FINAL DAYS to Register

Cambridge Healthtech Institute’s 14th Annual

Drug Discovery Chemistry

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

Optimizing Small Molecules for Tomorrow’s Therapeutics

CONFERENCE PROGRAMS

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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

DrugDiscoveryChemistry.com
CONFERENCE AT-A-GLANCE

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 selectively profiling in cells.
Instructor: Alexander Stasyuk, PhD, Assistant Professor, Department of Pharmacological and Pharmaceutical Sciences, University of Houston

SC2: Trends in Physical Properties of Drugs
Topics include: Properly impact drug efficacy, development, delivery and formulation, including pKa, taurocholic, crystal structure interpretation among others. Use of computational tools.
Instructors: Terry Stouk, PhD, President, RAD, Science for Solutions, LLC
Robert Flashkiewicz, PhD, Team Leader, Simulations Plus, Inc.
Max Tornoe, PhD, Principal Scientist, MSiSoft, 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 reconstitution assays, affinity mass spectrometry and biosensors.
Instructor: Annetta Ghosh, PhD, Professor, Department of Pharmacology, Midwestern University

Afternoon Short Courses

MONDAY, APRIL 8, 2:00 – 5:00 PM

SC4: Ligand-Receptor Interactions and Drug Design
Topics include: medicinal chemistry drug design principles illustrated via case study, lead optimization and 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: Marcel Tornet, PhD, Principal Research Scientist, Molecular Modeling, Abbvie

SC5: Methodologies for Optimizing Drug Clearance and Drug Interactions
Topics include: Transporter-mediated 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.
Instructor: Zhengyun 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.

SC6: Methodologies for Optimizing Drug Clearance and Drug Interactions
Topics include: Transporter-mediated 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.
Instructor: Zhengyun 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: newly published data on immunology (STING, RIG-1), epigenetic (HDAC, HAT), ubiquitin (DUBs, ligases) and autophagy targets; permeability and PK/ADME properties; synthetic strategies for macrocyclic formulation; including pKa, tautomerism, crystal structure interpretation among others.
Instructors: Eric Fischer, PhD, Assistant Professor, Cancer Biology, Dana-Farber Cancer Institute and Harvard Medical School
Alexander Stasyuk, PhD, Assistant Professor, Department of Pharmacological and Pharmaceutical Sciences, University of Houston

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 chemical space to sample. Instructors: Svetlana Belyanskaya, PhD, Encoded Library Technologies, R&D Platform Technology & Science, DSR Biotech
Ghosea Bvindh, PhD, Head, Post-Synthetic Chemistry Group, Encoded Library Technologies, R&D Platform Technology & Science, DSR

SC11: Targeted Protein Degradation Using PROTACs and Molecular Glues
Topics include: basic mechanistic biochemistry and pharmacology of the ubiquitin-proteasome system, including E1, E2, E3, and dual-activity 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: Alex Gichan, PhD, Scientist,Project Lead, Liana Therapeutics, Former Graduate Student, Laboratory of Drs. James Bruchet/Nathanial Gray, Harvard Medical School
Eric Fischer, PhD, Assistant Professor, Cancer Biology, Dana-Farber Cancer Institute and Harvard Medical School
Alexander Stasyuk, PhD, Assistant Professor, Department of Pharmacological and Pharmaceutical Sciences, University of Houston

Variation in the timing of the presentations indicates different sessions and topics covered on different days, with a variety of instructors from diverse fields contributing to the content. Each section is designed to provide in-depth knowledge on specific areas of drug discovery and development, offering practical insights and theoretical foundations for professionals in the drug discovery field. The inclusion of topics like GPCR-based drug discovery, covalent fragments, and genetic diseases highlights the comprehensive nature of the conference, aiming to cater to different research interests and expertise levels.
TARGETING MCL-1 AND BCL-2 COMPLEXES

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 TEAD•Yap inhibitors that selectively form a covalent bond targeting the intrinsically disordered N-terminal domain of the Androgen receptor (AR) to establish structure and fragment based drug discovery that identified hit series of compounds, some of which were subsequently selected for clinical candidates to cancer therapy.

10:40 Discovery of AZD5991, a Potent and Selective Macrocyclic Mcl-1 Inhibitor for Treatment of Cancer
Roderick E. Hubbard, PhD, Professor, University of York and Senior Fellow, Vernalis
Establishing structural support and understanding its limitations, choosing MIK665) that inhibits these protein-protein interactions. Major hurdles were identified for discovery of AMG 176. MCL1 inhibition rapidly induces apoptosis in subsets of cells, the compounds formed a covalent complex with TEAD4, inhibited its Yap co-activation of TEA domain (TEAD) transcription factors. We report the discovery of nodiaplam, and its full profile. This compound is currently completing pivotal clinical trials in all type SMA patients.

11:15 Chairperson’s Remarks
Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

11:20 Break

11:30 LUNCHEON: Discovery of Risdiplam; a Selective SMN2 Gene Splicing Modulator for the Treatment of Spinal Muscular Atrophy
Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute
Risdiplam is a selective SMN2 gene splicing modulator that acts by directly blocking a critical splice site to stabilize SMN2 pre-mRNA for the treatment of spinal muscular atrophy. We will discuss our recent efforts to unravel their molecular mechanism of action.

12:00 Welcome Reception in the Exhibit Hall with Poster Viewing

12:20 pm Session Break

12:35 Small-Molecule Covalent TEAD•Yap Antagonists
Samy Meroueh, PhD, Associate Professor, Department of Biochemistry and Molecular Pharmacology, University of California, San Francisco
Small-Molecule Covalent TEAD•Yap antagonists are potent and selectively modulate hypothalamic genes that control energy and insulin sensitivity. Here, we discuss our recent efforts to unravel their molecular mechanism of action.

13:00 Small-Molecule Covalent TEAD•Yap Antagonists
Samy Meroueh, PhD, Associate Professor, Department of Biochemistry and Molecular Pharmacology, University of California, San Francisco

13:15 Poster Awards Sponsored by Domainex

16:00 Poster Awards Sponsored by Domainex

16:00 Biophysics and Structural Biology: A Novel Approach to Targeting the Androgen Receptor
Michelle Akin, 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 design specific 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.

16:15 Discovery of 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 constitutive 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 “undruggable.”

16:30 Coffee Break in the Exhibit Hall with Poster Awards Announced

16:45 Path to Allosteric Drugs
Gregg Siegel, CEO, ZolBio
Allosteric drugs offer exciting new opportunities. ZolBio’s platform of biophysics and structural biology allows us to design small-molecule drugs 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 ABD-bound form and inhibit ATPase activity will be described.
**Small Molecules for Cancer Immunotherapy**

**Design of New Compounds and Combinations for Immuno- Oncology Targets**

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

**TUESDAY, APRIL 9**

**7:00 am Registration Open and Morning Coffee**

**NEW COMPORDS FOR SINGLE AND COMBINATION I THERAPY**

**8:00 Welcome Remarks**

Tanya Kopal, 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, SignaLymph Pharmaceuticals

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

Director of Operations, SignalRx Pharmaceuticals

**8:30 Toll-Like Receptor (TLR) 7 and 8 Agonists with Direct Immunosuppression**

Mercachem

**8:40 Chairperson’s Remarks**

Inder Bhardwaj PhD, Research Fellow, Medicinal Chemistry, RedPharma fileRXC004 is a potent and selective Porcupine inhibitor currently undergoing Phase I clinical evaluation in cancer patients. Porcupine is an membrane bound O-acetyltransferase responsible for post-translational modification of all Nls Vtg ligands. Porcupine inhibitors are efficacious in preclinical models of Wnt ligand driven cancers. Preclinical models demonstrate that RXC004 has an anti-tumor effect via an immune-stimulatory mechanism, both as a single agent or in combination with anti-PD1 antibodies.

**8:50 Rit-Like Receptor (TLR) 7 and 8 Agonists with Direct Immunosuppression**

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

**9:00 Welcome Remarks**

Tanya Kopal, PhD, Conference Director, Cambridge Healthtech Institute

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

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

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

**9:35定量imalonate Cancer Therapy**

Wayne W. Hancock, MD, PhD, Professor, Pathology and Chief of Transplant Immunology, Children's Hospital of Philadelphia and University of Pennsylvania Fasp+ Tregs predominate in the microenvironment of many “hot” tumors where they suppress anti-tumor immunity. There are currently no approved strategies that specifically focus on targeting intratumoral Fasp+ 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 shows 96% identity (111 of 116) with human Tip60, the relevance of our mechanistic studies in murine models to human disease appears compelling.

**10:00 Targeted Protein Degradation for Treatment of Cancer**

Michael Plowe, PhD, Vice President, Medicinal Chemistry, Cogen, Inc.

**10:30 TLR7/8 Agonists with Direct Immunosuppression**

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

**10:45 Chairperson’s Remarks**

Inder Bhardwaj PhD, Research Fellow, Medicinal Chemistry, RedPharma

**11:00 Targeted Protein Degradation for Treatment of Cancer**

Michael Plowe, PhD, Vice President, Medicinal Chemistry, Cogen, Inc.

**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. Holgaard, 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 TGFβ on the HSPC harboring TGFβ pathway inhibitor, galardinib 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 an anti-PD1 resulting in tumor regressions associated with enhanced Tcell activity. A second generation and potent TGFβ selective inhibitor, LY3350028, is currently in Phase I.

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

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

The histone acetyltransferase 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 MDC5 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 Microbiota to Modulate Novel Cancer Therapy**

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

**2:30 Chairperson’s Remarks**

Inder Bhardwaj PhD, Research Fellow, Medicinal Chemistry, RedPharma

**2:35 Plenary Technology Spotlight: Molecular Modelling for the Masses: Orion CloudEnabled Pharmaceutical**

The advent of cloud computing has been transformative for many fields that utilize computation, including drug discovery. The cloud offers robust, elastic, and on-demand computational power through a browser, decreased IT overhead, costs, and time to obtain actionable results. In this presentation I illustrate how, and in particular Orion CloudEnabled, can be used for drug discovery in practice, by modelling by providing easy to use access to cutting-edge molecular design tools coupled with essentially unlimited compute resources.

**3:05 Plenary Keynote Introduction (Sponsorship Opportunity Available)**

**3:15 Plenary Keynote: Chemical Biology of Proteostasis**

James Tonton, PhD, Professor, Department of Cellular and Molecular Pharmacology, University of California San Francisco

We have discovered several macromolecular compounds that potently and selectively modulate protein homeostasis. I will discuss our recent efforts to unravel their mechanisms of action and their potential usages.

**3:45 Welcome Remarks from Lead Conference Director**

Anjoy Shag, PhD, Senior Conference Director, Cambridge Healthtech Institute

**4:05 Chairperson’s Remarks**

Inder Bhardwaj PhD, Research Fellow, Medicinal Chemistry, RedPharma

**4:35 Plenary Technology Spotlight: Molecular Modelling by providing easy to use access to cutting-edge molecular design tools coupled with essentially unlimited compute resources.**

**5:05 Plenary Keynote: Chemical Biology of Protostasis**

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**5:10 Poster Awards Sponsored by Domainex**

**5:15 Poster Awards Sponsored by Domainex**

**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**

**Website for details**

**EMERGING ROLE OF PROTACs IN ONCOLOGY**

**8:30 Chairperson’s Remarks**

Markus Quessner, PhD, Scientific Leader, Protein Degradation DPU & R&D Future Pipeline Discovery, Gilead Sciences, Inc.

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

Markus Quessner, PhD, Scientific Leader, Protein Degradation DPU & R&D Future Pipeline Discovery, Gilead Sciences, Inc.

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

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

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

**9:35 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 Fasp+ Tregs predominate in the microenvironment of many “hot” tumors where they suppress anti-tumor immunity. There are currently no approved strategies that specifically focus on targeting intratumoral Fasp+ 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 96% identity (111 of 116) 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 Plowe, PhD, Vice President, Medicinal Chemistry, Cogen, Inc.

**11:30 Dual role of USP7 Inhibitors in Treatment of Malignant Diseases**

Taochao Liu, PhD, Professor, Progrima

**11:50 USP7 Inhibitors with Antitumor Activity and therapeutic effects in various cancer models.**

**8:00 Welcome Remarks**

Tanya Kopal, 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, SignaLymph Pharmaceuticals

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

Director of Operations, SignalRx Pharmaceuticals

**8:30 Toll-Like Receptor (TLR) 7 and 8 Agonists with Direct Immunosuppression**

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**9:00 Welcome Remarks**

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Michael Plowe, PhD, Vice President, Medicinal Chemistry, Cogen, Inc.

**11:30 Dual role of USP7 Inhibitors in Treatment of Malignant Diseases**

Taochao Liu, PhD, Professor, Progrima
Tyrosine kinase (BTK) and will share the results of this case-study and the selectivity. We have employed a series of biochemical and cellular enzymatic or signaling activity. Despite this interest, fundamental questions remain regarding the parameters most critical for achieving potency for evaluating drug efficacy, clearance, toxicity, and drug-drug interactions. Understanding the interactions between drug molecules and CYPs is critical responsible for clearing drug molecules through oxidative metabolism. Cytochrome P450 oxidases (CYPs) are heme-containing enzymes for which other than kinase targets have been identified 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.

Non-Kinase Targets of Protein Kinase Inhibitors
Lenka Munoz, PhD, Associate Professor, School of Medical Sciences, Discipline of Pharmacology, The University of Sydney.
Non-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 kinase. I will present kinase inhibitors for which other than kinase targets have been identified and discuss molecular pharmacology guidelines when using kinase inhibitors.

2:00 pm Break Session

NEW TARGETS & PROMISING CANDIDATES

11:00 Chairperson's Remarks
Lenka Munoz, PhD, Associate Professor, School of Medical Sciences, Discipline of Pharmacology, The University of Sydney

11:15 New Targets & Promising Candidates
Lenka Munoz, PhD, Associate Professor, School of Medical Sciences, Discipline of Pharmacology, The University of Sydney.

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 publicly accessible web-service for studying kinase pharmacology and drug discovery. KinaMetrix enables researchers to investigate and visualize the kinase conformational space as well as small molecule substrates that exhibit conformational specificity.

11:30 Lunch Presentation: Sensors for Continuous Monitoring of Protein Kinase & Phosphatase Activity
Erik Schaefer, President & CSO, Research & Development, KinaMetrix.

12:00 pm Session Break

NEW TARGETS & PROMISING CANDIDATES

1:15 Chairperson's Remarks
Lenka Munoz, PhD, Associate Professor, School of Medical Sciences, Discipline of Pharmacology, The University of Sydney

1:30 Reversing the Paradigm: Protein Kinase C as a Tumor Suppressor
Tim Baffi, Graduate Student, Alexandra Newton's Lab, Department of Pathology, The University of Sydney.

Protein kinase C (PKC) has historically been considered an oncoprotein. Our recent investigations reveal that most mutations are loss-of-function and none are activating; mechanisms for ERK1/2 and JNK/p38, of which we made use of as a novel drug target for signaling related diseases.

1:45 Protein Kinase Conformational Space with Machine Learning
Amer 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 publicly accessible web-service for studying kinase pharmacology and drug discovery. KinaMetrix enables researchers to investigate and visualize the kinase conformational space as well as small molecule substrates that exhibit conformational specificity.

1:55 Shuttle: New Targets & Promising Candidates
Erik Schaefer, President & CSO, Research & Development, KinaMetrix.

2:20 Targeting the Nuclear Translocation of MAPKs as a Novel Drug Target
Matthew Calabrese, PhD, Senior Principal Scientist and Structural Biology Group Leader, OpenEye Scientific Computing Group.

The presentation covers our efforts aiming for selective, pan-JAK inhibitor chemistry.

2:40 FEATURED PRESENTATION: Targeted Degradation of Bruton’s Tyrosine Kinase (BTK)
Matthew Calabrese, PhD, Senior Principal Scientist and Structural Biology Group Leader, OpenEye Scientific Computing Group.

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 specificity.

2:50 Chairperson’s Remarks
Aleks Denis, Head of Discovery Division, Oncodesign

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.

3:00 pm Break Session

NEW TARGETS & PROMISING CANDIDATES

3:30 Welcome Remarks from Lead Conference Director
Garth I. Stief, PhD, Senior Director, Discovery Sciences, GSK.

4:10 Plenary Session Spotlight: Molecular Modelling for the Masses

5:00 pm Break Session

5:30 Plenary Keynote Introduction (Sponsorship Opportunity Available)

5:40 PLINARY KEYNOTE: Sensors for Continuous Monitoring of Protein Kinase & Phosphatase Activity
Erik Schaefer, President & CSO, Research & Development, KinaMetrix.

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

7:00 Close of Day

Wednesday, April 10

10:00 Late Breaking Presentation
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 pharmacological 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 kinases for which we have developed hit identification strategies: ROCK1, ROCK2, and LRRK2.

12:00 pm Conference closing
10:00 Nitewing Coffee Break

10:10 The Discovery of Novel Allosteric MDM2 Binders by Fragment-Based Approaches

10:30 Linkage Selectivity

10:50 Fragment-Based Drug Discovery Campaigns with Proteasome Compounds that Modulate Protein-Protein Interactions

11:10 Inhibiting Mice with The Spondylochoondral-Alkyne Derivatives

11:30 FRAGMENT - DERIVED DRUG CANDIDATES

11:50 FRAGMENT-DERIVED CANDIDATES PROGRESSING IN THE CLINIC

Panel Chair: Chakravarti Ramnarine

12:00 Chakravarti Ramnarine

12:10 Erik J. Hembre, PhD, Research Fellow, Discovery Chemistry Research, Eli Lilly & Co.

12:20 pm Session Break

12:30 Pushing the Envelope for Fragment-Based Drug Discovery with Mini-Drug: Max Cherney, MPH, Senior Director, Molecular Sciences, Merck

12:50 A Framework for the Treatment of Alzheimer's Disease

1:10 A Framework for the Treatment of Alzheimer's Disease

1:30 Fragment Library Design: Quantitative Analysis of Molecular Shape and Functionality

1:50 Fragment Library Design: Quantitative Analysis of Molecular Shape and Functionality

2:10 Solvation Energy-Driven Docking in Library Design: Applications to Fragment-Based and Fragment-Assisted Approaches

2:30 Playing with Water: From Weak Binders to Potent Inhibitors of FXIa inhibitors

2:50 Pushing the Envelope for Fragment-Based Drug Discovery with Mini-Drug: Max Cherney, MPH, Senior Director, Molecular Sciences, Merck

3:10 Pushing the Envelope for Fragment-Based Drug Discovery with Mini-Drug: Max Cherney, MPH, Senior Director, Molecular Sciences, Merck

3:30 FRAGMENT SCREENING TECHNOLOGIES

Panel Chair: Paul Colbon, PhD, CEO, UK Headquarters, Liverpool

3:40 Paul Colbon

3:50 Drug Discovery Chemistry.com • 11

4:10 Pushing the Envelope for Fragment-Based Drug Discovery with Mini-Drug: Max Cherney, MPH, Senior Director, Molecular Sciences, Merck

4:30 Welcome Remarks from Lead Conference Director

4:40 FRAGMENT TECHNOLOGIES

Panel Chair: Wolfgang Jahnke, PhD, Director and Leading Scientist, Chemical Biology and Therapeutics, Novartis Institutes for Biomedical Research

4:50 Wolfgang Jahnke

5:10 FRAGMENT TECHNOLOGIES

Panel Chair: Jack Taunton, PhD, Professor, Department of Cellular and Integrative Biology, University of California San Francisco

5:20 Jack Taunton

5:40 BACE Inhibitor Drug Discovery - From Fragment-Based Hits to Clinical Candidates

6:00 Poster Awards Sponsored by Domainex

6:10 Poster Awards Sponsored by Domainex

6:20 Poster Awards Sponsored by Domainex

6:30 Poster Awards Sponsored by Domainex

6:40 Poster Awards Sponsored by Domainex

6:50 Poster Awards Sponsored by Domainex

7:00 Registration Open and Opening Coffee

7:30 New FBDD Approaches

8:00 Welcome Remarks

8:05 Chairperson's Opening Remarks

8:10 Application of Fragment-Based Drug Discovery to the Identification of Novel Hit-Identifiers for Thromboxane Pathway Inhibitors

8:30 Linkage Selectivity

8:50 The Fragment-Based Drug Discovery Challenge

9:10 From About Thin Films to About Thick: Thirteen Years of Fragment-Based Drug Discovery at BioAssayExpress

9:30 FRAGMENT-BASED DRUG DISCOVERY

Panel Chair: Maricel Torrent, PhD, Principal Research Scientist, Molecular Modeling, AbbVie

9:40 Maricel Torrent

9:50 NEW FBDD APPROACHES

Panel Chair: Dan Erlanson, PhD, Co-Founder, Carmot Therapeutics

10:00 NEW FBDD APPROACHES

10:20 NEW FBDD APPROACHES

10:40 NEW FBDD APPROACHES

11:00 NEW FBDD APPROACHES

11:20 NEW FBDD APPROACHES

11:35 NEW FBDD APPROACHES

11:50 NEW FBDD APPROACHES

12:00 NEW FBDD APPROACHES

12:15 NEW FBDD APPROACHES

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Directed Evolution-Based Drug Discovery | April 9-10, 2019

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
Asango 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
End by describing a method to greatly increase the diversity of molecular libraries on micro-beads. Such libraries can be achieved with cell-based assays for cellular functions and signaling. I will 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.

8:40 Employing Photoredox Catalysis for the Synthesis of DNA-Encoded Libraries
Brian Paegel, PhD, Associate Professor, Department of Chemistry, Department of Molecular Medicine, Scripps Research Institute

9:10 Unleashing DNA-Encoded Library Technology: Drug Discovery and Beyond
Lilian Xia, PhD, Senior Director, Head of Biochemistry & Informatics, WuMinappTec

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
Rani Haran, PhD, Project Manager & Group Leader, Early Discovery Biochemistry, Genentech Inc.

10:35 FEATURED PRESENTATION: Unnatural Amino Acids for Exotic Macromolecular Peptides and Targeting IL6R as a Case Study
Hikari 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 synthesized macrocyclic 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 displaying high-affinity binding.

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

4:35 Plenary Technology Spotlight: Molecular Modelling for the Masses: Orion
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 will illustrate how the cloud, and in particular OpenEye’s web-based platform Orion, is democratizing molecular modelling by providing easy access to cutting-edge molecular design tools coupled with essentially unlimited compute resources.

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 Institute

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, Massey Cancer Center, Virginia Commonwealth University

Diverse libraries of macrocyclic peptides are a potential storehouse for the discovery of therapeutically relevant receptors against many different PPI targets. 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 cyclic 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 GPCR
Pei-Pei Kung, PhD, Associate Research Fellow, Medicinal Chemistry, Pfizer

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 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 Dovianex

ENCODED LIBRARY APPLICATIONS

10:30 Design and Evolution of Macro cyclic Peptide Inhibitors of the Hedgehog Signaling Pathway
Raul Farias, 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 peptide inhibitors 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 Late Breaking Presentation

11:30 DEL for Membrane Proteins: Case Study of a GPCR
Dean G. Blixt, PhD, Director, External Chemistry, MTI Discovery, Discovery Sciences, IMED Biotech Unit, AstaZeneca

This talk compares a DNA-encoded library screen to identify antagonists at a photo-activated receptor (PAR2) with a fragment screen using a stabilized PAR2 GPCR receptor. From these efforts, we identified two lead antagonists, each of which bind to distinct previously unknown allosteric sites. These results illustrate the power of integrating stabilized GPCR technologies into established screening paradigms.

12:00 pm Close of Conference

Note: The scheduled program is subject to change.
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

Modulating the Ubiquitin-Proteasome System | April 10-11, 2019

UNDERTAKING AND OPTIMIZING THE USE OF PROTACs

UNDERSTANDING AND OPTIMIZING THE USE OF PROTACs

10:40 Chairperson’s Remarks

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

Markus Queisser, PhD, Scientific Leader, Protein Degradation DPU, R&D Future Pipelines Discovery, Genentech, Inc.

The advantages of the PROTAC technology lie in its modularity, 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.

11:05 Lessons from Viral Hijacking of Ubiquitin-Mediated Protein Degradation

Yue Kong, William R. Kenan, Jr. Professor of Biochemistry and Biophysics, University of North Carolina. Co-Founder, Culgen

Viruses has learned the use of ubiquitin-proteasome system to overcome the cellular defense mechanisms and无数insight into the small molecule design to target recent protein degradation for drug discovery. Understanding the role of a viral E3 complex will enhance the success rate of degrader. Protein-protein interaction between viral protein and E3 ligases may also lead us to the discovery of new E3 ligases.

11:33 Targeting Degubiquitylases (DUBs): Opportunities for Collaborative Drug Discovery

Jason Brown, PhD, Scientific and Business Development Director, Ubiquitogen LLC.

We will discuss Ubiquitin’s deubiquitylase (DUB) enzyme targets with small molecule hit-to-lead platform featuring our in house DUB-targeting computational and medicinal chemistry capability. We are currently 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.

12:00 pm Antibody-Mediated Delivery of Protein Degradators

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

Small molecules for treatment of MYD88 mutant lymphoma

Stewart Fisher, PhD, CSO, C4 Therapeutics

(Sponsorship Opportunity Available)

12:30 pm Luncheon Presentation

12:30 pm Registration Open

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

12:45 Networking Refreshment Break

4:50 Conformation, Complexation, and Catalysis in the AAA+ Family

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

With relevance to a critical unmet need in immune-oncology, we have developed a general approach to designing small molecule inhibitors for the p300/CBP bromodomain, an attractive therapeutic target. The bromodomain is a conserved structural module that associates with ubiquitin. This approach has yielded numerous protein that associates with ubiquitin. This approach has yielded numerous inhibitors, and in some cases activators, for deubiquitylases, E2 enzymes, E3 ligases 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.

1:30 Luncheon Break (Sponsorship Opportunity Available)

1:30 Breakout Discussions

DUBing the Undruggable

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

We will report progress on attacking sulfide tethering,

5:20 CUfido Disruption of IRAK4 Protein Via Heterobifunctional Protein Degradation Beyond Bi-functional Degraders

Michael Walczak, PhD, CSO, Capricer 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

9:05 Plenary Keynote Introduction

9:15 Plenary KEYNOTE: New Ways of Targeting K-Ras

Frank McCormick, PhD, Professor, K-H 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, de sulfating in silico drug design and biological methods such as Second Harmonic Generation (SHG). We will report progress on attacking two alleles in the RASopathies. Studies protein, cytosine-185 (the site of phosphorylation), and histidine-91, a residue unique to K-Ras, in addition to K-Ras, activating beta as well as the other two beta via the K-Ras GTPase activating protein, and other proteins.

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

2:15 Chairperson’s Remarks

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. Hankoff, MD, PhD, Chief Technology and Chief of Transplant Immunology, Children’s Hospital of Philadelphia and University of Pennsylvania

We have developed small molecule inhibitors of USP7, an important regulator of innate immunity, we have shown that USP7 is a key target for therapeutic regulation of FOXP3+ Treg cells through its regulation of Tg65 expression. We now provide evidence of direct activity of USP7 in Treg cells. USP7 inhibitors block the production of TGF-beta and IL-10 production by T cells, including modulation of tumor cell metabolism and impairment of the antitumor immune response. We will discuss the potential mechanisms of action provide a compelling rationale for USP7 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 MDMX. Using a structure-based drug design strategy, we have identified reversible USP7 inhibitors that are highly potent in biological 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 vivo.

3:30 Dubbling the Undruggable

Stephanos Ioannidis, PhD, Head, Early Portfolio, FORMA Therapeutics

FORMA Therapeutics deploys multi drug discovery screening platforms to explore the DUB family (DUBome) and along with DUB scaffolding, repurposing, automated parallel synthesis and computational/crystallographic insights specific and selective inhibitors within the DUBome have been identified. As part of a fully-integrated R&D strategy, DUB alliances which include FORMA and key collaborative networks have been forged to interpret the previous undruggable targets via specific DUB inhibition. In this presentation, FORMA’s novel approach to DUBs and druging the undruggable will be described.

3:50 Networking Refresh Break
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

1:00 Welcome Remarks
Anjani Shah, PhD, Senior Conference Director; Cambridge HealthTech Institute

1:15 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
Andrew 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 form of regulated necrosis independent of caspase-8-mediated apoptosis, is emerging as an important mediator of a number of human diseases. Activation of necroptotic signaling via TNFR-signaling or 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
Andrew Patel, PhD, Scientist, Discovery Chemistry, Genentech, Inc.

2:45 Welcome Remarks from Lead Conference Director
Anjani Shah, PhD, Senior Conference Director; Cambridge HealthTech Institute

3:00 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 in targeting 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.

4:45 Coffee Break in the Exhibit Hall with Poster Viewing

New Inflammation TARGETS for SMALL MOLECULES

10:45 Welcome Remarks
Swati Patel, PhD, Scientist, Discovery Chemistry, Genentech, Inc.

10:50 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 tools in mitochondrial quality control operated by targeted autophagy. It will also dwell on their targeting of mitochondrial pathways which define autophagy and inflammation. The presentation will therefore elaborate on the prominent in cell activity of the non-covalent K-Ras NRF2 protein-protein interaction that modulates this the switch between a state of protection and pathological state. Inflammation is structurally distinct from the covalent Keap1 modifiers (e.g., sulfonaphthoate) and highlight promising ligands targeting mitochondrial pathways involved in the inflammatory response.

11:10 Novel Small Molecule E3 Ligase Activators as Anti-Inflammatory Agents
Kumar Suresh, PhD, Senior Director; RDD Biology, Progena, Inc.
This talk will present our discovery and characterization of novel E3 ligase activators that suppress TH2 and TH17 differentiation and exhibit robust anti-inflammatory properties. Novel K-Ras family E3 ligases, including ITch, negatively regulate inflammatory immune responses by suppressing TH2 and TH17 differentiation and cytokine production. Genetic disruption of ITch ameliorates inflammation in a number of mouse models of multi-system disorders and lung inflammation.

11:45 CETSA® Enabled Drug Discovery
Michael Babwette, 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 6 years CETSA has been applied in hundreds of studies from early target validation to analysis of clinical samples. In this talk we will explore examples of applications and also discuss future perspectives in enabling drug discovery using the CETSA method.

12:00 pm Targeting TRAF3 E3 Ligase Activity with Small Molecules Combats Chronic Inflammation and Autoimmunity
Kayran Hadjian, PhD, Group Leader, Helmholtz Zentrum München Constitutional NF-E2-e xpression represents a hallmark of chronic inflammation and autoimmunity diseases. The E3 TRAF3 ligase acts as a key regulator bridging innate immunity, pro-inflammatory cytokines, and antigen receptors to the NFκB pathway. Here, we present an inhibitor of TRAF3-Lic3 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 Viewing

Awards Announced
Poster Awards Sponsored by Domainex

TARGET THE INNATE IMMUNE SYSTEM

2:15 Chairperson’s Remarks
Daniel Garovich, PhD, Senior Research Advisor, Medicinal Chemistry, Eli Lilly & Co.

2:30 Bacterial Mediated Chemical Transformations of Autoimmune Drug Molecules
Jason Michael Crawford, PhD, Associate Professor, Departments of Chemistry and Microbial Pathogenesis, Yale University
Photodynamic bacterial activity causes soft tissue infections of the skin. This bacterium produces the immunomodulator tapinarof during its development. Phototoxicity of this drug transforms into other novel potent products that activate the pathogenic immune system with clinical efficacy and kill the bacteria of the skin.

2:50 Discovery of Novel and Potent Spirocyclic RORγt Inhibitors
Chip Lugar, Senior Research Scientist, Discovery Chemistry Research, Eli Lilly & 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 a small set of diverse spiro cyclic inhibitors. We will present the 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 Thacker, PhD, CEO, Ophagen
This presentation will address the chemistry challenges we’re facing 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 Refresh Break

4:20 Presentation to be Announced

4:50 Targeting Soluble TNF to Eliminate Chronic Inflammation without Immunosuppression
PJ Trad, MD, CEO/CMO; Immune 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 the safety, efficacy and therapeutic opportunity.

5:15 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
NSGonitrose (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 buds in vitro and in vivo. The lead compound, SLP-891, is active in models of RA, IBD, and NASH among others.

5:50 Close of Conference

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Macrocylics & Constrained Peptides | April 10-11, 2019

MEDICINAL CHEMISTRY OF MACROCYCLIC PEPTIDES

10:40 Chairperson's Remarks

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

Petra Jansa, PhD, Senior Research Scientist II, Medicinal Chemistry, GSK

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 all oral antiviral combination therapy. An initial lead derived from the sanglifehrin 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

Toni K. Sawyer, PhD, Distinguished Scientist, Peptide Drug Discovery & Innovative Technologies, Merck & Co., Inc., West Point, PA

This talk will focus on how 4*STAR has enhanced the revitalization of peptide research and is evolving technologies to enable the development and adoption of new peptide modalities for protein-protein interactions. Examples targeting GTP and translational initiation (eIF-4F) pathways for oncology and multimodal biomarkers for immunology will highlight our recent advances in design, discovery, and chemistry and formulation.

11:45 FidiaMacro™: Macrolide Inspired Macrocyclics as Promising Templates for Unmet Medical Needs

Tanya Paljop, PhD, Group Leader, Medicinal Chemistry, Fidia Life Sciences

This project will present recent results on our macrolide inspired macrocyclic library preparation and SAR. Includes recent results on macrocyclic technology including in vitro screening, pharmacokinetic data as well as in vivo proof of concept data. Inhibition of IL-17A/IL-17R interaction will be presented as a case study of targeting cytokine/chemokine receptors. Examples of compounds supported as a novel macrocyclic compound that showed efficacy in the mouse bluelrocmin model and additional novel oral antibacterials with in vivo demonstrated Gram-negative activity will be discussed.

12:00 Discovery to Approval: Medicinal Chemistry Retrofitting 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

Lorlatinib is an orally bioavailable, brain-penetrating kinase inhibitor with >95% bioavailability. It was discovered with high potency against ALK and ROS1, with additional inhibitory activity against several other kinases. Lorlatinib exhibits broad in vitro cell activity, in vivo activity against a mouse xenograft model, and oral administration in patients with ALK-rearranged tumors. Lorlatinib was approved in 2018 for the treatment of ALK-positive NSCLC. Lorlatinib is currently in clinical trials as a blood-brain-barrier penetrant with activity against ALK, ROS1, and other kinases. Lorlatinib will be presented with focus on unique lab objective and safety challenges.

12:15 Poster Awards Ceremony

Poster Awards Sponsored by Domainex

12:30 Lunch Break in the Exhibit Hall with Poster Viewing

THURSDAY, APRIL 11

4:30 Refreshment Break in the Exhibit Hall with Poster Viewing

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

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

This talk will focus on how 4*STAR has enhanced the revitalization of peptide research and is evolving technologies to enable the development and adoption of new peptide modalities for protein-protein interactions. Examples targeting GTP and translational initiation (eIF-4F) pathways for oncology and multimodal biomarkers for immunology will highlight our recent advances in design, discovery, and chemistry and formulation.

5:00 4*STAR Peptide Engineering Platform (PEP): Targeting Macromolecular Modulators of Protein-Protein Interactions

Charles Johannes, PhD, Principal Scientist II & Head Director, Organic Chemistry, 4*STAR

This talk will focus on how 4*STAR has enhanced the revitalization of peptide research and is evolving technologies to enable the development and adoption of new peptide modalities for protein-protein interactions. Examples targeting GTP and translational initiation (eIF-4F) pathways for oncology and multimodal biomarkers for immunology will highlight our recent advances in design, discovery, and chemistry and formulation.

5:30 Breakout Discussions

See website for details.

6:15 Close of Day

6:30 Dinner Short Courses*

See website for details.

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

8:45 Welcome Remarks from Lead Conference Director

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

9:05 Plenary Keynote Introduction

Sponsored by OpenEye

8:55 PLURINARY KEYNOTE:

New Ways of Targeting K-Ras

McComick, 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-substituted binding, and biological 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

TARGET MODULATION WITH MACROLECULARS

2:15 Chairperson's Remarks

Lawrence W. Loewy, PhD, Professor, Global Discovery Chemistry, Novartis Institutes for BioMedical Research, Inc.

2:20 Macroyclic Inhibitors of Pim1/2 Kinase

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

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

Eric Marsaud, PhD, Professor, Medicinal Chemistry and Pharmacology, University of California, San Diego

Neurotensin mediates opioid independent analgesia via the NT1S and NT2S receptors. Careful exploration of optimal sites of cyization on Neurotensin B-13 led to two distinct series of macrocyclic pharmacological probes. Series 1 possesses low rm potency for both NT1S and NT2S, while series 2 is associated with low rm potency for NT2S and >1,000 fold selectivity vs NT1S. In vivo, these series allowed separation of the desired analgesia from the undesired hypothermia and hypotension.

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

David Speckene, PhD, CSIO, Circle Pharma

Circle Pharma deploys a structure–design/synthetic chemistry platform for macrocyclic therapeutic development 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 PIM3/MDM2/A, MCL1/BCL, cyclophilin-a, and beta catenin/Wnt. Examples of ongoing development will be presented.

3:50 Networking Refreshment Break

4:20 Macro cyclic 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 TMD do gp120 glycoproteins. cPTs have great pharmacokinetic/hydrophilicity balance and have good aqueous solubility, making them attractive as an alternative to the traditional GPG approach. Examples of promising pharmacokinetics (PK) is 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 Fournier, PhD, Director, Bacterial Resistance Group, Emergence, University

Weighing peptidomimetics will deliver 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 Retinol-3/ RXR Receptor, a Key Player in Multiple Diseases

Subhy Marwan, PhD, Postdoctoral Research Associate, Department of Medicine and Neuroscience, SUNY Upstate Medical University

The “helix imitator” molecular class of RXR agonists, RXR-RFXPs is a novel cyclic peptidomimetic that targets the undesired hypotension and hypothermia.

5:45 Close of Conference

DrugDiscoveryChemistry.com | 20
2:10 Structure-Based Ligand Discovery for Class ‘A’ GPCRs: New Targets and Approaches
Inna Kufareva, PhD, Associate Adjunct Professor, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California at San Diego
In the rapid accumulation of high-resolution crystallographic and NMR 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.

2:30 A Global Survey of GPCR Drug Development Programmes
Evan J. Gurevich, Senior Scientific Advisor, Johns Hopkins University
The global landscape of current GPCR drug development programmes will be surveyed, including the status and impact of these programmes in different therapeutic areas, the therapeutic areas that are emerging, and the contributions of new technologies and approaches to the field of GPCR drug discovery.

2:50 The Good, the Bad, and the Confusing: Binding Kinetics at GPCR Active Sites
Christopher Reynolds, PhD, Professor, Royal Society Industry Fellow, School of Neuroscience, University of North Texas Health Science Center
This talk will focus on the Key-Set hypothesis, which states that there is an optimal set of ligand binding interactions that define a functional GPCR conformation. The Key-Set is influenced by the intrinsic bias of the ligand, by receptor post-translational modifications and by the cellular environment. These factors can lead to different binding kinetics, which can be confusing when trying to interpret binding data. The talk will illustrate these concepts with case studies and will discuss the implications for GPCR drug discovery.

2:20 FEATURED PRESENTATION: One Receptor, Many Partners: How do GPCRs Stimulate Diverse Signal Transduction Pathways?
Brian Murphy, PhD, Senior Principal Scientist, CV and Fibrosis Drug Discovery, Bristol Myers Squibb
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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

Inaugural

SYMPOSIUM

Artificial Intelligence for Early Drug Discovery

Friday, April 12, 2019

7:30 am Registration Open and Morning Coffee

AI FOR DRUG DESIGN

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

8:00 Fast Molecular Electrostatic Surfaces Using Artificial Intelligence
Marcel Verdonk, PhD, Senior Director, Computational Chemistry & Informatics, Astex Pharmaceuticals

Electrostatic complementarity between protein and ligand is critically important to obtain optimal affinity. Here, we present a method that uses graph convolutional deep neural network technology to generate near-QM quality molecular electrostatic potential (ESP) surfaces for small molecules in a fraction of a second. We will demonstrate the utility of this approach, alongside methodology we have developed for generating fast QM-trained ESP surfaces for proteins as part of Astex’s fragment-based drug discovery (FBDD) platform.

8:30 Nature-Inspired de novo Drug Design with AI
Gebert 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 synthetizable 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
Sne Vaidhnam, 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
Anil Nair, PhD, Vice President, 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 (RNNs) vs. 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, Intarka

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.

11:00 Sponsored Presentation (Opportunity Available)

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 Chairpersons’ Remarks
Ron Afs, MD, PhD, Vice President, Discovery & Product, Recursion Pharmaceuticals

1:05 Re-Imagining Drug Discovery through AI
Ron Afs, MD, PhD, Vice President, Discovery & Product, Recursion Pharmaceuticals

Massively expanding and accelerating traditional approaches like phenotype 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.

1:30 Design of an Artificial Intelligence System for Drug Discovery
Ivan Eyre, 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 multivariate 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.

2:05 Realizing the Promise of Mechanistic Modeling in Drug Development Using Adaptive Intelligence
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

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 Genomic Medicine, Faculty of Life, 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, Sartorius Genomics

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.

Shivy Yarnazaki, 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

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3:35 Close of Conference

Future Dates: Inaugural

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Hao Sun, PhD, Principal Pharmacokineticist, DMPK, Sartorius Genomics

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4:35 Close of Conference

Sponsored by
**Symposium:** 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**

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**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**

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**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 tyrine 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-Iai 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**

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Lead Optimization for Drug Metabolism & Safety
Tools and Strategies for Predicting, Evaluating and Building Safety Into Drug Design
Friday, April 12, 2019 | Hard Rock Hotel | San Diego, CA

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

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

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.

11:00 Sponsored Presentation (Opportunity Available)

11:15 Luncheon Presentation: Drug Metabolism Optimization Strategies in the Ever Evolving World of Drug Discovery

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

12:00 pm Session Break

EVALUATING DRUG-DRUG INTERACTIONS

1:00 Chairperson's Remarks

Kari Morissey, 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 DMPP, Genentech, Inc.

2:05 Sponsored Presentation (Opportunity Available)

2:35 Networking Refreshment Break

AI FOR ADME/DMPP 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


Shriy Yamaoka, PhD, Department of Pharmacokinetics, Dynamics and Metabolism, La Jolla Laboratories, Pfizer Worldwide Research and Development

4:55 Close of Conference
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 ongoing 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
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**

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Showcase your company to a 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 attention 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.

**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!

**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
cooke@healthtech.com | 781-972-5412

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**CURRENT SPONSORS & EXHIBITORS AS OF JANUARY 25TH, 2019**

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Industry</th>
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**DEMONSTRATIONS**

- **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.

**EXHIBITORS**

- **Sponsors by**
  - Domainex
  - IntelliSyn
  - HitGen Ltd.
  - HarkerBIO
  - GE Healthcare
  - Frontier Scientific, Inc.
  - Evotec
  - Eurofins Pharma Discovery Services
  - Eurofins Advinus Limited
  - Enamine LLC
  - Eutech
  - Eutech Frontier Scientific, Inc.
  - GE Healthcare
  - HarkerBIO
  - HitGen Ltd.
  - horiba
  - Jublant Biosys
  - Key Organics
  - Kishida Chemical Co., Ltd
  - Liverpool ChiroChem
  - Mercachem
  - Mibitopes
  - OpenEye Scientific
  - Optibrium
  - Pelago Biosciences
  - Pharmalock
  - Piramal Pharma Solutions
  - Prestwick Chemical
  - Promega
  - Reaction Biology
  - RedShift BioAnalytics
  - SAI Life Sciences
  - SAKomics Biostructures
  - Simulations Plus
  - SpriChem AG
  - Signature Discovery
  - Synthorx
  - Tecaris, a BIO-TECHNE Brand
  - Tokyo Chemical Industry Co., Ltd
  - Ubiquigent
  - VezisM
  - Viva Biotech
  - Watanabe Chemical Industries

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**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**

**Poster Awards in the Exhibit Hall!**

Winners to be Announced:
- **Wednesday, 9:35** during the Coffee Break
- **Thursday, 1:30** during the Dessert Break

**Sponsored by**

- domainex