Use AI & Machine Learning for Identifying and Optimizing Compounds and Drug Combinations

April 12, 2019 | Hard Rock Hotel | San Diego, CA

FRIDAY, APRIL 12

7:30 am Registration Open and Morning Coffee

AI FOR DRUG DESIGN

7:55 Welcome and Opening Remarks
Tanuja Koppal, PhD, Conference Director

8:00 Integrating Artificial Intelligence and Fragment-Based Drug Discovery
Marcel Verdonk, PhD, Senior Director, Computational Chemistry & Informatics, Astex Pharmaceuticals
We will give a brief overview of Astex's efforts to integrate AI technology into their fragment-based drug discovery (FBDD) platform. We will also describe our efforts around electrostatic complementarity between protein and ligand, which is critically important for affinity. We will present AI methodology for generating ultra-fast, near-QM quality molecular electrostatic potential (ESP) surfaces for small molecules, as well as proteins. We will demonstrate the utility of this approach to our FBDD projects.

8:30 Nature-Inspired *de novo* Drug Design with AI
Gisbert Schneider, PhD, Professor, Computer-Assisted Drug Design, Department of Chemistry and Applied Biosciences, ETH Zurich
Drug discovery is inspired by natural products. We present automated *de novo* design for generating novel synthesizable compounds by transfer learning from natural product templates. The chemical synthesis and biological testing positively advocate this AI concept for prospective application in medicinal chemistry. This presentation will provide first disclosure of prospective natural product-inspired drug design with AI technology.

9:00 Networking Coffee Break

AI FOR LEAD OPTIMIZATION & MOA STUDIES

9:30 CASE STUDY: The Power of Networks: Network-Driven Drug Discovery (NDD) and New Chemical Entities
Sree Vadlamudi, PhD, Business Development, Programme Manager, e-Therapeutics plc
We have successfully implemented and validated a highly productive Network-driven Drug Discovery (NDD) approach to identify NCEs in diverse areas of biology. The majority of drug discovery approaches involve the search for a single binding target in a well-characterised pathway, but that does not reflect the complexity of pathway interactions which occur as a network. We will describe a case study highlighting the application of our proprietary NDD methodology in the discovery and optimisation of small molecules with a novel mechanism of action.

10:00 CASE STUDY: An Artificial Intelligence Platform for Predicting Voltage Gated Sodium (NaV) Channel Inhibition
David Mowrey, PhD, Senior Research Scientist, in silico Drug Discovery, Icagen
We discuss the development of a machine learning platform for predicting NaV channel inhibition. Here, we explore the use of data augmentation and multitask learning as a means to compensate for the presence of small data sets. We also compare the efficacy of recurrent neural networks (RNN) on SMILES strings, specifically the long-short term memory (LSTM) classifier compared to more spatially realistic 3D convolutional neural networks.

10:30 CASE STUDY: Combining Systems Biology and AI for Intelligent Drug Design
Aurélien Rizk, PhD, CTO, InterAx
Our ability to design drugs controlling cellular responses via membrane receptors relies on our understanding of how receptors encode and transfer information. We use mathematical models to combine theoretical knowledge of signaling networks with in-house generated experimental data. Novel parameters characterizing the mechanistic action of drug molecules can be derived from this cellular systems biology approach. Here, we show how these novel datasets pave the way for new AI applications for drug design and discovery.

Sponsored by IKTOS

11:00 Deep Learning Applied to Ligand-Based *De Novo* Design: A Real Life Lead Optimization Case Study
Yann Gaston-Mathé, Co-founder & CEO, Iktos

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

12:00 pm Session Break

AI FOR EARLY DECISION-MAKING

1:00 Chairperson's Remarks
Ron Alfa, MD, PhD, Vice President, Discovery & Product, Recursion Pharmaceuticals

1:05 Re-Imagining Drug Discovery through AI
Ron Alfa, MD, PhD, Vice President, Discovery & Product, Recursion Pharmaceuticals
Massively expanding and accelerating traditional approaches like phenotypic screening provide a feasible near-term solution to bringing substantial improvements to the efficiency of discovery and development efforts. This talk will detail how Recursion sees the use of AI in drug discovery and will describe some technical strategies to accelerate discovery using AI, including our image-based phenotypic screening platform. The use of deep learning models to build predictive tools for multiple stages in the drug discovery pipeline will be discussed.

1:35 Design of an Artificial Intelligence System for Drug Discovery
Istvan Enyedy, PhD, Principal Scientist, Biogen
Artificial intelligence systems have the potential of accelerating drug discovery by increasing the time scientists spend on designing the candidate for development. Multiple machine learning models can be used for driving multiparameter optimization. The use of statistical analysis of the machine learning models in an AI system provides information about the reliability of the predictions and helps in the decision-making process.

Sponsored by VERISIM Life

2:05 Recognizing the Promise of Adaptive Intelligence Using Mechanistic Modeling
Jo Varshney, DVM, PhD, Founder, CEO, VeriSIM Life
We're already seeing the impact of Artificial Intelligence adoption within healthcare, however the true potential of personalized medicine is constrained by the complexities of human/animal physiology. VeriSIM Life is complementing machine learning algorithms with the knowledge of biological systems to address this rate limiting step for drug development. The integration of differences in demographics, genetics, disease progression, and co-medication is enabling us to make critical decisions earlier than ever in the drug development process.

2:35 Networking Refreshment Break

AI FOR ADME/DMPK PREDICTIONS

3:05 FEATURED PRESENTATION: A Case Study in Machine Learning: Integrating Metabolism, Toxicity, and Real-World Evidence

S. Joshua Swamidass, MD, PhD, Assistant Professor, Department of Immunology and Pathology, Division of Laboratory and Genomic Medicine; Faculty Lead, Translational Informatics, Institute for Informatics, Washington University

Many medicines become toxic only after bioactivation by metabolizing enzymes, sometimes into chemically reactive species. Idiosyncratic reactions are the most difficult to predict, and often depend on bioactivation. Recent advances in deep learning can model bioactivation pathways with increasing accuracy, and these approaches are giving us deeper understanding of why some drugs become toxic and others do not. At the same time, deep learning can be used to understand drug toxicity as it arises in clinical data and why some patients are affected, but not others.

3:35 Modeling in Drug Metabolism for Drug Design and Development

Hao Sun, PhD, Principal Pharmacokineticist, DMPK, Seattle Genetics

Several categories of modeling approaches have been applied to drug metabolism. The talk will focus on: 1. structure-based molecular modeling with crystal structures of drug metabolizing enzymes for drug design and lead optimization; 2. data mining of high-resolution mass spectrometric data for metabolite identification; 3. pharmacokinetic modeling for preclinical *in vivo* study design; and 4. PK/PD modeling for dose prediction. These modeling approaches have significantly improved efficiency in drug metabolism-focused drug discovery and development.

4:05 Quantitative Prediction of Complex Drug-Drug Interactions Involving CYP3A and P-glycoprotein: A Case Study of Anticancer Drug Bosutinib

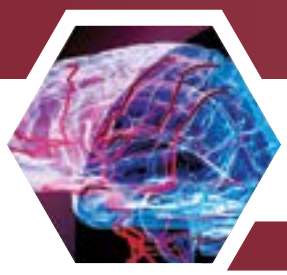
Shinji Yamazaki, PhD, Department of Pharmacokinetics, Dynamics and Metabolism, La Jolla Laboratories, Pfizer Worldwide Research and Development

Physiologically-based pharmacokinetic (PBPK) modeling is a powerful tool to quantitatively predict DDIs based on drug-dependent physicochemical and pharmacokinetic parameters with drug-independent physiological parameters. There is growing emphasis in developing PBPK models to assess potential risks on DDIs of new molecular entities. This presentation highlights a quantitative PBPK modeling approach to understand complex DDIs of bosutinib via not only CYP3A-mediated metabolism but also P-glycoprotein-mediated efflux on absorption.

4:35 Close of Conference

TRACK-HOPPING

Attendees at Drug Discovery Chemistry are encouraged to "track-hop" between concurrent sessions: Though you register for a particular conference or symposium, in reality you gain access to all concurrent conferences or symposia. For the best value and to best fit your research needs, register for a Premium Package that gives you access to either: all 9 conferences, 4 symposia, plus 2 short courses over five days of programming OR access to 9 conferences plus 4 short courses over four days of programming.



Blood-Brain Barrier and CNS Drug Discovery

Strategies and Tools to Address Hurdles in CNS Drug Discovery

April 12, 2019 | Hard Rock Hotel | San Diego, CA

FRIDAY, APRIL 12

7:30 am Registration Open and Morning Coffee

UNDERSTANDING THE BBB AND ITS IMPACT ON DRUG DISCOVERY

7:55 Welcome and Opening Remarks

Kaitlin Kelleher, Conference Director, Cambridge Healthtech Institute

Zoran Rankovic, PhD, Director, Chemistry Centers, Chemical Biology and Therapeutics, St. Jude Children's Research Hospital

8:00 FEATURED PRESENTATION: The BBB and Its Effect on Drug Delivery in Different Disease States

Quentin Smith, PhD, Senior Vice President, Research, Texas Tech University Health Sciences Center

8:30 How Does the Basement Membrane Regulate BBB Integrity in Physiological and Pathological Conditions?

Yao Yao, PhD, Assistant Professor, Pharmaceutical and Biomedical Sciences, University of Georgia

Although the blood brain barrier (BBB) attracts lots of attention, most research focuses on its cellular constituents, leaving its non-cellular component - the basement membrane (BM) - understudied. Recent studies show that the BM not only actively regulates BBB integrity, it also serves as the rate-limiting step in inflammatory cell extravasation. In this talk, I will discuss the biological function of the BM in BBB maintenance under both physiological and pathological conditions.

9:00 Networking Coffee Break

9:30 Fibrinogen in Neurological Diseases: Mechanisms, Imaging, Therapeutics

Katerina Akassoglou, PhD, Senior Investigator/Professor, Department of Neurology, Gladstone Institutes/University of California, San Francisco

Recent research has uncovered pleiotropic roles for fibrinogen in neuroinflammation, neurodegeneration, and inhibition of repair. Fibrin-targeting immunotherapy inhibits autoimmunity- and amyloid-driven neurotoxicity in animal models of multiple sclerosis and Alzheimer's disease, suggesting selective fibrin targeting might be beneficial for suppressing vascular-driven neurodegeneration.

10:00 BBB Organoids: A Next Generation *in vitro* Drug Screening Platform

Choi-Fong Cho, PhD, Instructor, Neurosurgery, Brigham and Women's Hospital, Harvard Medical School

Techniques to model the BBB *in vitro* are crucial tools to help predict brain uptake of drug candidates prior to *in vivo* studies. We describe here the utility of 3D multicellular BBB spheroids made of human brain endothelial cells (ECs), pericytes and astrocytes as a screening tool for brain-penetrating agents.

10:30 Theory and Practice of CNS Drug Design

Zoran Rankovic, PhD, Director, Chemistry Centers, Chemical Biology and Therapeutics, St. Jude Children's Research Hospital

Designing molecules that can overcome the blood-brain barrier and achieve optimal concentration at the desired therapeutic target in the brain is a specific and major challenge for medicinal chemists working in CNS drug discovery. Here we report experimental data analysis and case studies to illustrate the modern CNS pharmacokinetic concepts, drug discovery workflows and medicinal chemistry strategies for designing molecules with optimal brain exposure.

11:00 Sponsored Presentation *(Opportunity Available)*

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

12:00 pm Session Break

BLOOD-BRAIN AND CNS-PENETRANT INHIBITORS AND PLATFORMS FOR DRUG DELIVERY

1:00 Chairperson's Remarks

Yao Yao, PhD, Assistant Professor, Pharmaceutical and Biomedical Sciences, University of Georgia

1:05 The Atypical Regulation of GPCR Induced Inflammation and Vascular Leakage

Neil Grimsey PhD, Assistant Professor, Pharmaceutical and Biomedical Sciences, College of Pharmacy, University of Georgia, Athens

GPCR induced proinflammatory signaling is key to the breakdown of endothelial barrier integrity. Our work has identified a conserved atypical pathway for the induction of p38 MAPK signaling. Which is induced independent from the classical three tire kinase cascade and the activation of MKK3/6. Very little is understood as to how this pathway is regulated. Thus, providing a novel therapeutic target to specifically block proinflammatory GPCR signaling in the vasculature.

1:35 Discovery and Early Clinical Development of LY3202626, a Low-Dose, CNS-Penetrant BACE Inhibitor

Dustin Mergott, Senior Research Advisor, Group Leader, Discovery Chemistry Research & Technologies, Eli Lilly

Cerebral deposition of amyloid-β peptide (Aβ) plays a critical role in Alzheimer's disease (AD) pathogenesis. Owing to its role in the generation of Aβ, the BACE1 enzyme has been a prime target for designing drugs to prevent or treat AD. However, BACE1 has proven to be an exceedingly challenging target for drug discovery, especially due to the requirement for CNS penetration. This presentation will describe the discovery of LY3202626, a low-dose, CNS-penetrant BACE inhibitor capable of reducing CSF Aβ by > 90%.

2:05 Sponsored Presentation *(Opportunity Available)*

2:35 Networking Refreshment Break

3:05 A Roadmap for PI3Kγ Selectivity Design: Discovery of Orally Bioavailable, CNS-Penetrant PI3Kγ Inhibitors with Potential for the Treatment of Multiple Sclerosis

Philip Collier, PhD, Senior Research Scientist, Medicinal Chemistry, Vertex Pharmaceuticals, Inc.

We describe the evolution of a reported pan-PI3K inhibitor into a family of potent and selective inhibitors. Guided by structural data, our scaffold design strategy resulted in compounds devoid of efflux liabilities. Further optimization led to the discovery of a CNS-penetrant, orally bioavailable compound that showed efficacy in a preclinical model of MS.

3:35 Optimization of a Phenotypic Screening Hit in Yeast and the Identification of a Novel Target with the Potential to Treat Parkinson's Disease

Matthew Lucas, PhD, Senior Director of Chemistry, Medicinal Chemistry, Yumanity Therapeutics

The discovery, design, and phenotype-led optimization of the scaffold that resulted in the discovery of a novel target that plays an important and previously unrecognized role in the neurotoxicity caused by a-synuclein will be described. The a-Synuclein protein is a major driver of Parkinson's disease and related neurodegenerative disorders. Misfolding and aggregation of a-synuclein triggers a cascade of events, ultimately resulting in neurotoxicity.

4:05 A Versatile and Modular Targeted Nanoparticle Platform for Delivery of Combination Therapies to Adult and Pediatric CNS Tumors

Fred Chiu-lai Lam, MD, PhD, Research Scientist, Biology, Koch Institute for Integrative Cancer Research at MIT

We developed transferrin-functionalized nanoparticles (Tf-NPs) that can deliver combination therapies across the BBB to CNS tumors. Treatment of GBM mouse models with drug-loaded Tf-NPs enhances survival and decreases systemic drug toxicities, demonstrating the potential of this nanoscale platform for treatment of CNS tumors.

4:35 Close of Conference

Lead Optimization for Drug Metabolism & Safety

Tools and Strategies for Predicting, Evaluating and Building Safety Into Drug Design

April 12, 2019 | Hard Rock Hotel | San Diego, CA

FRIDAY, APRIL 12

7:30 am Registration Open and Morning Coffee

OPTIMIZING NEW CHEMICAL SPACE & DRUG MODALITIES

7:55 Welcome and Opening Remarks

Tanuja Koppal, PhD, Conference Director

Ganesh Rajaraman, PhD, MBA, Associate Director, DMPK, Celgene Corporation

8:00 ADME Strategies in Beyond the Rule of Five Space

Ganesh Rajaraman, PhD, MBA, Associate Director, DMPK, Celgene Corporation

As drug discovery is increasingly pushing new frontiers in deep hydrophobic targets, protein-protein interactions, protein degraders with PROTACS, etc., it requires compounds 'beyond the rule of five' (bRO5; Lipinski's rule). This poses major challenges with respect to permeability and oral bioavailability. Current *in vitro* tools are of limited value in predicting *in vivo* results, making it challenging to come up with a rational SAR strategy to improve on properties. The talk aims at exploring current challenges and attempts at possible solutions.

8:30 A Chemical Toxicologist's Perspective on the Validation and Application of Cutting-Edge *in vitro* Toxicity Assays for Lead Optimization

Tomoya Yukawa, PhD, Associate Scientific Fellow, Discovery Toxicology, Drug Safety Research & Evaluation, Takeda Pharmaceutical Company

There is a strong focus on the development of new *in vitro* assays that are predictive of adverse events linked to drug attrition. To leverage these assays for lead optimization, local validation analyses based on target class, mode-of-action and chemotype-similarity are essential to ensure applicability and utility. We present several case studies of validation/application of such assays including a 3D-liver microtissue model, a proximal tubule cell model and a hematopoietic stem cell derived myeloid model.

9:00 Networking Coffee Break

UNDERSTANDING DRUG TRANSPORT & CLEARANCE

9:30 Biotransformation of Antibody Drug Conjugates (ADCs) - Pathways and Enzymes

Donglu Zhang, PhD, Principal Scientist, Department of Drug Metabolism and Pharmacokinetics, Genentech, Inc.

Biotransformation of an ADC involves both hydrolysis of the protein portion and metabolism of payloads in addition to linker metabolism. Examples will be given to demonstrate biotransformation of commonly used peptide and disulfide linkers in which both cleavage and immolation are important. Further biotransformation of payloads could be important as DNA alkylation of DNA alkylators should be considered as a disposition pathway.

10:00 Modeling and Simulation to Study the Impact of Transporters on Drug Disposition and to Improve *in vitro* to *in vivo* Extrapolation (IVIVE)

Priyanka Kulkarni, PhD, Scientist, Pharmacokinetics and Drug Metabolism, Amgen, Inc.

IVIVE of transporter substrates is an industry-wide challenge due to multiple complicating factors. Modeling and simulation tools were used to address such experimentally challenging systems. Compartmental and semi-physiological models were used to assess the impact of uptake transporters on drug distribution and to determine system-independent "true" inhibition parameters of efflux transporters, respectively. Together, these results demonstrate the use of modeling and simulation techniques to improve IVIVE of transporter substrates and inhibitors.

10:30 Success and Challenges in Predicting Transporter Mediated Drug Disposition and Clearance from *in vitro* to *in vivo* Extrapolation

Na Li, PhD, Senior Scientist, Pharmacokinetics and Drug Metabolism, Amgen, Inc.

Although the scaling from *in vitro* to *in vivo* for predicting metabolic clearance has been successful, the prediction of drug transporter mediated drug disposition and clearance has remained as a challenge in the world of drug discovery. As transporters are ubiquitously expressed in all the tissues and organs, it is not only important for drug clearance, but also drives the tissue concentration which subsequently impact the drug efficacy and safety. Relative activity factor (RAF), transporter proteomics and PBPK modeling has demonstrated success to improve the understanding of the gaps between *in vitro* and *in vivo* studies. This talk focuses on the current challenges of predicting tissue drug concentration and transporter-mediated clearance and share the case studies of advancing IVIVE by improving *in vitro* transporter assays with incorporating transporter proteomics and modeling.

11:00 Luncheon Presentation: Drug Metabolism Optimisation Strategies in the Ever Evolving World of Drug Discovery

Sponsored by evotec

Patrick Barton, PhD, DMPK, Evotec (UK) Ltd

Improving success in drug discovery is a major focus for the industry with toxicity and efficacy remaining the major challenge. The talk will present the use of dose telemetry for assessment of project progress towards an acceptable clinical dose and a tool for use in a multi-parametric approach optimization in the LI/LO phase. This will be in the form of case studies which demonstrate the utility of this method relative to other well document metrics

11:45 pm Session Break

EVALUATING DRUG-DRUG INTERACTIONS

1:00 Chairperson's Remarks

Kari Morrissey, PhD, Scientist, Clinical Pharmacology, Genentech, Inc.

1:05 Understanding Transporter-Mediated DDIs – Regulatory DDI Guidance and Industry Case Studies

Michelle Liao, PhD, Associate Director, Clinical Pharmacology and DMPK, Clovis Oncology

Transporter-mediated clinically relevant drug-drug interactions (DDIs) are widely recognized. Drug regulatory agencies worldwide have issued guidance regarding transporter DDI in (1) evaluation of important drug transporters during preclinical drug development, (2) design of clinical DDI studies, and (3) drug labeling. This presentation will compare this DDI guidance and illustrate these concepts with case studies.

Lead Optimization for Drug Metabolism & Safety

Tools and Strategies for Predicting, Evaluating and Building Safety Into Drug Design

April 12, 2019 | Hard Rock Hotel | San Diego, CA

1:35 Determining the Clinical Relevance of DDI Predictions

Kari Morrissey, PhD, Scientist, Clinical Pharmacology, Genentech, Inc.

Interactions between drugs can have serious implications; therefore, it is important to understand the potential for and clinical relevance of DDIs early in drug development. This presentation will provide practical considerations and strategies on (1) incorporating nonclinical DDI predictions into clinical development plans, (2) timing, design and conduct of dedicated DDI studies, (3) interpretation of clinical data to determine the clinical relevance of a DDI and (4) implications of clinically relevant DDIs on product labeling.

2:05 Sponsored Presentation *(Opportunity Available)*

2:35 Networking Refreshment Break

AI FOR ADME/DMPK PREDICTIONS

3:05 FEATURED PRESENTATION: A Case Study in Machine Learning: Integrating Metabolism, Toxicity, and Real-World Evidence

S. Joshua Swamidass, MD, PhD, Assistant Professor, Department of Immunology and Pathology, Washington University

Many medicines become toxic only after bioactivation by metabolizing enzymes, sometimes into chemically reactive species. Idiosyncratic reactions are the most difficult to predict, and often depend on bioactivation. Recent advances in deep learning can model bioactivation pathways with increasing accuracy, and these approaches are giving us deeper understanding of why some drugs become toxic and others do not. At the same time, deep learning can be used to understand drug toxicity as it arises in clinical data and why some patients are affected, but not others.

3:35 Modeling in Drug Metabolism for Drug Design and Development

Hao Sun, PhD, Principal Pharmacokineticist, DMPK, Seattle Genetics

Several categories of modeling approaches have been applied to drug metabolism. The talk will focus on: 1. structure-based molecular modeling with crystal structures of drug metabolizing enzymes for drug design and lead optimization; 2. data mining of high-resolution mass spectrometric data for metabolite identification; 3. pharmacokinetic modeling for preclinical *in vivo* study design; and 4. PK/PD modeling for dose prediction. These modeling approaches have significantly improved efficiency in drug metabolism-focused drug discovery and development.

4:05 Quantitative Prediction of Complex Drug-Drug Interactions Involving CYP3A and P-glycoprotein: A Case Study of Anticancer Drug Bosutinib

Shinji Yamazaki, PhD, Department of Pharmacokinetics, Dynamics and Metabolism, La Jolla Laboratories, Pfizer Worldwide Research and Development

Physiologically-based pharmacokinetic (PBPK) modeling is a powerful tool to quantitatively predict DDIs based on drug-dependent physicochemical and pharmacokinetic parameters with drug-independent physiological parameters. There is growing emphasis in developing PBPK models to assess potential risks on DDIs of new molecular entities. This presentation highlights the quantitative PBPK modeling approach to understand complex DDIs of bosutinib via not only CYP3A-mediated metabolism but also P-glycoprotein-mediated efflux on absorption.

4:35 Close of Conference

4TH ANNUAL

SYMPOSIUM

Biophysical Approaches for Drug Discovery

New Methods and Lead Generation Strategies for Medicinal Chemists

April 12, 2019 | Hard Rock Hotel | San Diego, CA

FRIDAY, APRIL 12

7:30 am Registration Open and Morning Coffee

INTEGRATING BIOPHYSICAL APPROACHES

7:55 Welcome and Opening Remarks

Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute
Seungil Han, PhD, Associate Research Fellow, Structure Biology & Biophysics, Pfizer Global R&D

8:00 FEATURED PRESENTATION: Characterization of Novel STING Ligands Using SPR and Orthogonal Approaches

Gottfried Schroeder, PhD, Senior Scientist, Department of Pharmacology, Merck Research Labs - Boston

---

8:30 Advanced Biophysical Methods for Driving Lead Generation in the Right Direction

Mela Mulvihill, PhD, Scientist, Biochemical & Cellular Pharmacology, Genentech

Difficult to drug targets require advanced biophysical methods for hit identification, characterization, and optimization through the early discovery hit-to-lead phase. Using case studies, I will present our advanced toolkit of novel mass spectrometry and label-free biophysical assays used for screening, establishing mechanism of action, and kinetic measurements for compound optimization. The on-going projects I present will include a class of compounds that induce target degradation referred to as Chemical Inducers of Degradation (CIDEs).

9:00 Networking Coffee Break

INNOVATIONS IN BIOPHYSICAL APPROACHES

9:30 NMR Molecular Replacement: A Method to Probe Protein-Ligand Complexes in the Absence of Crystal Structures

Julien Orts, PhD, Professor, Laboratory of Physical Chemistry, Swiss Federal Institute of Technology, ETH

I will describe our novel NMR2 (NMR Molecular Replacement) method which we believe provides an avenue for the fast and robust determination of atomic resolution binding pocket structure of ligand-protein complexes when obtaining well-diffracting crystals is difficult. It is quicker than the current x-ray crystallography alternative of liquid-state NMR. I will present multiple NMR2 applications covering several ligand topologies ranging from peptidomimetic to small molecules that bind strongly or weakly to protein receptors.

10:00 Moderated Discussion Session

Ben Davis, PhD, Research Fellow, Biology, Vernalis Research

10:30 Studying Small Molecule-Membrane Protein Binding Kinetics Using Virion Oscillators

Guangzhong Ma, Graduate Student, Chemistry, Laboratory of N. Tao, Arizona State University

Our 'membrane protein binding kinetics' method measures binding induced charge change. We apply an alternating electric field to oscillate virions with GPCRs expressed on the surface and measure oscillation amplitude of the virions with sub-nm precision. The binding of small molecule changes the charge on the virion surface and thus changes the oscillation amplitude. By tracking the oscillation amplitude in real-time, the binding kinetics can be obtained.

11:00 Sponsored Presentation *(Opportunity Available)*

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

12:00 pm Session Break

CRYO ELECTRON-MICROSCOPY

1:00 Chairperson's Remarks

Mela Mulvihill, PhD, Scientist, Biochemical & Cellular Pharmacology, Genentech

1:05 CryoEM Applied to Drug Discovery

Seungil Han, PhD, Associate Research Fellow, Structure Biology & Biophysics, Pfizer Global R&D

1:35 Using Cryo-Electron Microscopy to Explore Endosomal GPCR Signaling

Alex Thomsen, PhD, Assistant Professor, Department of Surgery, Columbia University

We are applying a variety of electron microscopy (EM) and computational methods to obtain high-resolution structural information about the megaplex of a single GPCR that interacts simultaneously with β-arrestin and G protein, and to visualize GPCR signaling on the endosomal surface within living cells.

2:05 Structure-Based Drug Design with Cryo-EM Structures

Sponsored by SCHRÖDINGER

Eric Therrien, Principal Scientist II, Schrödinger

The presentation will highlight our recent development to expand the applicability of structure-based drug design using Cryo-EM structures and their use to accelerate drug discovery at Schrödinger.

2:35 Networking Refreshment Break

DRUG DISCOVERY APPLICATIONS

3:05 The Critical Role of Biophysical Methods (with a Focus on SPR) in Advancing CDK7 Drug Discovery

Kristin Hamman, MS, Research Investigator, Biochemistry, Syros Pharmaceuticals

We have established biochemical and biophysical methods to measure inhibition of CDK7 by both covalent and non-covalent inhibition. I will discuss our methods, focusing on our highly sensitive and robust SPR assay that has helped drive our lead optimization efforts for a next-generation oral CDK7 inhibitor. These studies have allowed us to better understand how inhibitor potency and residence time affect CDK7 occupancy in cells and lead to anti-proliferation and apoptosis of CDK7 inhibitor-sensitive cell lines.

3:35 Structural and Functional Characterization of Phospholipases as a Target for ALS

Jay Chodaparambil, PhD, Research Scientist, Chemical and Molecular Therapeutics, Biogen, Inc.

4:05 NMR and Enthalpy Screening of Combinatorial Libraries to Ligand Discovery

Maurizio Pellecchia, PhD, Professor of Biomedical sciences, UC Riverside, School of Medicine, Riverside, CA

We have recently proposed novel evolution-based ligand discovery approaches, in which the principles of positional scanning combinatorial chemistry and fragment-based drug design are combined with biophysical screening techniques, including NMR- and enthalpy- based strategies, to identify novel ligands from large collections of compounds (105-106 or larger). I will reiterate the basic principles of the approaches and report several recent applications including tackling challenging drug targets.

4:35 Close of Conference

SPONSORSHIP AND EXHIBIT OPPORTUNITIES

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

Sponsored Presentations – Available within the Main Agenda!

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

Luncheon Presentations

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

Invitation-Only VIP Dinner/Hospitality Suite

Sponsors will select their top prospects from the conference pre-registration list for an evening of networking at the hotel or choice local venue. CHI will extend the 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, or plated dinner with specific conversation focus).

One-on-One Meetings

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

Additional Opportunities Available for Sponsorship Include:

- Plenary Keynote Introduction
- ~~Poster Awards~~ SOLD!
- Welcome Reception Sponsor
- Conference Tote Bags
- ~~Badge Lanyards~~ SOLD!
- Hotel Room Keys
- Padfolios
- Program Guide Advertisements
- and more!

For more information, please contact:

Carolyn Cooke | Business Development Manager
ccooke@healthtech.com | 781-972-5412

EXHIBIT

Exhibitors will enjoy facilitated networking opportunities with 800+ qualified delegates, making it the perfect opportunity to launch a new product, collect feedback, and generate new leads from around the globe. Get noticed as a leader in the industry with an 8' x 20' exhibit space. Exhibit space sells quickly, so reserve yours today!

CURRENT SPONSORS & EXHIBITORS AS OF JANUARY 25TH, 2019

AChemBlock
AMRI
Analyticon Discovery
Apollo Scientific
AssayQuant
Biodesy, Inc.
BioDura
Biosensing Instrument
BioSolveIT
Biotage
BPS Bioscience
Bruker BioSpin
Calixar
Cfm Oskar Tropitzsch
ChemBridge Corporation
Chemical Computing Group
ChemPartner
Collaborative Drug Discovery
Cresset
Domainex
Enamine LLCS
Eurofins Advinus Limited
Eurofins Pharma Discovery Services
Evotec
Frontier Scientific, Inc.
GE Healthcare
HarkerBIO
HitGen Ltd.
horiba
IntelliSyn
Jubilant Biosys
Key Organics
Kishida Chemical Co., Ltd
Liverpool ChiroChem
Mercachem
Mimotopes
OpenEye Scientific
Optibrium
Pelago Biosciences
PharmaBlock
Piramal Pharma Solutions
Prestwick Chemical
Promega
Reaction Biology
RedShift BioAnalytics
SAI Life Sciences
SARomics Biostructures
Simulations Plus
SpiroChem AG
Sygnature Discovery
Synthonix
Tocris, a BIO-TECHNE Brand
Tokyo Chemical Industry Co., Ltd.
Ubiquigent
VeriSIM
Viva Biotech
Watanabe Chemical Industries
ZoBio

Hotel & Travel Information

Main Conference Venue:
San Diego Convention Center
111 West Harbor Drive
San Diego, CA 92101

Symposia Venue & Host Hotel:
Hard Rock Hotel
207 Fifth Avenue
San Diego, CA 92101
619-702-3000

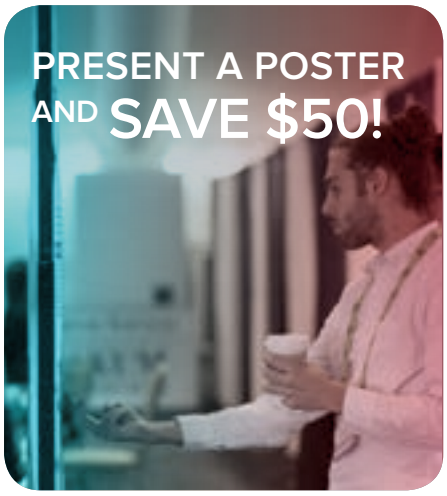
Discounted Room Rate:
$259 s/d studio rooms
$279 s/d suites

Discounted Cut-off Date: March 12, 2019

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

Student Fellowships Now Available

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

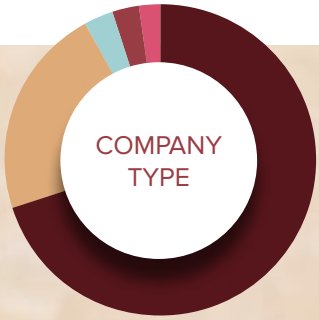


Dedicated poster sessions for Symposia and Conference Programs

Cambridge Healthtech Institute encourages attendees to gain further exposure by presenting their work in the poster sessions. To secure a poster board and inclusion in the conference materials, your abstract must be submitted, approved and your registration paid in full by **February 22, 2019.** 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

2018 ATTENDEE DEMOGRAPHICS



- Biotech & Pharma **70%**
- Academic & Government **22%**
- Healthcare **3%**
- Services **3%**
- Other **2%**

- USA **68%**
  USA Breakdown
  West Coast **51%**
  East Coast **37%**
  Midwest **12%**
- Europe **16%**
- Asia **13%**
- Rest of World **3%**

- Scientist/Technologist **34%**
- Executive & Director **31%**
- Sales & Marketing **12%**
- Professor **12%**
- Manager **6%**
- Other **5%**

Poster Awards in the Exhibit Hall!

Winners to be Announced:

WEDNESDAY, 9:35 during the Coffee Break
and
THURSDAY, 1:30 during the Dessert Break

Sponsored by domainex the faster route to drug discovery

PRICING & REGISTRATION INFORMATION

PREMIUM CONFERENCE PRICING, *BEST VALUE* *(Includes access to two conferences/Training Seminar, two short courses, and one symposium OR two conferences/Training Seminar and four short courses)*	Commercial	Academic, Government, Hospital Affiliated
Registrations after March 1, 2019 and on-site	$3399	$2199

STANDARD CONFERENCE PRICING *(Includes access to two conferences/Training Seminar, excludes short courses and symposia)*		
Registrations after March 1, 2019 and on-site	$2699	$1299

BASIC CONFERENCE PRICING *(Includes access to one conference/Training Seminar, excludes short courses and symposia)*		
Registrations after March 1, 2019 and on-site	$1999	$1099

SHORT COURSE PRICING *(April 8 & 10)*		
1 Short Course	$749	$429
2 Short Courses	$1049	$729
3 Short Courses	$1249	$829
4 Short Courses	$1449	$929

SYMPOSIUM PRICING *(April 12)*		
1 Symposium	$1049	$599

Short Courses - April 8

10:00 am to 1:00 pm

SC1: Covalent Fragments: Applications in Target-Based and Phenotypic Screens

SC2: Trends in Physical Properties of Drugs

SC3: Introduction to GPCR-Based Drug Discovery

2:00 pm to 5:00 pm

SC5: Ligand-Receptor Molecular Interactions and Drug Design

SC6: Methodologies for Optimizing Drug Clearance and Drug-Drug Interactions

SC7: Emerging Targets for Cancer Immunotherapy

6:00 pm to 9:00 pm

SC9: Advancing Tools and Technologies for Fragment-Based Design

SC10: Diversity-Oriented Platforms for Ligand Discovery

SC11: Targeted Protein Degradation Using PROTACs and Molecular Glues

Concurrent Conferences *(April 9-10)*	Concurrent Conferences/ Training Seminar *(April 10-11)*	Concurrent Symposia Hard Rock Hotel *(April 12)*
C1: Protein-Protein Interactions	**C6:** Modulating the Ubiquitin-Proteasome System	**S1:** Artificial Intelligence for Early Drug Discovery
C2: Small Molecules for Cancer Immunotherapy	**C7:** Inflammation Inhibitors	**S2:** Lead Optimization for Drug Metabolism & Safety
C3: Kinase Inhibitor Chemistry	**C8:** Macrocyclics & Constrained Peptides	**S3:** Blood-Brain Barrier and CNS Drug Discovery
C4: Fragment-Based Drug Discovery	**C9:** GPCRs & Membrane Proteins	**S4:** Biophysical Approaches for Drug Discovery
C5: Directed Evolution-Based Drug Discovery	**TS1:** Introduction to Small Molecule Drug Metabolism and Applications to Discovery and Development	

Dinner Short Courses *(April 10, 6:30 - 9:00 pm)*

SC13: Biochemistry and Pharmacology of the Ubiquitin-Proteasome System

SC14: Immunology Basics for Chemists

SC15: Macrocyclic Compounds for Drug Discovery: Opportunities, Challenges and Strategies

SC16: GPCR Structure-Based Drug Discovery

CONFERENCE DISCOUNTS

Dedicated poster sessions for Symposia and Conference Programs

Poster Submission – Discount ($50 Off): Poster abstracts are due by **February 22, 2019.** Once your registration has been fully processed, we will send an email containing a unique link allowing you to submit your poster abstract. If you do not receive your link within 5 business days, please contact jring@healthtech.com. *CHI reserves the right to publish your poster title and abstract in various marketing materials and products.

Register 3 – 4th Is Free: Individuals must register for the same conference or conference combination and submit completed registration form together for discount to apply.

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

Group Discounts: Discounts are available for multiple attendees from the same organization. For more information on group rates contact Uma Patel at 781-972-5447, upatel@healthtech.com.

ADDITIONAL REGISTRATION DETAILS

Each registration includes all conference sessions, posters and exhibits, food functions, and access to the conference proceedings link. Handicapped Equal Access: In accordance with the ADA, Cambridge Healthtech Institute is pleased to arrange special accommodations for attendees with special needs. All requests for such assistance must be submitted in writing to CHI at least 30 days prior to the start of the meeting. To view our Substitutions/ Cancellations Policy, go to healthtech.com/regdetails Video and or audio recording of any kind is prohibited onsite at all CHI events.

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

How to Register: **DrugDiscoveryChemistry.com**

reg@cambridgehealthtech.com | P: 781.972.5400 or Toll-free in the U.S. 888.999.6288

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

Please refer to the Registration Code below:

Cambridge HEALTHTECH Institute

A Division of Cambridge Innovation Institute

250 First Avenue, Suite 300
Needham, MA 02494, USA
Healthtech.com
Fax: 781-972-5425