FINAL AGENDA

CAMBRIDGE HEALTHTECH INSTITUTE'S 15th ANNUAL

Drug Discovery Chemistry

OPTIMIZING SMALL MOLECULES FOR TOMORROW'S THERAPEUTICS

AUGUST 24 - 28, 2020 | SAN DIEGO, CA | HILTON SAN DIEGO BAYFRONT

AUGUST 25 - 26

- Ubiquitin-Induced Protein Degradation
- Fragment-Based Drug Discovery
- Kinase Inhibitor Chemistry
- Macrocyclics & Constrained Peptides
- Training Seminar: GPCR Drug Discovery

AUGUST 26 - 27

- Protein-Protein Interactions
- Artificial Intelligence for Early Drug Discovery
- Small Molecules for Immunology & Oncology
- Encoded Libraries for Small Molecule Discovery
- Training Seminar: Drug Metabolism

AUGUST 28

- RNA as a Small Molecule Target
- Biophysical Approaches
- Lead Optimization for Drug Metabolism

PLENARY KEYNOTES

Medicinal Chemistry: Where Are We Headed?

Wendy Young, PhD

Senior Vice President, Small Molecule Discovery, Genentech

Translational Chemistry

Phil Baran, PhD

Professor, Department of Chemistry, Scripps Research

DrugDiscoveryChemistry.com

Conference at-a-Glance

Monday AUGUST 24	Tuesday AUGUST 25	Wednesday AUGUST 26	Thursday AUGUST 27	Friday AUGUST 28
PRE-CONFERENCE SHORT COURSES*	UBIQUITIN-INDUCED PROTEIN DEGRADATION	DINNER SHORT COURSES*	PROTEIN-PROTEIN INTERACTIONS	RNA AS A SMALL MOLECULE TARGET
	FRAGMENT-BASED DRUG DISCOVERY		ARTIFICIAL INTELLIGENCE FOR EARLY DRUG DISCOVERY	BIOPHYSICAL APPROACHES
	KINASE INHIBITOR CHEMISTRY		SMALL MOLECULES FOR IMMUNOLOGY & ONCOLOGY	LEAD OPTIMIZATION FOR DRUG METABOLISM
	MACROCYCLICS & CONSTRAINED PEPTIDES		ENCODED LIBRARIES FOR SMALL MOLECULE DISCOVERY	
	TRAINING SEMINAR: GPCR DRUG DISCOVERY		TRAINING SEMINAR: DRUG METABOLISM	

*Best Value or separate registration required.

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PLENARY KEYNOTES

Medicinal Chemistry: Where Are We Headed?

Wendy Young, PhD, Senior Vice President, Small Molecule Discovery, Genentech

Major shifts in the way medicinal chemists discover novel medicines have evolved over the past few decades. Technological advances have significantly increased the ability to triage compound design and synthesize compounds faster. New approaches in structural biology have enhanced our ability to visualize molecules and their corresponding binding sites. Drug discovery teams have moved from local to global and our deepened understanding of biology has extended our reach. This lecture will explore past trends in drug discovery, current status of the industry, and the future of medicinal chemistry.

Translational Chemistry

Phil Baran, PhD, Professor, Department of Chemistry, Scripps Research

There can be no more noble undertaking than the invention of medicines. Chemists that make up the engine of drug discovery are facing incredible pressure to do more with less in a highly restrictive and regulated process that is destined for failure more than 95% of the time. How can academic chemists working on natural products help these heroes of drug discovery – those in the pharmaceutical industry? With selected examples from our lab and others, this talk will focus on that question highlighting interesting findings in fundamental chemistry and new approaches to scalable chemical synthesis.

Short Courses*

*Best Value or separate registration required.

Morning Short Courses

MONDAY, APRIL 13 | 10:00 AM - 1:00 PM

SC1: Biochemistry and Pharmacology of the Ubiquitin-Proteasome System

Instructor:

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

- Mechanisms of E1, E2, E3, and deubiquitinating enzymes (DUBs)
- Assays and technologies, enzyme inhibitors
- PROTACs and molecular glues

SC2: Immunology Basics for Chemists

Instructor:

Timothy Bauler, PhD, Assistant Professor, Biomedical Sciences, Western Michigan University School of Medicine

- Organization of the immune system
- Inflammation and innate immunity
- Functions of T cells and B cells
- Molecular basis of pathogenic immune responses

SC3: Pharmacology Tricks of the Trade: Identifying Highly Active Compounds and Avoiding Assay Artifacts

Instructor:

Sam Hoare, PhD, Founder, Pharmechanics LLC

- Designing assays for successful lead optimization and discovery
- Assay properties discussed: binding kinetics, buffer compositions, target concentration, artificial signaling systems

Afternoon Short Courses

MONDAY, APRIL 13 | 2:00 - 5:00 PM

SC4: Fragment-Based Drug Design: Tools and Techniques

Instructors:

Daniel Erlanson, PhD, Vice President, Chemistry, Frontier Medicines

Ben Davis, PhD, Research Fellow, Vernalis Research

- Pros and cons of fragment-based approaches
- Properties of a good fragment and a good fragment library
- Finding, validating, and characterizing low-affinity ligands
- What to do with a fragment: growing, linking, and more
- Orthogonal screening methods

SC5: Macrocyclic Compounds for Drug Discovery: Opportunities, Challenges, and Strategies

Instructors:

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

Mark Peterson, PhD, COO, Cyclenium Pharma, Inc.

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

SC6: Emerging Chemical Tools for Phenotypic Screening and Target Deconvolution

Instructors:

Paul Brennan, PhD, Associate Professor, Medicinal Chemistry, University of Oxford; Principal Investigator, Target Discovery Institute, Structural Genomics Consortium

Brent Martin, PhD, Senior Principal Scientist, Chemical Biology/Chemoproteomics, Molecular & Cellular Pharmacology, Janssen R&D

Hua Xu, PhD, Associate Director, Chemical Biology Platforms, Cygnal Therapeutics

- Chemical biology tools and probes for MoA studies
- Constructing annotated chemical sets for effective screening
- Case studies highlighting use of small molecules for target identification and validation

Dinner Short Courses

MONDAY, APRIL 13 | 6:00 - 9:00 PM

SC8: Targeted Protein Degradation Using PROTACs, Molecular Glues, and More

Instructor:

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

Chandrasekhar Abbineni, PhD, Senior Group Leader, Aurigene Discovery Technologies Limited

Tauseef Butt, PhD, President and CEO, Progenra, Inc.

- Molecular events required for PROTAC-mediated degradation
- New screening technologies available to discover PROTAC and molecular glues for E3 ligases
- Applying enzymology concepts to the optimization of targeted protein degraders
- Protein degradation beyond bifunctional degraders

SC9: GPCR Structures and Enabling Biophysical Tools

Instructor:

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

- Structurally characterizing GPCRs (X-ray crystallography, cryoEM, NMR)
- Review of GPCR structures and their implications for drug discovery
- Biophysical tools for membrane proteins (NMR, fluorescence spectroscopy, EPR, and SPR)

SC10: Trends in Physical Properties of Drugs

Instructors:

Terry Stouch, PhD, President, R&D, Science for Solutions, LLC

Robert Fraczkiewicz, PhD, Team Leader, Simulations Plus, Inc.

Max Totrov, PhD, Principal Scientist, MolSoft, LLC

Properties impacting drug efficacy, development, delivery, and formulation including:

- Position and intensity of pKa throughout molecules
- Bioisosteres in medicinal chemistry
- Crystal structure interpretation, PAINS, tox alerts, and other physical chemical properties

Dinner Short Courses

WEDNESDAY, APRIL 15 | 6:30 - 9:30 PM

SC12: DNA-Encoded Libraries & Affinity Selection Methods for Small and Large Molecules

Instructors:

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

Jonas Schaefer, PhD, Laboratory Head, Encoded Library Technologies, Novartis Institutes for Biomedical Research, Chemical Biology & Therapeutics (CBT), Novartis Pharma AG

Ghotas Evindar, PhD, Senior Director, Drug Discovery, Exo Therapeutics

- Overview, comparison, and challenges of affinity-based screening methods for small molecules, peptides, alternative scaffolds, and antibodies
- Platforms discussed: Phage, Yeast, Ribosome, and mRNA Display
- DNA-Encoded Libraries (DEL): chemistry and library synthesis, selection methods, data analysis, basic chemistry follow-up, comparison of different platforms, case studies

SC13: Principles of Immuno-Oncology

Instructors:

Timothy Bauler, PhD, Assistant Professor, Biomedical Sciences, Western Michigan University School of Medicine

Thomas Sundberg, PhD, Senior Group Leader, Center for Development of Therapeutics, Broad Institute of MIT and Harvard

- Basic principles of anti-tumor immune responses
- Strategies to enhance anti-tumor T/NK cell activity (e.g., CAR-T, checkpoint blockade)
- Activation of innate cells to initiate anti-tumor immunity
- Small molecule immuno-oncology targets

Short Courses*

*Best Value or separate registration required.

Dinner Short Courses (Continued)

WEDNESDAY, APRIL 15 | 6:30 - 9:30 PM

SC14: Ligand-Receptor Molecular Interactions and Drug Design

Instructor:

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

- Medicinal chemistry drug design principles
- Interpretation of atomic-level protein X-ray and modeled structures of binding mode
- Understanding the relative amounts of potency gain from different interactions
- Case studies to illustrate all the design strategies

SC15: Methodologies for Optimizing Drug Clearance and Drug-Drug Interactions

Instructors:

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

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

- Applications of drug metabolism in lead optimization
- *In vitro* methods for detecting and characterizing bioactivation and soft-spot metabolites
- Common *in vitro* assays and methodologies for predicting metabolic clearance
- CYP regulation and induction
- Methodologies for predicting drug-drug interactions

Training SEMINARS

By Cambridge Healthtech Institute

See website for full details

TS1: Targeting GPCRs for Drug Discovery

TUESDAY, AUGUST 25 - WEDNESDAY, AUGUST 26 | DAY 1: 8:00 AM - 7:00 PM | DAY 2: 7:30 AM - 12:00 PM

INSTRUCTOR:

Terry Kenakin, PhD, Professor, Department of Pharmacology, University of North Carolina School of Medicine

This training seminar is designed for medicinal chemists, biologists, and scientists concentrating on discovering and developing drugs against G protein-coupled receptors (GPCRs). The challenge the seminar addresses is how to predict therapeutic activity – because drug candidate profiles seen in *in vitro* test systems often do not adequately reflect *in vivo* responses due to the drug candidates' interaction with variable ambient physiology. More specifically, this seminar describes the pharmacological procedures needed to convert 'descriptive data' (what we see) to 'predictive data' (what will be seen) through universal pharmacological scales, such as affinity, efficacy, cooperativity parameters, offset rates, etc. The desired outcome is to more fully define ligand properties to reduce attrition in late-stage drug development. Three major classes of GPCR ligands will be discussed: (1) agonists (with special reference to biased signaling); (2) antagonists (with inverse agonists); and (3) allosteric modulators (characterization of NAMs, PAMs). I will illustrate how concepts introduced over the past 15 years have considerably expanded and revitalized the possibilities for GPCRs as therapeutic targets.

Topics to be covered in the seminar:

- How to measure the 4 Main Universal Activity Parameters for Drugs
- Strengths and weaknesses of functional, binding assays, and kinetic assays
- Agonists: affinity vs. efficacy: biased agonist signaling and how to use it for drug development
- Antagonists: affinity vs. efficacy (positive or inverse agonism), non-competitive, irreversible, and hemi-equilibria
- Constitutive activity: inverse agonism and its relevance
- Allosterism: binding models, parameters for characterizing agonists, antagonists, PAMs, NAMs, and NAM antagonists

TS2: Introduction to Small Molecule Drug Metabolism and Applications to Discovery and Development

WEDNESDAY, AUGUST 26 - THURSDAY, AUGUST 27 | DAY 1: 1:30 PM - 6:00 PM | DAY 2: 8:00 AM - 5:50 PM

INSTRUCTORS:

John Erve, PhD, DABT, Jerve Scientific Consulting, Inc.

Yurong Lai, PhD, Senior Director, Drug Metabolism, Gilead Sciences

This 1.5-day lecture-based interactive seminar, which focuses on small molecule drug metabolism, will begin with a historical background in the origin of the field before reviewing the both well-recognized and more recently discovered drug metabolism pathways. *In vitro* assays used to access metabolic clearance and medicinal chemistry strategies for modifying structures to overcome metabolism-dependent clearance during lead optimization will be discussed. The topic of drug toxicity will be discussed in the context of drugs that are toxic through bioactivation to reactive metabolites, with examples of drug structure-toxicity relationships and the relevance of idiosyncratic toxicity to the pharmaceutical industry. The role of metabolite identification studies in preclinical and clinical development will be compared and the steps involved in identifying and characterizing metabolites by mass spectrometry will be explained. Advances in the use of *in silico* tools in the context of drug metabolism will be explored. An overview of the pharmacological properties and functions of drug transporters and some preclinical approaches to investigate drug transport mechanisms will be presented, as well as current regulatory guidance on transporters.

Topics to be covered in the seminar:

- Historical background in the field of drug metabolism
- Basic drug biotransformation reactions and the enzymes responsible
- Newly recognized drug biotransformation reactions
- *In vitro* assays used to access metabolism-based clearance
- Medicinal chemistry strategies for overcoming poor metabolic stability
- Bioactivation pathways to reactive drug metabolites
- Role of reactive metabolites in drug toxicity, including idiosyncratic toxicity
- Role of metabolite identification studies in discovery and development
- Four steps for identifying and characterizing drug metabolites by mass spectrometry
- *In silico* tools to address drug metabolism and reactive metabolite formation
- Pharmacological properties and functions of drug transporters
- Preclinical approaches to investigate drug transport mechanisms
- Role of transporters in drug PK, PD, efficacy, safety, and drug-drug interactions (DDI)
- Impact of transporter studies on drug discovery and development
- Recommendations from the current regulatory guidance and International Transporter Consortium (ITC) white papers on transporter evaluation during drug development

Sponsorship Opportunities

Comprehensive sponsorship packages allow you to achieve your objectives before, during, and long after the event. Signing on earlier will allow you to maximize exposure to hard-to-reach decision-makers.

PODIUM PRESENTATIONS - Available Within the Main Agenda!

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

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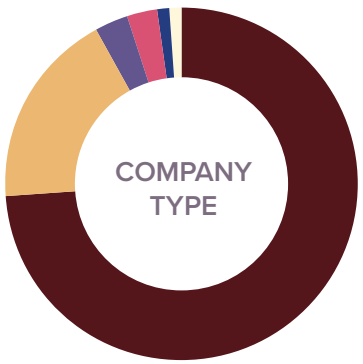
2019 ATTENDEE DEMOGRAPHICS



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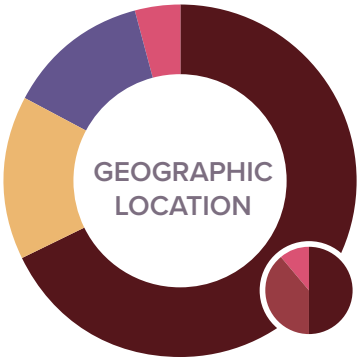

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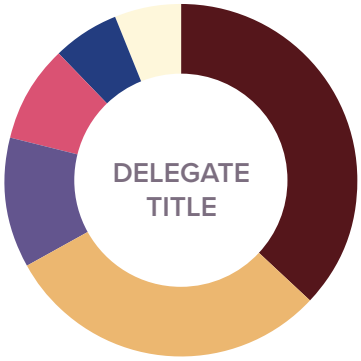

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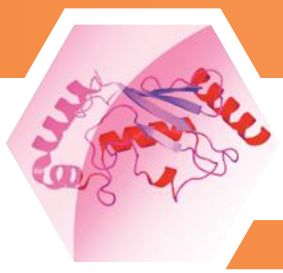


Ubiquitin-Induced Targeted Protein Degradation

Optimizing PROTACs and Small Molecule Degrader for Pursuing Undruggable Targets

August 25-26, 2020 | Hilton San Diego Bayfront | San Diego, CA

TUESDAY, APRIL 14

7:00 am Registration Open and Morning Coffee

ASSAYS & MODELS FOR STUDYING DEGRADATION & TARGET SPECIFICITY

8:00 Welcome Remarks

Tanuja Koppal, PhD, Senior Conference Director, Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks

Denise Field, PhD, Senior Scientist, I&I Chemistry and Chemical Biology, Pfizer Inc.

8:10 Target Engagement and Protein Degradation: Lessons Learned and Future Applications

Denise Field, PhD, Senior Scientist, I&I Chemistry and Chemical Biology, Pfizer Inc.

Protein degradation occurs through additional mechanisms other than bifunctional molecules. This talk will highlight some recent discoveries of compound induced degradation, as well as current approaches to validate compound target engagement mechanisms.

8:40 Engineered Ubiquitin Variants as Tools to Find Small Molecules Targeting Ubiquitin Enzymes

Jacky Chung, PhD, Scientist, Laboratory of Dr. Sachdev Sidhu, Donnelly Center, University of Toronto

Although proteins in the ubiquitin system have been the focus of therapeutic efforts for decades, little progress has been made to identify therapeutically relevant small molecules. Here, we present a general strategy where we use engineered protein binders as a platform for small molecule discovery. Our approach can lead to the quick identification of small molecules targeting an array of ubiquitin enzymes.

9:10 Shifting Focus - CETSA MS Proteomics in Protein Degradation Drug Discovery

Sponsored by PELAGO BIOSCIENCE

Stina Lundgren, Principal Project Advisor, Pelago Bioscience

The CETSA MS profiling of degraders allow simultaneous study of both direct binding both its intended protein target, involved E3-ligase and potential off-targets. In this talk we will present recent CETSA MS profiles on both protacs and molecular glue molecules in living cells including the degradation specificity and efficacy.

9:25 Sponsored Presentation *(Opportunity Available)*

9:40 Networking Coffee Break

10:05 Computational Exploration of Novel Drug Targets, Modalities, and Design

Yuan Wang, PhD, Senior Principal Scientist, Head of TPD Data Science, UCB Pharma

Modern drug discovery calls for increased use of phenotypic screens, and novel targets and modalities are being explored in the process. The use of potent and selective chemical tools (probes) can help understand underlying biological processes, deconvolute unknown mechanisms, or design new modulators of targets; e.g., linkers are attached to known inhibitors to make PROTACs. In this talk, we would like to explore rules that define those mechanisms using computational methods.

10:35 Use of Tip60 PROTACs in Cereblon-Knockin Mice

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

Finding new ways to target histone acetyltransferases, such as Tip60, is important for advances in immuno-oncology, and the PROTAC approach makes this possible. However, mice have a single amino acid substitution that blocks efficient iMID-dependent recruitment of the E3-ligase, Cereblon, limiting experimental studies. We report use of Tip60 PROTACs in WT vs. Cereblon knock-in mice in which PROTAC-dependent recruitment is now rendered active, allowing use of murine models for testing of this and other PROTAC molecules.

11:05 Chemical Tools to Evaluate E3: (Neo)Substrate Pairs

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

Two major principles of targeting the ubiquitin system have emerged: direct targeting of the enzymes that control protein ubiquitination and hijacking E3 ligases to induce protein degradation. In this lecture, I will outline the discovery of novel probes UbFluor, cross-linking reagents, and kinase targeting PROTACS to discover small molecule inhibitors/activators and hijackers for Cullin-RING/RBR/HECT E3 ligases.

11:35 Session Break

11:45 LUNCHEON CO-PRESENTATION: E3scan™ Ligand Binding Assay Platform and EFC Biosensor Cell Lines for Targeted Protein Degradation and PROTAC Discovery

Sponsored by eurofins | DISCOVERY

Ksenya Cohen Katsenelson, PhD, Senior Scientist Group Leader, San Diego R&D, Eurofins Discovery

Chao-Tsung Yang, PhD, Principal Scientist, Research & Development, Eurofins DiscoverX

Eurofins Discovery will present how the novel E3scan technology has been applied to diverse E3 ligases, including CRBN, VHL, MDM2, MDMX, cIAP1, cIAP2, and XIAP. We will also present how engineered biosensor cell lines employing gene editing with CRISPR/Cas9 and our well-established EFC technology will enable sensitive quantitation of PROTAC-mediated degradation of the target of interest in physiologically relevant cell models using a homogeneous assay format.

12:30 pm Session Break

TARGETED PROTEIN DEGRADATION FOR ONCOLOGY

1:15 Chairperson's Remarks

Chris Nasveschuk, PhD, Vice President, Chemistry, C4 Therapeutics

1:20 Degrader Drug Space: What Rules?

Chris Nasveschuk, PhD, Vice President, Chemistry, C4 Therapeutics

Targeted protein degradation, through the use of heterobifunctional degraders that act as catalytic activators for an E3 ligase and target protein ubiquitination event, have the potential to transform drug discovery. This seminar will focus on *in vitro* to *in vivo* correlation, oral bioavailability as well as initial insights into likely drivers of these two key parameters of drug discovery.

1:50 Targeted Degradation of Bromodomain-Containing Proteins for Cancer Therapy

Chandrasekhar Abbineni, PhD, Senior Group Leader, Aurigene Discovery Technologies Limited

Inhibition of bromodomain-containing proteins, such as BET and SMARCA2, is being evaluated as a therapeutic strategy in cancer. While these inhibitors affect only the reader function of these proteins, their degradation causes a global assembly defect, leading to anti-proliferative activity. Here we present the discovery of lower molecular weight, orally bioavailable, and efficacious degraders of bromodomain-containing targets using our proprietary ALMOND (ALgorithm for Modelling Neosubstrate Degraders) technology.

2:20 Ubiquitin-Mediated Small Molecule-Induced Target Elimination (uSMITE) for Cancer

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

Targeted protein degradation using bifunctional molecules to remove specific proteins by hijacking the ubiquitin proteasome system has emerged as a novel drug discovery approach. Several challenges remain in designing optimal

degraders that also show efficacy *in vivo*. We will present case studies from our ongoing efforts in the design and biological evaluation of novel degraders that are orally active in mouse xenograft models.

2:50 A Modular PROTAC Design for Target Destruction Using Single Amino Acid-Based Degradation Signal
Hai Rao, PhD, Professor, Molecular Medicine, University of Texas Health
Proteolysis targeting chimeras (PROTACs) are bivalent molecules that bring a cellular protein to a ubiquitin ligase E3 for ubiquitylation and subsequent degradation. Here we adopt single amino acid based PROTACs to target ERRa for proteasomal degradation by the N-end rule pathway and inhibit the proliferation of breast cancer cells. The method offers unique advantages, including smaller molecular size with shortest degradation sequences and degradation speed modulation with different amino acids.

3:20 Fragment Screening and Biophysical Hit Validation
Sponsored by 药明康德 WuXi AppTec
Michael Raba, Deputy Head, Biophysics and Screening, Crelux, WuXi AppTec
CRELUX, is an integral part of the WuXi AppTec Research Services Division (RSD). We deliver tailored solutions in structure-based drug discovery. By screening our proprietary fragment library using powerful biophysical techniques such as MST, SPR or nanoDSF we successfully support clients already in early stage drug discovery campaigns

3:35 Refreshment Break in the Exhibit Hall with Poster Viewing
(Sponsorship Opportunity Available)

4:35 Plenary Welcome Remarks from Event Director with Poster Finalists Announced
Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

4:45 Plenary Technology Spotlight: Accelerating Drug Discovery from Hit Finding to Candidate Selection with Physics and Machine Learning-Based Calculations
Sponsored by SCHRÖDINGER
Matt Repasky, PhD, Vice President, Life Sciences Products, Schrödinger
The impact of the Schödinger computational platform in drug discovery is illustrated using recent case studies from internal and collaborative discovery projects. The Platform facilitates halving the number of synthesized molecules and time to candidate relative to industry standards. Key elements of the Platform are described including Free Energy Perturbation to accurately predict relative protein-ligand binding, machine learning to generate and rapidly assess millions of ideas, and collaborative sharing of project information through LiveDesign.

5:10 Plenary Keynote Introduction *(Sponsorship Opportunity Available)*

5:15 PLENARY KEYNOTE:

Medicinal Chemistry: Where Are We Headed?
Wendy Young, PhD, Senior Vice President, Small Molecule Discovery, Genentech
Major shifts in the way medicinal chemists discover novel medicines have evolved over the past few decades. Technological advances have significantly increased the ability to triage compound design and synthesize compounds faster. New approaches in structural biology have enhanced our ability to visualize molecules and their corresponding binding sites. Drug discovery teams have moved from local to global and our deepened understanding of biology has extended our reach. This lecture will explore past trends in drug discovery, current status of the industry, and the future of medicinal chemistry.

6:00 Welcome Reception in the Exhibit Hall with Poster Viewing
(Sponsorship Opportunity Available)

7:00 Close of Day

WEDNESDAY, APRIL 15

7:30 am Continental Breakfast Breakout Discussions
In this session, attendees fill their plate from the breakfast buffet and then choose a specific roundtable discussion to join. Each group has a moderator to ensure focused conversations around key issues within the topic. The small-group format allows participants to informally meet potential collaborators, share examples from their work, and discuss ideas with peers. Discussion topics and moderators will be listed on the website.

TARGETED KINASE DEGRADATION STRATEGIES

8:30 Chairperson's Remarks
Philip Chamberlain, DPhil, Executive Director, Structural and Chemical Biology, Celgene

8:35 New Activities for Cereblon Modulators
Philip Chamberlain, DPhil, Executive Director, Structural and Chemical Biology, Celgene
Cereblon can be redirected to degrade neo-substrate proteins using low-molecular-weight small molecules. An understanding of the structural basis of substrate recruitment has enabled the discovery of new neo-substrates, including proteins that lack canonical small-molecule binding sites.

9:05 So Many Ubiquitin Ligases and So Few PROTACs: Carving a New Path with Novel Ligases
Tauseef Butt, PhD, President and CEO, Progenra, Inc.
PROTAC field is at its infancy. Only the well-known ligases (Cereblon, VHL, HDM2 and cIAPs) have been exploited by medicinal chemists. Too many resources are devoted to these ligases as vehicles for PROTACs. We have validated applications of novel ligases by designing PROTACs with promiscuous kinase inhibitor that degrades a number of kinases not degraded by traditional ligase PROTACs. Kinetics and dose response studies have established their application in oncology, inflammatory and neuroscience.

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

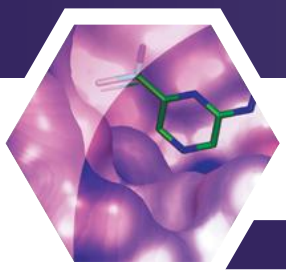
10:30 Molecular Mechanisms of Small Molecule-Mediated Ubiquitin Ligase Targeting
Eric Fischer, PhD, Assistant Professor, Cancer Biology/ Biological Chemistry and Molecular Pharmacology, Dana-Farber Cancer Institute/Harvard Medical School
Small molecules that induce protein degradation through ligase-mediated ubiquitination, have shown considerable promise as a new pharmacological modality. Thalidomide and related IMiDs provided the clinical proof of concept, while significant progress has recently been made towards chemically induced targeted protein degradation using heterobifunctional small molecule ligands. We will present recent work towards a better understanding of the molecular principles that govern neo-substrate recruitment, and other small molecule degraders.

11:00 Targeting Focal Adhesion Kinase with PROTACs: From Tool to *in Vivo*
Robert Law, PhD, Investigator, Medicinal Chemistry, GSK Medicine Research Centre
New modalities, such as PROTACs, are powerful tools that allow biology assessment of oncogenic targets beyond the conventional kinase inhibition. Focal Adhesion Kinase (FAK) is a key mediator of tumour progression and is overexpressed in many solid tumours; to date, inhibitors targeting FAK kinase activity have shown low success in the clinic. Here we report the design and characterization of a highly potent FAK degrader with increased efficacy over FAK inhibitor, as well as extended *in vivo* efficacy.

11:30 ADME Properties of PROTACs and Oral Bioavailability Improvement Strategies
Upendra Dahal, PhD, Senior Scientist, Pharmacokinetics and Drug Metabolism, Amgen, Inc.
PROTACs are bifunctional molecules, designed to bind with target protein and E3 ligase to degrade target protein by hijacking the cell's own ubiquitin proteasome system. PROTACs have several advantages, but challenges remain in designing optimal PROTACs that have acceptable absorption, distribution, metabolism and excretion (ADME) properties to demonstrate efficacy *in vivo*. Literature-published PROTACs have high MW (beyond rule of 5), low permeability, and low oral bioavailability. This presentation will focus on ADME properties of PROTACs with special focus on strategy to improve oral bioavailability.

12:00 pm Close of Conference

12:45 Dessert Break in the Exhibit Hall with Poster Viewing
(Sponsorship Opportunity Available)



15TH ANNUAL

Fragment-Based Drug Discovery

From Hits to Leads and Lessons Learned

August 25-26, 2020 | Hilton San Diego Bayfront | San Diego, CA

TUESDAY, APRIL 14

7:00 am Registration Open and Morning Coffee

FRAGMENT LIBRARY DESIGN & SCREENING APPROACHES

8:00 Welcome Remarks

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

8:05 Chairperson's Opening Remarks

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

8:10 Fragment Hits and Leads: More than Meets the Eye

Fabrizio Giordanetto, PhD, Head, Medicinal Chemistry, D E Shaw Research

An analysis of the molecular and binding properties of fragment hits and leads is presented with special focus on features that these hits and leads tend to have in common, as well as on properties where clear differences occur. Taking account of these preferences in designing and selecting fragments to screen, and in evolving fragments to leads may increase the chances of success in fragment-based drug discovery campaigns.

8:40 Fragment Screening of GPCRs Using NMR

Isabelle Krimm, PhD, Principal Investigator, University of Lyon

G protein-coupled receptors, which constitute the largest family of proteins targeted by approved drugs, still represent a huge opportunity to develop new drugs for "old" targets or orphan receptors. Significant progresses have been made in the field of fragment screening against those challenging membrane proteins. Recent results obtained with the adenosine receptor using NMR and Microscale thermophoresis (from NanoTemper Technologies) will be discussed.

9:10 Biophysics-Based Drug Discovery for Epitranscriptomics

Sponsored by ZOBIO

Gregg Siegal, CEO, ZoBio

Modulation of enzymes that modify RNA (epitranscriptomics) is gaining interest in drug discovery. Gotham Therapeutics and ZoBio are developing inhibitors of METTL3/METTL14, a SAM-dependent methyltransferase that modifies adenosine in mRNA to generate m6A, and thereby regulates protein expression. Here we will present an update on progress.

9:40 Networking Coffee Break

10:05 FEATURED PRESENTATION: Delivering and Exploiting Routine Crystal-Based XChem Fragment Screening

Frank von Delft, PhD, Principal Beamline Scientist, Diamond Light Source and Structural Genomics Consortium; Professor, Structural Chemical Biology, University of Oxford

The dominant problem of fragment approaches remains progressing hits to potency; yet surprisingly, best practice and processes are elusive. With crystal-based screening now routine, including at Diamond's XChem facility supporting 30-50 campaigns annually, the problem is now acute. We are developing approaches to allow users to routinely progress their high-quality hits to measurable potency, and are exploring Machine Learning approaches to advancing straight to potency.

10:35 Optimization of Fragment Hit Rates: CrystalsFirst's Proprietary Toolbox

Sponsored by CRYSTALS FIRST

Serghei Glinca, PhD, CEO, CrystalsFirst

The application of X-ray crystallography as a primary fragment screening method is widely underutilized due to the limited availability of robust soaking systems and solubility issues of fragments. CrystalsFirst's SmartSoak® technology, whose origins can be traced to the laboratory of Dr. Gerhard Klebe, is tailored to address those issues. Case studies will be presented demonstrating the advantages of the direct crystallographic screening to identify best possible chemical matter for subsequent FBDD campaigns.

11:05 Fast NMR Structure Determination of Protein-Fragment Complexes

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

Although the evolution from initial fragment to advanced hit or lead is possible without routine crystallographic support, high resolution structures of the protein–fragment complex greatly facilitate the process. However, it can often be challenging to routinely obtain these crystal structures. In these instances, NMR spectroscopy is the method of choice to guide the medicinal chemistry campaign. We will present our recent development in NMR structure-based drug design for fragments. Case studies will be presented.

11:35 Session Break

11:45 LUNCHEON PRESENTATION: Improve Screening Success of Fragment-based Drug Discovery Libraries with Dianthus

Sponsored by NANOTEMPER

Peter Fung, PhD, Senior Manager, Customer Marketing, NanoTemper Technologies

A big hurdle in fragment-based drug discovery (FBDD) screening is confidently identifying positive hits in a timely manner. Screening fragment libraries is challenging with current methodologies that are either time-consuming or lack detection sensitivity. Dianthus NT.23PicoDuo utilizes a biophysical detection method for fast, precise and confident hit identification, target validation and lead optimization. An example of single-dose and affinity screening against histone methylase G9a, known to be associated with cancer onset, will be discussed.

12:30 pm Session Break

COVALENT FRAGMENTS

1:15 Chairperson's Remarks

Daniel Erlanson, PhD, Vice President, Chemistry, Frontier Medicines

1:20 How to Be Selectively Promiscuous

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

I will present our approach to the design and discovery of lysine-targeted chemoproteomic probes. Such probes have shown utility in mechanistic cell biology and target engagement experiments.

1:50 Electrophile-Fragment Screening for Rapid Covalent Fragment Probe Screening

Nir London, PhD, Senior Scientist, Weizmann Institute of Science

Covalent chemical probes and drugs can display unmatched potency, selectivity and duration of action; however, their discovery is challenging. We constructed a library of mildly electrophilic fragments and characterized it by a new high-throughput thiol-reactivity assay. I will present the screening results of this library against a wide array of protein targets. We found selective hits for most targets, and combination with high-throughput crystallography allowed rapid progression in several cases.

2:20 Covalent Fragments Technology for Drug Lead Generation: Past, Present, and Future

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

Covalent fragments is a new lead generation technology, which rests on principles of covalent drug design and fragment-based drug discovery. The main advantage of covalent fragments relative to reversible fragments is that they have enhanced potency and that crystal structures of covalent fragments bound to protein targets can readily be obtained. I will talk about the use of

this technology to discover E3 ligase inhibitors and the technology's future applications in target-based and phenotypic screens.

2:50 Lys- and Tyr-Covalent Ligands: Expanding the Druggable Space for Protein-Protein Interactions Antagonists

Maurizio Pellecchia, PhD, Professor, Biomedical Sciences Division, School of Medicine, University of California, Riverside

I will report on several recent studies from the laboratory aimed at deriving derive potent, selective, cell-permeable, and efficacious, protein-protein interactions (PPIs) antagonists by designing agents that can react with lysine, tyrosine, or histidine, given that these are more ubiquitously present at binding interfaces of PPIs compared to cysteine. Examples will include potent and selective Lys- and Tyr-covalent agents targeting various PPIs including IAPs, EphAs, and Bcl-2 proteins.

3:20 Enable Pharma and Biotech Innovation through Open-access Platform

Sponsored by 药明康德 WuXi AppTec

Jane Wang, PhD, Vice President, International Discovery Service Unit, Research Service Division, WuXi AppTec (Shanghai) Co., Ltd.

WuXi AppTec has built a comprehensive drug discovery capability and capacity platform to improve the success of research and shorten the time of development. In this presentation, we will discuss how to use our platform to support Pharma and Biotech drug discovery in ubiquitin-induced protein degradation more quickly and cost-effectively.

3:35 Refreshment Break in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

4:35 Plenary Welcome Remarks from Event Director with Poster Finalists Announced

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

4:45 Plenary Technology Spotlight: Accelerating Drug Discovery from Hit Finding to Candidate Selection with Physics and Machine Learning-Based Calculations

Sponsored by SCHRÖDINGER

Matt Repasky, PhD, Vice President, Life Sciences Products, Schrödinger

The impact of the Schödinger computational platform in drug discovery is illustrated using recent case studies from internal and collaborative discovery projects. The Platform facilitates halving the number of synthesized molecules and time to candidate relative to industry standards. Key elements of the Platform are described including Free Energy Perturbation to accurately predict relative protein-ligand binding, machine learning to generate and rapidly assess millions of ideas, and collaborative sharing of project information through LiveDesign.

5:10 Plenary Keynote Introduction *(Sponsorship Opportunity Available)*

5:15 PLENARY KEYNOTE:

Medicinal Chemistry: Where Are We Headed?

Wendy Young, PhD, Senior Vice President, Small Molecule Discovery, Genentech

Major shifts in the way medicinal chemists discover novel medicines have evolved over the past few decades. Technological advances have significantly increased the ability to triage compound design and synthesize compounds faster. New approaches in structural biology have enhanced our ability to visualize molecules and their corresponding binding sites. Drug discovery teams have moved from local to global and our deepened understanding of biology has extended our reach. This lecture will explore past trends in drug discovery, current status of the industry, and the future of medicinal chemistry.

6:00 Welcome Reception in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

7:00 Close of Day

WEDNESDAY, APRIL 15

7:30 am Continental Breakfast Breakout Discussions

Moderator: Derek Cole, PhD, Senior Director, GI Chemistry, Takeda California

In this session, attendees fill their plate from the breakfast buffet and then choose a specific roundtable discussion to join. Each group has a moderator to ensure focused conversations around key issues within the topic. The small-group format allows participants to informally meet potential collaborators, share examples from their work, and discuss ideas with peers. Discussion topics and moderators will be listed on the website.

FRAGMENT-BASED LEAD GENERATION (AND BEYOND?) STORIES

8:30 Chairperson's Remarks

Mary Harner, PhD, Research Investigator II, Mechanistic Biochemistry, BristolMyers Squibb R&D

8:35 Fragmentology – Fragments of Stories

Rod Hubbard, PhD, Senior Fellow, Vernalis (R&D) Ltd.

Fragments are a mature approach to the discovery of potent, selective hit and lead compounds. In this presentation, I will summarise some new developments and examples taken from various projects including: 1) high-throughput crystallography of crude reaction mixtures to support rapid fragment and hit optimisation; 2) fragment-derived enzyme activators; and 3) using fragments to explore structural determinants of kinase selectivity.

9:05 FBDD Approaches for Diverse Series for Novel Cancer Target, Vps34

Jenny Viklund, Director, Protein Science & Drug Design, Sprint Biosciences

FBDD approaches were used to create diverse chemical series that inhibit the unexplored cancer target Vps34. Initially, the parameters which are most important for *in vivo* efficacy (potency, selectivity, PK-profile, tumor permeability, etc) were unknown. Hence, we intentionally selected diverse fragment hits, which were optimized to represent differing profiles for the parameters above. Representative chemical structures will be shared. The *in vivo* results will be shown in a later presentation at this event.

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

Poster Awards Sponsored by Enamine Ltd

10:30 FEATURED PRESENTATION: Fragment-to-Market Discovery of the pan-FGFR inhibitor BalversaTM (Erdafitinib)

Valerio Berdini, PhD, Director, Computational Chemistry, Astex

FGFR is a family of 4 related receptor tyrosine kinases, each upregulated in several human cancers with high unmet need. This lecture will present the NICR/Astex and Astex/J&J collaboration that lead to the finding of BalversaTM (Erdafitinib): the first inhibitor of FGFR kinases to be approved by FDA and marketed in 2019. From the fragment based screening that identified the early hits, through the medicinal chemistry that progressed them, we will show the criteria leading to the selection of the clinical candidate: a low dose, pan FGFR molecule.

11:00 Fragment Synergies to Deliver Multiple Shots at Moving Targets

Chun-Wa Chung, PhD, Director, Structural & Biophysical Sciences, GlaxoSmithKline, UK

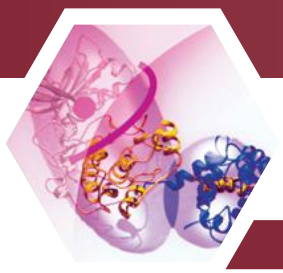
11:30 Design in the Dark – Illuminating the Druggability of 53BP1 with REFiL in the Absence of Structural Data

Beatrice Chiew, Graduate Student, Laboratory of Martin Scanlon, Department of Medicinal Chemistry, Monash University

Structural data is heavily relied on to develop weakly binding fragments into tight binding leads. Unfortunately, structural data is not always available and this can prove to be a roadblock for exciting but difficult targets. We present a target and structure agnostic workflow: REFiL (Rapid Elaboration of Fragment into Leads), which was applied without structural data to the oncology target 53BP1 to expedite the delivery of improved potency leads.

12:00 pm Close of Conference

12:45 Dessert Break in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*



Kinase Inhibitor Chemistry

Emerging Targets, New Tools and Strategies, and Targeted Kinase Degraders

August 25-26, 2020 | Hilton San Diego Bayfront | San Diego, CA

TUESDAY, APRIL 14

7:00 am Registration Open and Morning Coffee

NEW TARGETS AND PROMISING CANDIDATES

8:00 Welcome Remarks

Nandini Kashyap, Conference Director, Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks

Felix Gonzalez Lopez de Turiso, PhD, Team Leader, Medicinal Chemistry, Drug Discovery, Biogen

8:10 Discovery of Brain-Penetrant ASK1 Inhibitors for the Treatment of Neurological Diseases

Felix Gonzalez Lopez de Turiso, PhD, Team Leader, Medicinal Chemistry, Drug Discovery, Biogen

ASK1 is one of the key mediators of the cellular stress response and modulation of this pathway with the ATP-competitive inhibitor, Selonsertib, is being tested in the clinic for the treatment of liver fibrosis. To test the therapeutic value of inhibiting ASK1 in neurological disease, we have identified novel ASK1 brain-penetrant inhibitors using a structure-based drug design approach. The results from this effort will be presented.

8:40 Targeted Therapy in Patients with PIK3CA-Related Overgrowth Syndrome

Guillaume Canaud, MD, PhD, Professor of Medicine, Hospital Necker Enfants Malades, Paris

PIK3CA-related overgrowth syndromes (PROS) are genetic disorders that result from somatic gain-of-function mutations of the PIK3CA gene. PROS has no specific treatment. We created the first mouse model of PROS that recapitulates the human disease and demonstrated the efficacy of BYL719, PIK3CA inhibitor. On the basis of these results, we used BYL719 to treat 19 patients with PROS. The drug improved the disease symptoms in all patients and was not associated with any substantial side effects.

9:10 Interfering with the Immune System: DMXD-011, a Potential Treatment for Systemic Lupus Erythematosus (SLE)

Sponsored by domainex

Trevor Perrior, MA, PhD, FRSC, CEO, Domainex Limited

Diseases arising from dysfunction of interferon signaling cause serious morbidity, can be life-threatening, and are poorly treated by existing medicines. The kinases, IKK-epsilon and TBK1, are key mediators of the production of pro-inflammatory cytokines and Type 1 interferons. I will outline the fragment-based drug design of DMXD-011, a selective inhibitor of these two kinases, and describe its preclinical profile to illustrate why we believe this is a potential new treatment for SLE and other interferonopathies.

9:40 Networking Coffee Break

10:05 Comprehensive Evaluation of CDK Inhibitor Landscape in Cells

Carrow Wells, Research Associate, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill

Although CDK inhibitors have proven to be therapeutically important, many CDK inhibitors lack family-wide profiling. To address this gap, we evaluated known CDK inhibitors against the full panel of cellular CDK assays. Utilizing the NanoBRET assay platform, we identified selective and potent CDK inhibitors, as well as broadly active compounds which can aid in the design of new CDK inhibitors and our ability to match a kinase to a phenotype.

10:35 CDKs: Core Regulators of Transcription and Emerging Targets in Cancer Therapeutics

Pabitra Parua, PhD, Research Fellow, Robert P. Fisher Lab, Department of Oncological Sciences, Icahn School of Medicine at Mount Sinai

Cyclin-dependent kinases (CDKs) regulate the cell-division and RNA polymerase II-dependent transcription cycles. Transcriptional CDKs have recently emerged as potential therapeutic targets in cancer, but deeper understanding of their functions and interactions is needed to guide new drug discovery and development. Through chemical genetics, we identified novel substrates of a transcriptional CDK, Cdk9, and uncovered distinct Cdk9-phosphatase switches that govern key transitions at the beginning and end of the transcription cycle.

11:05 Application of Large-Scale FEP Simulations for Lead Optimization

Tara Mirzadegan, PhD, Senior Director, US Head of Computational Chemistry, Janssen Pharmaceutical Companies of Johnson & Johnson

Application of binding free energy using Free Energy Perturbation (FEP) against several projects will be discussed. This rigorous method requires extended simulation times, but recent advances in graphics processing units (GPUs) and both cluster- and cloud-based computing have made possible the use of this method to prioritize large numbers of molecules. We will discuss the application of large-scale FEP+ experiment against a kinase target.

11:35 Session Break

11:45 LUNCHEON PRESENTATION: Sensors for Continuous Monitoring of Protein Kinase & Phosphatase Activity

Sponsored by AssayQuant® TECHNOLOGIES INC.

Erik Schaefer, President, AssayQuant Technologies

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

12:30 pm Session Break

NEW TOOLS AND STRATEGIES

1:15 Chairperson's Remarks

Istvan J. Enyedy, PhD, Principal Scientist, Biogen

1:20 High-Resolution Structure and Inhibition of a Neuropsychiatric Disorder Linked Pseudokinase ULK4

Susmita Khamrui, PhD, Post-Doctoral Fellow, Pharmacological Sciences, Icahn School of Medicine at Mont Sinai Hospital

ULK4, a pseudokinase with some unusual mutations in the kinase catalytic motif, has genetically been linked to some neuropsychiatric disorders like schizophrenia. The first crystal structure of the human ULK4 kinase at high resolution will be discussed here. ULK4 has no apparent phosphotransfer activity, but can bind to ATP in a Mg2+ independent manner. A virtual, as well as an experimental, screening was performed to identify small molecule binders of ULK4.

1:50 Machine Learning Models for Optimizing Brain Penetrant Kinase Inhibitors

Istvan J. Enyedy, PhD, Principal Scientist, Biogen

The design of kinase inhibitors for neurological indications is challenging because of limits in physicochemical properties that compounds should have in order to be brain penetrant. Models were developed for predicting P-gp- and BCRP-mediated efflux and Kpuu. The talk will overview the performance of these models and the physicochemical properties that brain penetrant kinase inhibitors have.

2:20 Discovery of New Vaccinia-Related Kinase (VRK) Inhibitors as Chemical Probes for Target Validation

Hatylas Azevedo, PhD, MBA, R&D Manager, Drug Discovery, Aché Laboratórios

The vaccinia-related kinases 1and 2 (VRK1 and VRK2) were recently associated with poor prognosis, tumor growth and metastasis. The development of chemical probes with appropriate potency and selectivity is a key step to validate their role in cancer and confirm the findings from siRNA or CRISPR/Cas9-based experiments. In this talk, it will be presented the efforts to develop new chemical probes for VRK1 and VRK2 using structure-based drug design approaches.

TARGETED KINASE DEGRADATION STRATEGIES

2:50 Targeting CDK Protein by Covalent Inhibitor and PROTAC Degrader

Tinghu Zhang, Scientist, Nathanael Gray Lab, Cancer Biology, Dana-Farber Cancer Institute/Harvard Medical School

This talk will discuss following about the second generation of CDK7 covalent inhibitor YKL5-124; selective inhibiting CDK12/13 by covalent inhibitor; discovery of first CDK9 degrader with a pan CDK binder SNS032; and selective degrade CDK4 and CDK6 with PROTAC technology.

3:20 SAR by Space: Enriching BRD4 Inhibitor Hit Sets from the Chemical Space

Sponsored by BioSolveIT

Franca Klingler, PhD, Head, Services, Discovery Services, BioSolveIT

We introduce SAR by Space, a concept to drastically accelerate SAR elucidation. Hits from the REAL Space were combi-docked into the binding site of BRD4, thus avoiding time-consuming simulations. Five micromolar hits have been synthesized, and verified within less than 6 weeks, including the measurement of IC50 values.

3:35 Refreshment Break in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

4:35 Plenary Welcome Remarks from Event Director with Poster Finalists Announced

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

4:45 Plenary Technology Spotlight: Accelerating Drug Discovery from Hit Finding to Candidate Selection with Physics and Machine Learning-Based Calculations

Sponsored by SCHRÖDINGER

Matt Repasky, PhD, Vice President, Life Sciences Products, Schrödinger

The impact of the Schödinger computational platform in drug discovery is illustrated using recent case studies from internal and collaborative discovery projects. The Platform facilitates halving the number of synthesized molecules and time to candidate relative to industry standards. Key elements of the Platform are described including Free Energy Perturbation to accurately predict relative protein-ligand binding, machine learning to generate and rapidly assess millions of ideas, and collaborative sharing of project information through LiveDesign.

5:10 Plenary Keynote Introduction *(Sponsorship Opportunity Available)*

5:15 PLENARY KEYNOTE:

Medicinal Chemistry: Where Are We Headed?

Wendy Young, PhD, Senior Vice President, Small Molecule Discovery, Genentech

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7:00 Close of Day

WEDNESDAY, APRIL 15

7:30 am Continental Breakfast Breakout Discussions

In this session, attendees fill their plate from the breakfast buffet and then choose a specific roundtable discussion to join. Each group has a moderator to ensure focused conversations around key issues within the topic. The small-group format allows participants to informally meet potential collaborators, share examples from their work, and discuss ideas with peers. Discussion topics and moderators will be listed on the website.

TARGETED KINASE DEGRADATION STRATEGIES (CONT.)

8:30 Chairperson's Remarks

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

8:35 New Activities for Cereblon Modulators

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

Cereblon can be redirected to degrade neo-substrate proteins using low-molecular-weight small molecules. An understanding of the structural basis of substrate recruitment has enabled the discovery of new neo-substrates, including proteins that lack canonical small-molecule binding sites.

9:05 So Many Ubiquitin Ligases and So Few PROTACs: Carving a New Path with Novel Ligases

Tauseef Butt, PhD, President and CEO, Progenra Inc.

PROTAC field is at its infancy. Only the well-known ligases (Cereblon, VHL, HDM2 and cIAPs) have been exploited by medicinal chemists. Too many resources are devoted to these ligases as vehicles for PROTACs. Progenra has focused its attention to novel ubiquitin ligases and discovered an entirely new class of PROTACs. We have validated applications of novel ligases by designing PROTACs with promiscuous kinase inhibitor that degrades a number of kinases not degraded by traditional ligase PROTACs. Kinetics and dose response has established their application in oncology, inflammatory and neuroscience.

9:35 Coffee Break in the Exhibit Hall with Poster Awards Announced Poster Awards *Sponsored by* **Enamine Ltd**

10:30 Molecular Mechanisms of Small Molecule-Mediated Ubiquitin Ligase Targeting

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

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

11:00 Targeting Focal Adhesion Kinase with PROTACs: From Tool to *in Vivo*

Joao Nunes, PhD, Investigator, Protein Degradation Group, Medicinal Science and Technology, GSK Medicine Research Centre

New modalities, such as PROTACs, are powerful tools that allow biology assessment of oncogenic targets beyond the conventional kinase inhibition. Focal Adhesion Kinase (FAK) is a key mediator of tumour progression and is overexpressed in many solid tumours; to date, inhibitors targeting FAK kinase activity have shown low success in the clinic. Here we report the design and characterization of a highly potent FAK degrader with increased efficacy over FAK inhibitor, as well as extended *in vivo* efficacy.

11:30 ADME Properties of PROTACs and Oral Bioavailability Improvement Strategies

Upendra Dahal, PhD, Senior Scientist, Pharmacokinetics and Drug Metabolism, Amgen, Inc.

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12:00 pm Close of Conference

12:45 Dessert Break in the Exhibit Hall with Poster Viewing
(Sponsorship Opportunity Available)

"This conference is a macrocyclic mecca and that's why we make the pilgrimage every year. It's illuminating to see the state of the art from some of the big pharma players, some of the smaller companies, and some of the academics."

Cameron P., Unnatural Products

"The talks and topics were the best that I've been a part of from 20 years of going to conferences."

Charles W., Novartis

TRACK HOPPING

Attendees at Drug Discovery Chemistry are encouraged to "track-hop" between concurrent sessions: Though you register for a particular conference or symposium, in reality you gain access to all concurrent conferences or symposia. For the best value and to best fit your research needs, register for a Premium Package that gives you access to either: all 8 conferences, 3 symposia, plus 2 short courses over five days of programming OR access to 8 conferences plus 4 short courses over four days of programming.

Macrocyclics & Constrained Peptides

Discovery and Design of Cell-Penetrating, Middle-Sized Molecules for Oral-Based Meds

August 25-26, 2020 | Hilton San Diego Bayfront | San Diego, CA

TUESDAY, APRIL 14

7:00 am Registration Open and Morning Coffee

NEW APPROACHES FOR CONSTRUCTING MACROCYCLIC SCAFFOLDS

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

8:05 Chairperson's Opening Remarks
Christian Cunningham, PhD, Scientist, Early Discovery Biochemistry, Genentech

8:10 Macrocycles to Control Peptide Conformation and Activity
Paramjit Arora, PhD, Professor, Chemistry, New York University
We are pursuing a systematic approach to develop synthetic inhibitors of PPIs. Proteins often utilize small folded domains for recognition of other biomolecules. The basic hypothesis guiding our research is that by mimicking these domains, we can modulate the function of a particular protein with metabolically stable synthetic molecules. This presentation will discuss covalent constraints to stabilize protein domain mimics (PDMs) in isolated sequences.

8:40 Encoded Macrocyclic Peptide Libraries in Drug Discovery
Christoph Dumelin, PhD, Laboratory Head and Project Leader, Chemical Biology & Therapeutics, Novartis Institutes for Biomedical Research
The pharmaceutical industry is continuously expanding into unchartered territory in terms of both target space and therapeutic modalities. The identification of suitable chemical matter suitable enabling such projects using the libraries and screening technologies developed over the last decades has turned out to be challenging. This talk will give an overview of how we apply our encoded macrocyclic peptide library platform to tackle these challenges.

9:10 Oncodesign's Integrated Drug Discovery Services for Developing New Drug Candidates and Cyclic Inhibitors
Sponsored by Oncodesign
Alexis Denis, PhD, Director, Discovery Medicinal Chemistry, Oncodesign
Oncodesign's Integrated Drug Discovery Services combine pharma drug discovery expertise, from hits finding to preclinical candidates, across platforms: medicinal chemistry, pharmacology, pharmaco-imaging & DMPK, for the fast development of new drug candidates. Our medicinal chemistry expertise also covers the macrocyclization of small Lead-like which is the core of our kinase drug discovery programs. We will present some examples of current ongoing programs using either the optimization of preformed macrocycle or fragments to macrocycle approach.

9:40 Networking Coffee Break

10:05 Syrbactin Proteasome Inhibitors for Oncology and Immune Disorders
Michael Pirrung, PhD, Distinguished Professor of Chemistry, University of California Riverside
Drug candidates based on the syrbactins, macrocyclic peptide natural products, are being developed for autoimmune disorders and bortezomib-resistant multiple myeloma. They show irreversible, covalent proteasome modification, high specificity for particular proteasome catalytic subunits in cell culture, no off-targets in adverse drug reaction screens, and a good therapeutic index in animal models. We exploit the syrbactin macrocycle to predict, analyze, and control the 3D conformations of our drug candidates, which affect their proteasome selectivity.

10:35 Targeting NRF/Keap1 with a Cyclic Peptide
Adrian Whitty, PhD, Associate Professor, Department of Chemistry and Department of Pharmacology and Applied Therapeutics, Boston University
The protein-protein interaction of KEAP1 with Nrf2 is a target of high current interest that, due to the highly charged nature of the interface, poses special problems for inhibitor discovery. I will describe progress toward developing a cyclic peptide inhibitor of KEAP1, with emphasis on how we approached optimizing ring size, eliminating strain, occupying binding energy hot spots, and eliminating charged groups that hinder cell permeability.

11:05 Passively Permeable Macrocycles: Inspiration from Nature and the Translation to the Bench
Cameron Pye, PhD, CEO and Co-Founder, Unnatural Products
We've been using passively permeable macrocycles found in nature as therapeutics for decades. However, designing this property into synthetic cyclic peptides has proved to be challenging despite the myriad of screening and selection platforms available. This talk will explore how we leverage our platform to turn impermeable binders into passively permeable leads.

11:35 Session Break

11:45 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

12:30 pm Session Break

CONSTRAINED PEPTIDES

1:15 Chairperson's Remarks
J. Jean Cui, CSO, Turning Point Therapeutics, Inc.

1:20 Cyclotides as Scaffolds for Intracellular Targets
David Craik, PhD, ARC Laureate Fellow – Group Leader, Institute for Molecular Bioscience, Queensland University, Australia
Cyclotides are ultra-stable peptides that are able to penetrate cells. This presentation will describe their membrane interactions and cell-penetrating ability, along with their ability to be loaded with epitopes for intracellular targets.

1:50 A Constrained Peptide for an E3 Ligase
Laura Itzhaki, PhD, Professor, Pharmacology, University of Cambridge
E3 ligases are key regulators of the cell cycle and cell proliferation and important therapeutic targets. The proteins from which they are derived adopt extended, non-helical bioactive conformations, presenting challenges for the rational design of chemical constraints. I will present our work on peptides designed to inhibit two E3 ligases. I will also discuss how we are exploiting our findings and methodologies for targeted protein degradation.

2:20 Constrained Peptides for Drug Discovery
Rami Hannoush, PhD, Principal Scientist, Group Leader, Early Discovery Biochemistry, Genentech

2:50 Elucidating Quality Control at the Ribosome with the Natural Product, Ternatin
Keely Oltion, Graduate Student, Chemistry and Chemical Biology, Laboratory of Jack Taunton, University of California San Francisco
Natural products often provide novel insights into biological processes. We discovered that ternatin, a cyclic peptide natural product, inhibits translation elongation by trapping the elongation factor, EF1A, at the ribosome. Ternatin, but not didemnin B, a structurally unrelated natural product with the same binding site, causes degradation of EF1A. I will describe work towards the mechanism for ternatin-induced EF1A degradation, which may represent a novel form of ribosome quality control.

3:20 Sponsored Presentation *(Opportunity Available)*

3:35 Refreshment Break in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

4:35 Plenary Welcome Remarks from Event Director with Poster Finalists Announced

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

4:45 Plenary Technology Spotlight: Accelerating Drug Discovery from Hit Finding to Candidate Selection with Physics and Machine Learning-Based Calculations

Sponsored by SCHRÖDINGER

Matt Repasky, PhD, Vice President, Life Sciences Products, Schrödinger

The impact of the Schödinger computational platform in drug discovery is illustrated using recent case studies from internal and collaborative discovery projects. The Platform facilitates halving the number of synthesized molecules and time to candidate relative to industry standards. Key elements of the Platform are described including Free Energy Perturbation to accurately predict relative protein-ligand binding, machine learning to generate and rapidly assess millions of ideas, and collaborative sharing of project information through LiveDesign.

5:10 Plenary Keynote Introduction *(Sponsorship Opportunity Available)*

5:15 PLENARY KEYNOTE:

Medicinal Chemistry: Where Are We Headed?

Wendy Young, PhD, Senior Vice President, Small Molecule Discovery, Genentech

Major shifts in the way medicinal chemists discover novel medicines have evolved over the past few decades. Technological advances have significantly increased the ability to triage compound design and synthesize compounds faster. New approaches in structural biology have enhanced our ability to visualize molecules and their corresponding binding sites. Drug discovery teams have moved from local to global and our deepened understanding of biology has extended our reach. This lecture will explore past trends in drug discovery, current status of the industry, and the future of medicinal chemistry.

6:00 Welcome Reception in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

7:00 Close of Day

WEDNESDAY, APRIL 15

7:30 am Continental Breakfast Breakout Discussions

In this session, attendees fill their plate from the breakfast buffet and then choose a specific roundtable discussion to join. Each group has a moderator to ensure focused conversations around key issues within the topic. The small-group format allows participants to informally meet potential collaborators, share examples from their work, and discuss ideas with peers. Discussion topics and moderators will be listed on the website.

MACROCYCLIC-BASED DRUG LEADS

8:30 Chairperson's Remarks

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

8:35 FEATURED PRESENTATION: Identification of Novel Macrocyclic Bactericidal Inhibitors Targeting the Essential Bacterial ABC transporter MsbA

Christian Cunningham, PhD, Scientist, Early Discovery Biochemistry, Genentech

We detail the use of mRNA display technologies and a unique selection and protein engineering strategy to discover potent macrocycle-based inhibitors of MsbA, an essential bacterial ABC transporter for LPS. A high-resolution cryo-electron microscopy structure reveals the molecular basis for state-dependent inhibition of MsbA. Unexpectedly, peripherally-bound LPS molecules are also observed, expanding our understanding of the mechanisms of substrate transport.

9:05 Type IV Macrocyclic Inhibitors of BRAF Kinase Block Paradoxical Signaling in Resistant Melanomas

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

We describe the proof of concept for macrocyclic peptides that inhibit BRAF through binding to the dimerization interface of the RAF kinases. Furthermore, we applied the REPLACE strategy to identify and optimize the peptides for BRAF affinity and increased drug-likeness. The compounds block paradoxical signaling resulting from aberrant activation of BRAF by ATP competitive drugs and thus, have potential as next-generation BRAF inhibitors for treating resistant melanomas.

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

Poster Awards Sponsored by Enamine Ltd

10:30 Engineered Cyclotides with Potent Broad Antimicrobial Activity

Julio Camarero, PhD, Professor, Pharmaceutical Sciences, University of Southern California

The search for novel antimicrobial agents is intensifying, in response to both the threat of microbial pathogens in bioterrorism and the increasing development of drug resistance to current antibiotics. We will present work of the development of novel cyclotides with a good pharmacokinetic profile and effective broad-spectrum antibacterial activity against several ESKAPE bacterial strains. The most active cyclotide showed good activity *in vivo* using a P. aeruginosa peritonitis animal model.

11:00 Design and Development of Repotrectinib, a Next Generation Macrocyclic ROS1/TRK/ALK Inhibitor

J. Jean Cui, CSO, Turning Point Therapeutics, Inc.

Drug-resistance mutations have emerged as a major challenge to targeted therapies. Repotrectinib was designed with a novel macrocycle having a much smaller size (MW 355) than current ROS1/TRK/ALK inhibitors and located at the center of the highly conserved ATP site without direct contact with clinical resistance mutations. Repotrectinib potently inhibited both wild type and many mutant ROS1/TRK/ALK. Repotrectinib was well tolerated and demonstrated encouraging overall clinical activity in patients with ROS1 fusion-positive NSCLC and TRK fusion-positive solid tumors.

11:30 Discovery of Synthetic Macromolecules as High Affinity Reagents by Mega - HTS using Fiber Optic Array Scanning Technology (FAST)

Michal Avital-Shmilovici, PhD, Research Scientist, Drug Discovery, SRI International

FAST is capable of screening ~5M assay points in 1 minute. We have used this to design and screen large libraries (107 – 108) of synthetic non-natural polymer macromolecules to routinely find nanomolar to sub-nanomolar binders to 'undruggable' targets, such as K-Ras and asialoglycoprotein receptor. With remarkable biological stability and extended *in vivo* PK half-life, these represent early examples of a new class of synthetic macromolecular modality for therapeutics discovery.

12:00 pm Close of Conference

12:45 Dessert Break in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

Protein-Protein Interactions

Targeting PPIs and Nucleic Acid Complexes for Therapeutic Interventions

August 26-27, 2020 | Hilton San Diego Bayfront | San Diego, CA

WEDNESDAY, APRIL 15

12:30 pm Registration Open

12:45 Dessert Break in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

NEW PPI TARGETS

1:30 Welcome Remarks

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

1:35 Chairperson's Opening Remarks

Samantha Allen, PhD, Principal Scientist, Discovery Sciences, Janssen R&D

1:40 FEATURED PRESENTATION: Fragment-Based Discovery of an Apolipoprotein E4 (apoE4) Stabilizer

Andrew Petros, PhD, Senior Principal Research Scientist, Protein & Assay Sciences, AbbVie

Apolipoprotein E is a lipid carrier protein that exists as three isoforms denoted apoE2, apoE3, and apoE4 with the apoE4 protein exhibiting reduced thermal stability compared to apoE2 and apoE3. Genome-wide association studies indicate that the possession of two E4 alleles is a strong genetic risk factor for late-onset Alzheimer's disease. NMR-based screening on the N-terminal domain of apoE4 identified a fragment binder that was subsequently, using SBDD, elaborated into a single-digit micromolar stabilizer.

2:10 Using cryo-EM to Understand RET Receptor Tyrosine Kinase Activation by Neurturin and GFRα2

Jenny Sandmark, PhD, Associate Principal Scientist, Drug Discovery, AstraZeneca R&D

RET signalling is implicated in a number of disease states. Overactivity may result in cancer, but stimulation of the system is being considered as treatment for neurodegenerative diseases such as Parkinson's and Alzheimer's disease. We have determined the cryo-EM structure of the hexameric signalling complex formed between RET, the NRTN ligand and GFRα2 co-receptor. The structure highlights the importance of the cysteine-rich domain of RET for the complex assembly and signalling.

2:40 Inhibitors of Sec61 as Novel Anti-Cancer Therapeutics

Dustin McMinn, PhD, Senior Director, Head of Chemistry, Kezar Life Sciences

Post-translational functionalization of most secreted and transmembrane proteins requires co-translational translocation to the ER through Sec61. Translocation is negotiated by protein interactions between Sec61 and unique signal sequences specific to each translating protein. Disruption of these interactions in specific or multi-signal sequence fashion presents an opportunity to modulate protein homeostasis toward therapeutic benefit. Development of signal and multi-signal sequence selective Sec61 inhibitors as novel anti-cancer agents will be discussed.

3:10 Sponsored Presentation *(Opportunity Available)*

3:40 Refreshment Break and Book Signing in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

INFECTIOUS DISEASE TARGETS

4:30 Late Breaking Presentation: A New 'Inhibition-Friendly' Binding Site for Ral GTPases

Samy Meroueh, PhD, Associate Professor, Biochemistry & Molecular Biology, Indiana University

5:00 Leveraging Viral Protein-Protein Interactions to Generate Inhibitors of BK and JC Polyomavirus in Early-Stage Drug Discovery

Charles Wartchow, PhD, Senior Investigator, Global Discovery Chemistry, Novartis Institutes for Biomedical Research

BK and JC viruses reactivate during immunosuppression, resulting in nephropathy or multifocal leukoencephalopathy, respectively. To establish anti-viral MOAs involving viral protein-protein interactions, we examined capsid proteins VP1 and VP2 and identified a VP2-derived peptide with anti-viral activity. With biophysical and biochemical screens, we identified hits that bind VP1 and these compounds inhibit a VP1 and VP2 interaction *in vitro*.

5:30 Breakout Discussions

In this session, attendees choose a specific roundtable discussion to join. Each group has a moderator to ensure focused conversations around key issues within the topic. The small group format allows participants to informally meet potential collaborators, share examples from their work, and discuss ideas with peers. Discussion topics and moderators will be listed on the website.

6:15 Close of Day

6:30 Dinner Short Courses*

See Short Courses pages (3-4) for details. Best Value or separate registration required for Short Courses.

THURSDAY, APRIL 16

8:00 am Breakfast Plenary Technology Spotlight *(Sponsorship Opportunity Available)* **or Morning Coffee**

8:45 Plenary Welcome Remarks from Event Director with Poster Finalists Announced

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

8:55 Plenary Keynote Introduction *(Opportunity Available)*

9:00 PLENARY KEYNOTE:

Translational Chemistry

Phil Baran, PhD, Professor, Department of Chemistry, Scripps Research

There can be no more noble undertaking than the invention of medicines. Chemists that make up the engine of drug discovery are facing incredible pressure to do more with less in a highly restrictive and regulated process that is destined for failure more than 95% of the time. How can academic chemists working on natural products help these heroes of drug discovery – those in the pharmaceutical industry? With selected examples from our lab and others, this talk will focus on that question highlighting interesting findings in fundamental chemistry and new approaches to scalable chemical synthesis.

9:45 Coffee Break in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

TARGETING KRAS: PRECLINICAL COMPOUNDS

10:40 Chairperson's Remarks
Kevin Lumb, PhD, Senior Director, Lead Discovery, Janssen R&D LLC

10:45 Covalent Fragment-Based Drug Discovery: KRAS and Beyond
Daniel Erlanson, PhD, Vice President, Chemistry, Frontier Medicines
Fragment-based drug discovery (FBDD) has delivered roughly 50 drugs into the clinic, three of which have been approved. The protein KRAS has been intensively studied as an oncology target for decades, but has largely resisted drug discovery efforts. This presentation will describe how FBDD has led to novel, irreversible small molecule inhibitors of the oncogenic G12C mutant form of KRAS.

11:15 Translating Frontier Oncology Targets to Outsmart Cancer
James Aggen, PhD, Senior Director, Medicinal Chemistry, Revolution Medicines
We have developed tri-complex inhibitors of KRASG12C(ON) that selectively drive formation of KRASG12C-inhibitor-CypA ternary complexes through significant non-covalent interactions combined with a druglike cysteine-targeted warhead to potently and irreversibly inhibit KRASG12C(ON). In cellular models, KRASG12C(ON) inhibitors show differentiation to first generation KRASG12C(OFF) inhibitors in cancer cell lines bearing KRASG12C mutations and drive dose-dependent tumor regressions in a KRASG12C NSCLC xenograft mouse model.

Sponsored by
WAC™ Weak Affinity Chromatography

11:45 Fragment Screening by Weak Affinity Chromatography (WAC) Against PPIs
Björn Walse, CEO, SARomics Biostructures/Red Glead Discovery
The advantage of WAC™ for FBS are the detection of weak binders by screening fragments at low concentrations (<5 µM) and its immediate ranking of hits. Here we compare the result of a WAC™ screen towards SMARCA4 with results from fragment screens using other techniques

12:00 pm Targeting KRAS Directly with Novel Drug Discovery Efforts at the NCI RAS Initiative
Dominic Esposito, PhD, Director, Protein Expression Laboratory, Frederick National Laboratory for Cancer Research (FNLCR)
The NCI RAS Initiative, led by scientific director, Frank McCormick of UCSF, combines novel drug discovery approaches (covalent tethering, computational modeling, and structure-guided fragment-based screening) to identify new compounds that directly target KRAS and its oncogenic mutants. These techniques provide a potential set of new targets in RAS drug discovery which have not yet been fully explored and will be discussed in this presentation.

12:30 Session Break

12:40 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:30 Dessert Break in the Exhibit Hall with Poster Awards Announced *(Sponsorship Opportunity Available)*

TARGETING KRAS: COMPOUNDS IN THE CLINIC

2:15 Chairperson's Remarks
Charles Wartchow, PhD, Senior Investigator, Global Discovery Chemistry, Novartis Institutes for Biomedical Research

2:20 Targeting Mutant KRAS by Direct and Indirect Approaches
Michael Gmachl, PhD, Principal Scientist, New Therapeutic Concepts, Boehringer-Ingelheim
KRAS is the most frequently mutated oncogene. Boehringer-Ingelheim has developed small molecule inhibitors binding and blocking KRAS independently of the mutation and activation status as well as an NCE targeting SOS1, an exchange factor, necessary for the conversion of inactive to active KRAS. The features of both of these molecules *in vitro* as well as *in vivo* will be discussed.

2:50 Discovery and Early Development of MRTX849, a Selective, Covalent Inhibitor of KRAS G12C
Matt Marx, Vice President, Drug Discovery, Mirati Therapeutics
MRTX849 is an irreversible, covalent inhibitor of KRASG12C currently undergoing clinical investigation in cancer patients with this mutation. This compound binds in the switch-II pocket of GDP-bound KRAS, locking the protein in the inactive state. Previously, we have described the structure-based design of the *in vivo* tool compound MRTX1257, and this talk will highlight the liabilities of this tool molecule and the strategies utilized for its final optimization to MRTX849.

3:20 High-Throughput Mass Spectrometric Analysis of Covalent Protein-Inhibitor Adducts for the Discovery of KRAS G12C Inhibitors
John McCarter, PhD, Head, Affinity Screening Technologies, Amgen
A high-throughput MS platform was used to accurately detect and quantitate different covalent modifications of proteins including KRAS G12C which contain one or more reactive cysteines, lysines, or other nucleophilic residues. We employed the Agilent RapidFire system to rapidly quantitate the extent of covalent protein inhibitor adduct formation by MS for several proteins including KRAS G12C and human serum albumin. We used this approach to screen large numbers of potential covalent inhibitors in an automated fashion and to test medicinal chemistry compounds as part of a regular lead optimization cycle for KRAS G12C.

3:50 Networking Refreshment Break

MORE RAS AND BEYOND

4:20 Design of Small Molecule Allosteric Reversible Inhibitors of K-Ras with Antitumor Activity
Juan Perez, PhD, Professor, Molecular and Industrial Biotechnology, Polytechnic University of Barcelona
We disclose the design and synthesis of a novel series of small molecule inhibitors that reversibly bind to K-Ras at the nanomolar scale. Tested in a xenograft model for non-small-cell lung cancer (NCI-H358) in daily doses of 0.1 mg/kg ip, these compounds prevent tumor growth without any significant loss of body weight and do not exert any obvious toxic effect. These results suggest that it is possible to design reversible allosteric inhibitors of the K-Ras, opening the door for a new class of therapeutic agents.

4:50 Discovery of First-in-Class Allosteric Inhibitors of BAX
Evris Gavathiotis, PhD, Professor, Biochemistry, Albert Einstein College of Medicine
The BCL-2 family protein BAX is a critical effector of apoptotic cell death in response to a diverse range of stimuli. Efforts to rationally target BAX have been elusive, despite the promising therapeutic potential for a host of diseases. My presentation will discuss the use of NMR and biochemical methods to screen and characterize the first inhibitors of inactive BAX that bind to a previously unrecognized allosteric pocket. Structure-based and mechanistic insights, cell-based and preclinical *in vivo* studies with this challenging PPI target will be discussed

5:20 Targeting Regulatory Protein-Protein Interactions of Calcium-handling Enzymes for Drug Discovery
Russell Dahl, PhD, CEO, Neurodon Corporation
Disruption of intracellular calcium ion homeostasis leads to the unfolded-protein response and endoplasmic reticulum stress. These phenomena are recognized as causal features of major diseases such as diabetes and neurodegeneration. Recent observations suggest that these conditions initiate pro-inflammatory pathways that are fundamental to the pathogenesis of these diseases. Herein we describe the use of FRET screening techniques for the discovery and optimization of small molecule calcium-handling modulators and their development to deliver drug candidates for these diseases.

5:50 Close of Conference

Artificial Intelligence for Early Drug Discovery

AI & Machine Learning for Drug Design and Lead Optimization

August 26-27, 2020 | Hilton San Diego Bayfront | San Diego, CA

WEDNESDAY, APRIL 15

12:30 pm Registration Open

12:45 Dessert Break in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

AI FOR DRUG DESIGN, COMPOUND SCREENING AND PRIORITIZATION

1:30 Welcome Remarks

Tanuja Koppal, PhD, Senior Conference Director, Cambridge Healthtech Institute

1:35 Chairperson's Opening Remarks

Yuan Wang, PhD, Senior Principal Scientist, Head of TPD Data Science, UCB Pharma

1:40 Applied Machine Learning in Compound Mechanism Deconvolution

Yuan Wang, PhD, Senior Principal Scientist, Head of TPD Data Science, UCB Pharma

Modern drug discovery calls for increased use of phenotypic screens and novel targets and modalities are being explored in the process. The use of potent and selective chemical tools (probes) in phenotypic screens can help understand underlying biological processes or help deconvolute unknown mechanisms. We have used computational analytics and machine learning models to: 1) select tool compounds; 2) predict targets; and 3) design better sets of compounds.

2:10 AI Powered Design of Small Molecules Accelerated by Structure-based Constraints

Anthony Bradley, PhD, Head of Structural Bioinformatics, Exscientia

Structural data are central to many of our projects since they enable clear and directed hypothesis and constraint generation. In this talk we present three ways in which they empower Centaur ChemistTM through examples from our fully validated design engine. First, we show how our best-in-class AI systems use 3D ligand and protein-ligand structures to accelerate compound design. Second, we present how feedback between 3D and 2D models enable identification of gaps in data. Finally, we outline how a new breed of Deep Neural Networks and Generative Models promise a further step-change in productivity.

2:40 Deep Generative Autopilot for the Real-World Design of Novel Lead Compounds

Sang Ok Song, PhD, Co-Founder and Chief Transformation Officer, Standigm, Inc.

Standigm has applied deep generative models to design novel therapeutic compounds and launched Standigm BEST®, a proprietary molecular generative platform for lead discovery and optimization. On top of the main molecular generative algorithm, we developed an automated molecular design workflow to optimize and prioritize machine generated compounds for further synthesis and experimental validation. The most recent progress including real-life case studies will be shared.

3:10 Structure-guided *De Novo* Drug Design Via AI/deep Generative Modeling

Sponsored by IKTOS

Yann Gaston-Mathé, Co-Founder, CEO, Iktos

Artificial Intelligence is an emerging research field in the context of drug discovery. Complementing its ligand-based deep generative modeling technology for *de novo* drug design, Iktos has developed structure-guided deep generative modeling technology that overcomes the applicability domain limitations of ligand-based methods. We will present this novel technology and a case study where the structure-guided generation of small molecules enabled the discovery of AI-designed molecules similar to known ligands.

3:40 Refreshment Break and Book Signing in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

USE OF AI/ML TO PREDICT ADME & DRUG SAFETY

4:30 FEATURED PRESENTATION: Benefits, Limitations and Diversity of AI Models in Drug and Target Discovery

Ruben Abagyan, PhD, Professor, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego

Computer models that are capable of predicting several thousands of biological activities for any chemical along with their ADMET properties have improved dramatically with the rapid growth of experimental data. The resulting network, illustrated by cancer drugs, has an extensive multi-target profile for each drug. These models use different mathematical methods, and help to predict new targets for known compounds, repurpose to new indications, search for compounds with specific multi-target profile, or identify potential liabilities.

5:30 Breakout Discussions

In this session, attendees choose a specific roundtable discussion to join. Each group has a moderator to ensure focused conversations around key issues within the topic. The small group format allows participants to informally meet potential collaborators, share examples from their work, and discuss ideas with peers. Discussion topics and moderators will be listed on the website.

6:15 Close of Day

6:30 Dinner Short Courses*

See Short Courses pages (3-4) for details. Best Value or separate registration required for Short Courses.

THURSDAY, APRIL 16

8:00 am Breakfast Plenary Technology Spotlight *(Sponsorship Opportunity Available)* **or Morning Coffee**

8:45 Plenary Welcome Remarks from Event Director with Poster Finalists Announced

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

8:55 Plenary Keynote Introduction *(Opportunity Available)*

9:00 PLENARY KEYNOTE:

Translational Chemistry

Phil Baran, PhD, Professor, Department of Chemistry, Scripps Research

There can be no more noble undertaking than the invention of medicines. Chemists that make up the engine of drug discovery are facing incredible pressure to do more with less in a highly restrictive and regulated process that is destined for failure more than 95% of the time. How can academic chemists working on natural products help these heroes of drug discovery – those in the pharmaceutical industry? With selected examples from our lab and others, this talk will focus on that question highlighting interesting findings in fundamental chemistry and new approaches to scalable chemical synthesis.

9:45 Coffee Break in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

PREDICTING DDI AND DRUG-TARGET INTERACTIONS

10:40 Chairperson's Remarks

Maria A. Miteva, PhD, Research Director, Molécules Thérapeutiques in silico (MTi), Inserm Institute

10:45 Integration of Structure-Based and Machine Learning Approaches to Predict Inhibition of Drug Metabolizing Enzymes

Maria A. Miteva, PhD, Research Director, Molécules Thérapeutiques in silico (MTi), Inserm Institute

We will present *in silico* approach to predict inhibition of drug metabolizing enzymes. We focus on Cytochrome P450 (CYP) responsible for the metabolism of 90% drugs and on sulfotransferase (SULT), a conjugate Phase II metabolizing enzyme. We developed an original *in silico* approach for the prediction of CYP2C9 and SULT1A1 inhibition combining protein structure knowledge, dynamic behaviors in response to ligand binding and modern machine learning modeling.

11:15 Leveraging Image-Derived Phenotypic Measurements for Drug-Target Interaction Predictions

Arvind Rao, PhD, Associate Professor, Department of Computational Medicine and Bioinformatics, University of Michigan

We propose a novel *in silico* drug discovery approach to identify kinase targets that impinge on nuclear receptor signaling with data generated using high-content analysis (HCA). Using imaging-derived descriptors, we provide prediction results of drug-kinase-target interactions based on single-task learning, multi-task learning, and collaborative filtering methods. These results suggest that imaging-based information can be used as an additional source of information for existing virtual screening methods, thereby making drug discovery more efficient.

Sponsored by CDD VAULT Complexity Simplified

11:45 Complexity Simplified - Comprehensive Data Management for Complex World

Heather Mattson Arnaiz, PhD, Customer Engagement Scientist, Collaborative Drug Discovery

CDD brings drug discovery full circle. From unstructured experiments to structured registrations, we ensure data is accessible from a single, secure location. CDD Vault fits with your informatics and AI tools as the platform for managing data. This is easily accomplished within CDD Vault that includes an API for automation.

12:00 pm Explainable Biology for Improved Therapies

Igor Jurisica, PhD, DrSc, Senior Scientist, Krembil Research Institute; Professor, University of Toronto; Visiting Scientist, IBM CAS

Integrative computational biology and AI help improve treatment of complex diseases by building explainable models. From systematic data analysis to improved biomarkers, drug mechanism of action, and patient selection, such analyses influence multiple steps of drug discovery pipeline. Data mining, machine learning, graph theory and advanced visualization help with accurate predictions, making disease modeling more comprehensive by intertwining computational prediction and modeling with biological experiments.

12:30 Session Break

12:40 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:30 Dessert Break in the Exhibit Hall with Poster Awards Announced *(Sponsorship Opportunity Available)*

EMERGING APPLICATIONS OF AI/ML PREDICTIONS

2:15 Chairperson's Remarks

Wenjin Zhou, PhD, Assistant Professor, Department of Computer Science, University of Massachusetts Lowell

2:20 New Anti-Cancer Peptide Design Using a GAN-Based Deep Learning Method

Wenjin Zhou, PhD, Assistant Professor, Department of Computer Science, University of Massachusetts Lowell

Cancer is a deadly disease that causes an estimated 9.6 million deaths a year. Pharmaceutical drugs are important, but developing new drugs is difficult and expensive. Here we generate a new peptide for PD-1, which is closely linked to a wide variety of cancers, using a new application called GANDALF to design new peptides. We present a peptide generated by our prototype to bind with PD1 and compare it to FDA approved drugs and results from a comparable method, Pepcomposer.

2:50 AI for Accelerated Pre-Clinical Drug Discovery: From Data Mining to Screening Automation

Amol Jadhav, PhD, Industry Consultant, Transformational Health, Frost & Sullivan

This presentation will focus around the role of life sciences big data, technologies and emerging application of AI for the early drug discovery. The case studies discussing the impact of automation and miniaturization approaches coupled with machine learning on the speed and efficiency for the compound screening will be discussed. Additionally, a brief assessment of the therapeutics area-wise activity, current trends will be provided.

3:20 FEATURED PRESENTATION: Artificial Intelligence and Small-Molecule Drug Metabolism

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

We have been building artificial intelligence models of metabolism and reactivity. Metabolism can both render toxic molecules safe and safe molecules toxic. The artificial intelligence models we use quantitatively summarize the knowledge from thousands of published studies. The hope is that we could more accurately model the properties of medicines, to determine whether metabolism renders drugs toxic or safe. This is just one of many places where artificial intelligence could give traction on the difficult questions facing the industry.

3:50 Networking Refreshment Break

4:20 Sponsored Presentation *(Opportunity Available)*

4:50 Applications of Deep Learning-Based Approaches for Non-Target Based Drug Discovery

Arash Keshavarzi Arshadi, MS, Doctoral Student/Research Fellow, College of Medicine, University of Central Florida

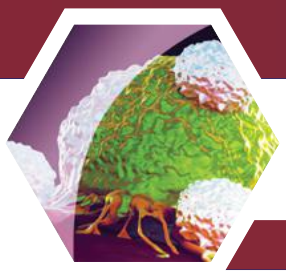
My talk will be about applying DL-based approaches for non-target based virtual screening and drug repurposing. I will describe how DeepMalaria (our patented model) could identify 87.75% of all macrocyclic hits as the first attempt at using AI-based models for malaria drug discovery and repurposing. Also, I will present a model we developed using transfer learning/unsupervised studies for discovery of Anti-Microbial Peptides (AMP) as a state of art approach (AMPDeep).

5:20 Drug Hybridization Approach to Drug Design

Clinton Egbe, PharmD, Master's Student in Drug Design and Discovery, University of Salford

Drug hybridisation approach to drug design is an innovative approach to design drugs that are safe, effective, and affordable. The "Drug Hybridizer" is a bioinformatic tool that will combine *in silico* molecular fragments of two or more old drugs to produce hybrid compounds that can modify more than one pharmacological target simultaneously for the treatment of multi-pathological disorders such as strokes, cancers and infectious diseases. It will also help to address the problem of drug resistance.

5:40 Close of Conference



INAUGURAL

Small Molecules for Immunology & Oncology

Drug Discovery against Molecular Targets in Inflammation, Autoimmunity and Cancer

August 26-27, 2020 | Hilton San Diego Bayfront | San Diego, CA

WEDNESDAY, APRIL 15

12:30 pm Registration Open

12:45 Dessert Break in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

TARGETING STING

1:30 Welcome Remarks

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

1:35 Chairperson's Opening Remarks

Jennifer Venable, PhD, Senior Scientific Director, Discovery Chemistry, Janssen Research & Development

1:40 UnderstandING STING in Inflammation and Cancer

Jeonghyun Ahn, PhD, Research Professor, Laboratory of Glen Barber, Department of Cell Biology, University of Miami School of Medicine

Stimulator of IFN genes (STING) is one of the innate immunity sensors activated by cytosolic DNA, such as cyclic dinucleotides (CDNs) secreted by intracellular bacteria or generated by a cellular cGAMP synthase (cGAS). While transient STING function has found to be essential for protection of the host against viral infection, chronic STING activity by self-DNA leaked from the nucleus has been implicated in causing lethal autoinflammatory diseases. I will illustrate how the molecular mechanisms of STING enable it to both, be a target for combatting inflammatory disease as well as a providing a novel therapeutic strategy for converting an immunologically "cold" tumor to "hot" by stimulating anti-tumor immune responses.

2:10 Characterization of Novel STING Ligands

Gottfried Schroeder, PhD, Senior Scientist, Department of Quantitative Biosciences, Merck Research Labs Boston

Modulation of the innate immune receptor STING is of pharmacological interest for both oncology and autoimmune indications. Binding of cyclic dinucleotide 2'3'-cGAMP to dimeric STING stabilizes a 'lid-closed' protein conformation, ultimately inducing interferon production. Biophysical characterization of different classes of STING ligands using surface plasmon resonance (SPR) has revealed significant differences in binding kinetics, stoichiometry and mode of action. The results of complimentary techniques further support these observed mechanistic differences.

2:40 FEATURED PRESENTATION: Discovery of STING Agonist with Systemic Anti-Tumor Response

Scott Pesiridis, PhD, Associate Fellow, Scientific Leader, Discovery Biology, GlaxoSmithKline

Medicines targeting STING are intensely pursued as innate immune modulators with potential to complement other immuno-oncology agents. While the first wave of STING agonists are derived from cyclic dinucleotides limited to intra-tumoral delivery, we discovered a small molecule dimeric ligand known as the ABZI series that is selective STING agonists with remarkable single agent efficacy upon intravenous delivery.

3:10 CETSA HT, A Powerful Assay for Small Molecule Drug Discovery

Sponsored by PELAGO BIOSCIENCE

Stina Lundgren, Principal Projects Advisor, Pelago Bioscience

The CETSA® HT assay offers a robust label-free method for studying protein−compound interactions in a cellular environment. Welcome to learn about the CETSA HT methodology and principles for drug profiling including generation of relevant structure-activity relationship (SAR) data, screening and hit confirmation.

3:25 Sponsored Presentation *(Opportunity Available)*

3:40 Refreshment Break and Book Signing in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

TARGETING CELL SURFACE IMMUNO/ONCO-RELATED PROTEINS

4:30 Targeting av Integrins for Fibrosis

Katerina Leftheris, PhD, Vice President, Chemistry, Pliant

Av integrins are a subset of a family of heterodimeric transmembrane proteins that mediate cell-cell and cell-extracellular matrix signaling. Targeting av integrins with small molecules has been a challenge in the drug discovery field, primarily due to limited approaches to selectivity, complex signaling mechanisms, poor ADME properties and poor translation to a clinical setting. This talk will focus on our approach to addressing these concerns, leading to *in vivo* active molecules that translate to human disease.

5:00 CryoEM for Drug Discovery against 'Immuno' Important Membrane Proteins

Seungil Han, PhD, Cryo-EM Lab Head, Structural & Molecular Sciences, Pfizer Global R&D

This talk will describe applications of cryo-EM to investigations of solute carrier transporter proteins to enable drug discovery. The prospects of studying large disease-relevant macromolecular complexes without having to generate single crystal are very appealing and cryo-EM is becoming a part of lead generation in more and more research departments. The introduction of direct electron detectors, the resolution and range of biological molecules amenable to single particle cryo-EM have enabled this.

5:30 Breakout Discussions

In this session, attendees choose a specific roundtable discussion to join. Each group has a moderator to ensure focused conversations around key issues within the topic. The small group format allows participants to informally meet potential collaborators, share examples from their work, and discuss ideas with peers. Discussion topics and moderators will be listed on the website.

6:15 Close of Day

6:30 Dinner Short Courses*

****See Short Courses pages (3-4) for details. Best Value or separate registration required for Short Courses.***

THURSDAY, APRIL 16

8:00 am Breakfast Plenary Technology Spotlight *(Sponsorship Opportunity Available)* **or Morning Coffee**

8:45 Plenary Welcome Remarks from Event Director with Poster Finalists Announced

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

8:55 Plenary Keynote Introduction *(Opportunity Available)*

9:00 PLENARY KEYNOTE:

Translational Chemistry

Phil Baran, PhD, Professor, Department of Chemistry, Scripps Research

There can be no more noble undertaking than the invention of medicines. Chemists that make up the engine of drug discovery are facing incredible pressure to do more with less in a highly restrictive and regulated process that is destined for failure more than 95% of the time. How can academic chemists working on natural products help these heroes of drug discovery – those in the pharmaceutical industry? With selected examples from our lab and others, this talk will focus on that question highlighting interesting findings in fundamental chemistry and new approaches to scalable chemical synthesis.

9:45 Coffee Break in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

INTRACELLULAR IMMUNO-TARGETS: KINASES, NUCLEAR RECEPTORS

10:40 Chairperson's Remarks

Songqing Na, PhD, Senior Scientist, Biotechnology & Autoimmunity Res-AME, Eli Lilly and Company

10:45 Discovery and Development of BIIB068: A Selective, Potent, Reversible Inhibitor of Bruton's Tyrosine Kinase (BTK)

Bin Ma, PhD, Senior Scientist, Medicinal Chemistry, Biogen

Covalent modification of BTK has been proven to be beneficial for cancer patients with multiple drugs on market while their safety profiles are concerned for autoimmune disease indications. A reversible non-covalent BTK inhibitor will have the promise to address this unmet need. We will report our discovery of BIIB068, an exquisitely selective, potent, reversible BTK inhibitor, together with the med chem strategy and Phase I clinical results.

11:15 Regulation of Inflammatory Cell Death Signaling by RIP Kinases

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

11:45 Talk Title to be Announced

Sponsored by amri

Mark Wolf, PhD, Section Head, Buffalo Medicinal Chemistry, AMRI

12:00 pm An ROR-Gamma Inverse Agonist for the Treatment of Psoriasis

Murali Ramachandra, PhD, CEO, Aurigene Discovery Technologies Limited

This presentation will cover the discovery and development of AUR101, an ROR-gamma inverse agonist, which is currently in Phase 1 clinical trials for the treatment of psoriasis.

12:30 Session Break

12:40 Luncheon Presentation to be Announced

Sponsored by PharmaBlock

1:30 Dessert Break in the Exhibit Hall with Poster Awards Announced *(Sponsorship Opportunity Available)*

NEW IMMUNO-TARGETS

2:15 Chairperson's Remarks

Scott Pesiridis, PhD, Associate Fellow, Scientific Leader, Discovery Biology, GlaxoSmithKline

2:20 Small-Molecule TEAD-Yap Covalent Antagonists

Samy Meroueh, PhD, Associate Professor, Biochemistry & Molecular Biology, Indiana University

Yap1 creates a signaling hub that promotes tumor growth and immune evasion. Yap1 tightly binds to TEAD transcription factors making the development of small-molecule inhibitors challenging. Here, we report small-molecule TEAD-Yap inhibitors that form a covalent bond with a cysteine in the palmitate-binding pocket of TEADs. In mammalian cells, the compounds formed a covalent complex with TEAD4, inhibited its binding to Yap1, blocked its transcriptional activity, and suppressed expression of connective tissue growth factor.

2:50 Targeting Vps34 Induces a Proinflammatory Microenvironment Resulting in Tumor Growth Inhibition and Sensitization to PD-1/ PD-L1 Blockade

Santiago Parpal, PhD, Principal Scientist, Biology, Sprint Bioscience

New combination strategies are needed to increase therapeutic efficacy of anti-PD-1/PD-L1-based immunotherapy. Autophagy has been associated with a proinflammatory response regulating innate immunity. We found that genetic and pharmacological inhibition of the novel autophagy target Vps34 reduce tumor growth and increase the infiltration of immune cells with cytotoxic activity. Furthermore, treatment with small molecule Vps34 inhibitors (whose discovery is described in an earlier presentation on 'FBDD' conference track) significantly improved the efficacy of anti-PD-L1/anti-PD1 therapy.

3:20 Discovery of GB1211, the First Orally Available galectin/ galectin 3 inhibitor to be Taken into Clinic as a Potential Treatment for Non Alcoholic Steatohepatitis (NASH)

Fredrik Zetterberg, PhD, Director, Medicinal Chemistry, Galecto Biotech AB

Fibrosis have been estimated to account for 45% of all deaths in the industrialized world. Galectin 3 have been shown to be associated with the pathology of fibrosis in different organs such as lung and liver. We have discovered and taken two novel small molecule galectin 3 inhibitors to clinic GB0139 (Phase 2b) and GB1211(Phase 1). This lecture will describe the discovery and development of GB1211, the first orally available galectin inhibitor taken into clinical studies.

3:50 Networking Refreshment Break

ENCODED LIBRARY-ORIGIN COMPOUNDS FOR ONCOLOGY

4:20 DEL-Enabled Discovery of Novel MoA and Structurally Unique IDO1 Inhibitors

Bing Xia, PhD, NCE Encoded Library Technologies, RD Medical Science & Technology, GlaxoSmithKline

Indoleamine 2,3-dioxogenase-1 (IDO1) is induced and activated in response to viral and bacterial infection causing a dysfunctional immune response in clearing pathogens. IDO1 inhibitors (IDO1i) have the potential to restore immune function in indications such as cancer and infection. A structurally-unique IDO1i class was discovered through the affinity selection of a novel DNA-encoded library. After additional medicinal chemistry iterations, the compound series was elaborated into potential best in class preclinical molecule.

4:50 Discovery and Application of a Novel Cell Death Mechanism in Oncology

Maria Soloveychik, PhD, CEO, SnyntheX

We developed STX100, a peptide originating from an encoded library, targeting an intracellular protein-protein interaction in the homologous recombination DNA repair pathway. STX100-mediated cell killing is independent of canonical cell death mechanisms; it relies on acute calcium release from its target to elicit cell death. The mechanism translates to *in vivo* models, where a local delivery of STX100 and a combination of immune checkpoint blockade (ICB) agents can cure established tumors resistant to ICB therapies.

5:20 Talk Title to be Announced

Speaker to be Announced, Nuevolution

5:50 Close of Conference

Encoded Libraries for Small Molecule Discovery

Expanding Chemical Space for New Drug Leads

August 26-27, 2020 | Hilton San Diego Bayfront | San Diego, CA

WEDNESDAY, APRIL 15

12:30 pm Registration Open

12:45 Dessert Break in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

LIBRARY SAMPLING OF CHEMICAL SPACE

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

1:35 Chairperson's Opening Remarks
Brian Paegel, PhD, Professor, Department of Chemistry, University of California, Irvine

1:40 Dual-Display DEL Technology and Beyond
Joerg Scheuermann, PhD, Senior Lecturer, Chemistry & Applied Biosciences, ETH Zurich
DNA-Encoded Libraries (DELs) of dual-display setup have been used for discovering simultaneously binding fragments. Furthermore, dual-display can now be combined with conventional split-and-pool derived single-display libraries yielding very large high-quality DELs by combinatorial assembly. Such libraries feature large structural diversity and selection results with these libraries will be presented for a panel of target proteins.

2:10 A Solution Phase Platform to Characterize Chemical Reaction Compatibility with DNA-Encoded Chemical Library Synthesis
Anokha Ratnayake, PhD, Principal Scientist, Design and Synthesis Sciences, DNA Encoded Library Technology (DELT) Group, Pfizer
The growing scope of chemistries for DNA-encoded chemical library (DECL) synthesis has intensified the need for quantitative methods for validating their compatibility with DNA. We have developed a comprehensive approach for the assessment of chemical fidelity (reaction yield and purity), encoding fidelity (ligation efficiency), and readability (DNA compatibility), revealing the fate of the DNA-tag during DECL chemistry from a single platform. I will describe its utility in screening on-DNA chemistries.

2:40 Target Class-Focused DEL Libraries
Raphael Franzini, PhD, Assistant Professor, Medicinal Chemistry, University of Utah
DNA-encoded libraries (DELs) are widely used in drug discovery. Large generic DEL platforms are typically used for these purposes. While these methods have been proven effective, such platforms are expensive to make and can be associated with technical problems such as library heterogeneity and undersampling. We tested the possibility of generating DELs that are focused to specific protein classes allowing to achieve high screening productivity at low cost and providing reliable structure-activity information. The concept was demonstrated with a library targeting proteins with NAD(+)-binding pockets.

3:10 Sponsored Presentation *(Opportunity Available)*

3:40 Refreshment Break and Book Signing in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

4:30 Methods for Estimating Affinity from DEL Primary Selection Data
Justin Hall, PhD, Principal Scientist, Structural Biology & Biophysics, Pfizer
It is typical to find more candidate binders from DEL selections than is reasonable to pursue. Common practice is to limit synthesis to compounds estimated to be high-affinity binders; of the factors contributing to this estimation, the strength of the sequence signals of a compound is always important. We describe here methods and equations to relate sequence signal to the prospective estimation of compound affinity and chemical yield from DEL selection data.

5:00 New Approaches in the Selection of DNA-Encoded Chemical Libraries
Xiaoyu Li, PhD, Associate Professor, Department of Chemistry, The University of Hong Kong
The selections of DNA-encoded chemical libraries (DELs) have been mostly performed with purified recombinant proteins. Recently we have expanded the target scope of DEL by developing several new methods that are capable of selecting DELs against non-immobilized endogenous proteins in cell lysates or on live cells. We will describe the methodology development as well as the applications of these new selection methods.

5:30 Breakout Discussions
In this session, attendees choose a specific roundtable discussion to join. Each group has a moderator to ensure focused conversations around key issues within the topic. The small group format allows participants to informally meet potential collaborators, share examples from their work, and discuss ideas with peers. Discussion topics and moderators will be listed on the website.

6:15 Close of Day

6:30 Dinner Short Courses*
See Short Courses pages (3-4) for details. Best Value or separate registration required for Short Courses.

THURSDAY, APRIL 16

8:00 am Breakfast Plenary Technology Spotlight *(Sponsorship Opportunity Available)* **or Morning Coffee**

8:45 Plenary Welcome Remarks from Event Director with Poster Finalists Announced
Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

8:55 Plenary Keynote Introduction *(Opportunity Available)*

9:00 PLENARY KEYNOTE:

Translational Chemistry
Phil Baran, PhD, Professor, Department of Chemistry, Scripps Research
There can be no more noble undertaking than the invention of medicines. Chemists that make up the engine of drug discovery are facing incredible pressure to do more with less in a highly restrictive and regulated process that is destined for failure more than 95% of the time. How can academic chemists working on natural products help these heroes of drug discovery – those in the pharmaceutical industry? With selected examples from our lab and others, this talk will focus on that question highlighting interesting findings in fundamental chemistry and new approaches to scalable chemical synthesis.

9:45 Coffee Break in the Exhibit Hall with Poster Viewing *(Sponsorship Opportunity Available)*

INNOVATIONS IN APPROACHES TO SCREENING

10:40 Chairperson's Remarks
Svetlana Belyanskaya, PhD, Encoded Library Technologies, R&D Platform Technology & Science, GlaxoSmithKline Boston

10:45 Before and After IDO1 ELT Selection: Protein Construct Assessment and High Throughput Binder Confirmation

Eric Shi, PhD, Investigator, Encoded Library Technologies, NCE Molecular Discovery, GlaxoSmithKline

Protein construct assessment before ELT selection is crucial for the success of ELT selection. We utilized affinity selection-mass spectrometry (ASMS), dynamic light scattering, and Bioanalyzer to characterize the constructs and optimize ELT selection conditions with various buffers and temperatures. Many features were successfully selected in the IDO1 ELT selection. To achieve high throughput binder confirmation (HTBC), ASMS was used in the follow-up assay and confirmed 139 ELT primary binders.

11:15 FEATURED PRESENTATION: Off-DNA DNA-Encoded Library Screening Technology

Brian Paegel, PhD, Professor, Department of Chemistry, University of California, Irvine

DNA-encoded libraries (DEL) sample vastly larger and more diverse chemical spaces than standard HTS collections, but rely on affinity selection of DNA-displayed small molecules to identify hits. The DNA tags are a known interference for some targets, particularly nucleic acid-binding proteins. We have developed an off-DNA macromolecular binding analysis using solid-phase DELs, microfluidic droplets, and fluorescence polarization detection. Application to several targets will be discussed.

11:45 Progression of A DNA Encoded Library Hit to an *In Vivo* Active Lead Series, & Methods for Accessing Encoded Heterocycles

Sponsored by WuXi AppTec

Alex Satz, Senior Director, DEL Strategy and Operations, Research Services Division, WuXi AppTec

We will discuss the discovery of a selective inhibitor of discoidin domain receptor1 (DDR1) and the progression from a DNA-encoded library hit to an *in vivo* active lead series, challenges of on-DNA synthesis of highly-functionalized and rigid heterocycles, and present possible solutions using the Pictet-Spengler reaction as an example.

12:00 pm Encoded Library Technologies as Integrated Lead Finding Platforms for Drug Discovery

Jonas Schaefer, PhD, Laboratory Head, Encoded Library Technologies, Novartis Institutes for Biomedical Research, Chemical Biology & Therapeutics (CBT), Novartis Pharma AG

Finding suitable chemical matter with the current compound collections is proving increasingly difficult. Encoded library technologies allow for the rapid exploration of a large chemical space for the identification of ligands for such targets. In the presentation, we will discuss how we apply these platforms in our research, including how we narrow the myriad of hits to a few leads, and why we believe it is beneficial to run both pipelines in house.

12:30 Session Break

12:40 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:30 Dessert Break in the Exhibit Hall with Poster Awards Announced *(Sponsorship Opportunity Available)*

MOVING FROM ENCODED LIBRARY HITS TO DRUG LEADS

2:15 Chairperson's Remarks

Anokha Ratnayake, PhD, Principal Scientist, Design and Synthesis Sciences, DNA Encoded Library Technology (DELT) Group, Pfizer

2:20 mRNA/DNA-Encoding Library of Pseudo-Natural Products and RaPID Screening

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

This talk describes the latest development of mRNA/DNA-encoding library of pseudo-natural products derived from Lactazole A and their library display, allowing for the RaPID discovery of *de novo* ligands/inhibitors against proteins of interest.

2:50 New Methodologies for DNA-encoded Chemical Library Synthesis

Nicholas Simmons, PhD, Scientist, Chemistry Capabilities Group, Janssen

DNA-encoded chemical libraries (DECLs) are large collections of DNA-tagged compounds typically produced through split-and-pool processes involving thousands to millions of sterically and electronically distinct substrate pairs. Although the list of synthetic methodologies compatible with the platform is expanding, robust synthetic procedures are generally needed to ensure the production of diverse, high quality chemical matter. Here I will describe our work on adapting several methodologies to the DECL platform

3:20 PANEL DISCUSSION: What Is the Status of DNA-Encoded Library Technology in Small Molecule Drug Discovery?

Sponsored by HITGEN

DEL technology has attracted significant interest with the practitioners of early-stage drug discovery in the past few years. We'll assemble a panel of providers and users, and debate the following topics:

- What is the perspective from "big pharma," "biotech," and academia?
- How does it differ from other "lead discovery" strategies in terms of ROI: Is there synergy?
- How can the technology be improved – what are the challenges?
- Questions from attendees

Moderator:

Barry Morgan, PhD, CSO, HitGen, Ltd.

Panelists to be Announced

3:50 Networking Refreshment Break

ENCODED LIBRARY-ORIGIN COMPOUNDS FOR ONCOLOGY

4:20 DEL-Enabled Discovery of Novel MoA and Structurally Unique IDO1 Inhibitors

Bing Xia, PhD, NCE Encoded Library Technologies, RD Medical Science & Technology, GlaxoSmithKline

Indoleamine 2,3-dioxogenase-1 (IDO1) is induced and activated in response to viral and bacterial infection causing a dysfunctional immune response in clearing pathogens. IDO1 inhibitors (IDO1i) have the potential to restore immune function in indications such as cancer and infection. A structurally-unique IDO1i class was discovered through the affinity selection of a novel DNA-encoded library. After additional medicinal chemistry iterations, the compound series was elaborated into potential best in class preclinical molecule.

4:50 Discovery and Application of a Novel Cell Death Mechanism in Oncology

Maria Soloveychik, PhD, CEO, SnyntheX

We developed STX100, a peptide originating from an encoded library, targeting an intracellular protein-protein interaction in the homologous recombination DNA repair pathway. STX100-mediated cell killing is independent of canonical cell death mechanisms; it relies on acute calcium release from its target to elicit cell death. The mechanism translates to *in vivo* models, where a local delivery of STX100 and a combination of immune checkpoint blockade (ICB) agents can cure established tumors resistant to ICB therapies.

5:20 Talk Title to be Announced

Speaker to be Announced, Nuevolution

5:50 Close of Conference

INAUGURAL

RNA as a Small Molecule Target

Expanding the Boundaries of Druggable Targets

August 28, 2020 | Hilton San Diego Bayfront | San Diego, CA

FRIDAY, APRIL 17

7:30 am Registration Open and Morning Coffee

OPTIMIZING SMALL MOLECULES FOR RNA TARGETS

7:55 Welcome and Opening Remarks

Mana Chandhok, Conference Producer, Cambridge Healthtech Institute

Amanda Hargrove, PhD, Assistant Professor of Chemistry, Duke University

8:00 Targeting Structurally and Functionally Diverse RNAs with Drug-Like Small Molecules

John Schneekloth Jr. (Jay), PhD, Senior Investigator, Chemical Biology Laboratory; Head, Chemical Genetics Section, Center for Cancer Research, National Cancer Institute, NIH

The past twenty years have seen an explosion of interest in the structure and function of RNA and DNA. While some 80% of the human genome is transcribed into RNA, just ~3% of those transcripts code for protein sequences. Here we discuss our group's efforts to target RNA and DNA with drug-like small molecules using a Small Molecule Microarray (SMM) screening platform and the molecular basis for these interactions.

8:30 Repurposing Tools for RNA – And What to Consider When Doing It

Jenifer Kaplan, PhD, Scientist II, Biophysics and Assay Development, Arrakis Therapeutics

The identification of drug-like small molecule medicines that directly bind to RNA and modulate its biological function will vastly increase our therapeutic target space, but targeting RNA comes with its own inherent challenges. The ensemble of conformations an RNA can adapt needs to be forefront when interpreting the results of biophysical and biochemical assays. We use a combination of repurposed tools to characterize the binding event and gain insight into how the ligands are interacting with the RNA target.

9:00 Deciphering Patterns in Selective Small Molecule:RNA Interactions

Amanda Hargrove, PhD, Assistant Professor of Chemistry, Duke University

To gain fundamental insights into drivers of selectivity in small molecule:RNA recognition, we analyzed patterns in RNA-biased small molecule chemical space to reveal distinct physicochemical, structural, and spatial properties for selective RNA ligands. We further used pattern recognition protocols to identify RNA topologies that can be differentially recognized by small molecules. These insights have led to improved recognition of medicinally relevant RNA targets, including viral and long noncoding RNA structures.

9:30 Networking Coffee Break

FEATURED SESSION: TARGETING SPLICING MECHANISMS

10:00 Targeting Pre-mRNA Splicing with Small Molecules

Marla Weetall, PhD, Vice President, Pharmacology, PTC Therapeutics

Pre-mRNA splicing is emerging as a key control point in the expression of disease-modifying genes. Mutations causing alterations in splicing may result in diseases. Small molecules that affect pre-mRNA splicing have been identified and are being clinically developed. At PTC, we have developed a general approach to discover and develop drugs targeting splicing. Here we describe the application of this approach to spinal muscular atrophy, familial dysautonomia, and Huntington's disease.

10:30 Discovery of Risdiplam, a Selective Survival of Motor Neuron-2 (SMN2) Gene Splicing Modifier for the Treatment of Spinal Muscular Atrophy (SMA)

Hasane Ratni, PhD, Expert Scientist, Medicinal Chemistry, F. Hoffmann-La Roche, Basel, Switzerland

SMA is an inherited disease that leads to loss of motor function and ambulation, and a reduced life expectancy. We have been working to develop orally-administrated, systemically-distributed small molecules to increase levels of functional SMN protein. Herein, we describe the discovery risdiplam that focused on thorough pharmacology, DMPK and safety characterization and optimization. This compound is completing pivotal clinical trials and is a promising medicine for the treatment of patients in all ages and stages of SMA.

11:00 Sponsored Presentation *(Opportunity Available)*

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

12:00 pm Session Break

TARGETING SPLICING MECHANISMS (CONT.)

1:00 Chairperson's Remarks

Pramod Pandey, Principal Scientist, Merck Research Labs Exploratory Science Center

1:05 Discovering Novel RNA-Binding Proteins for Small Molecule Drug Discovery

Pramod Pandey, PhD, Principal Scientist, Merck Research Labs Exploratory Science Center

A large fraction of the genome is transcribed into non-coding RNAs and many of these have been implicated in influencing diseases. We are studying these in the context of diseases, relating to barrier function/dysfunction. Towards that goal, we are developing chemical biology tools to study the RNA protein interactions and find novel targets for small molecule drug discovery.

1:35 RNA Splicing Modulation… Application to CD33

Tom Chappie, Associate Research Fellow, Pfizer

GWAS studies on large populations of patients with late-onset Alzheimer's Disease have identified a SNP in the innate immune-response receptor CD33 (Siglec 3) that is protective for Alzheimer's disease. This protective SNP is hypothesized to induce an exon skipping event in the translation of CD33 protein. A phenomimetic strategy for hit identification of small molecule splicing modulators will be described.

Sponsored by Veritas In Silico

2:05 CO-PRESENTATION: Paving the Way for the Discovery of Small-Molecule Drugs Targeting the mRNA

Ella Morishita, PhD, Senior Investigator, Basic Research Division, Veritas In Silico

Shingo Nakamura, PhD, CEO, Veritas In Silico

The potential of targeting mRNAs with small molecules has been unlocked, but the path that would lead to their discovery remains unclear. We are finding druggable motifs on any given mRNA and discovering small molecules targeting them using our ibVIS-SMD platform, which combines informatics with biophysical and cellular biology approaches. Here, we will describe how the ibVIS-SMD platform enables target identification, tailored screening of chemical libraries, hit validation, and structure-based lead optimization.

2:35 **Networking Refreshment Break**

UTILIZING BIOLOGY AND BIOPHYSICAL APPROACHES

3:05 **Drugging RNA**
Natalie Dales, PhD, Director, Global Discovery Chemistry, Novartis

3:35 **FIRESIDE CHAT: What Lies Ahead?**
Hasane Ratni, PhD, Expert Scientist, Medicinal Chemistry, F. Hoffmann-La Roche, Basel, Switzerland
Marla Weetall, PhD, Vice President, Pharmacology, PTC Therapeutics
How will targeting RNA revolutionize drug discovery? Are there specific technologies that will help bring this around?

4:05 **Successes and Challenges in Targeting RNA with Small Molecules**
Nathan Baird, PhD, Interim Chair, Department of Chemistry & Biochemistry, Associate Professor of Biochemistry, University of the Sciences
Efforts targeting RNA with small molecules have been deterred by the inherent propensity of structured RNA molecules to adopt multiple conformations. The Baird Lab works to take direct advantage of RNA structural flexibility to discover small molecule inhibitors of RNA by simultaneously evaluating RNA structures and chemical screens. Our results demonstrate that targeting non-functional RNA structures is a challenging yet effective approach for therapeutic development.

4:35 **Close of Symposium**

"The Drug Discovery Chemistry event is absolutely the best. The topics are spot-on, the networking opportunities are exactly what we need, the speakers are high quality, and the whole event is run very smoothly and efficiently."

Maricel T., Abbvie

5TH ANNUAL

Biophysical Approaches for Drug Discovery

Lead Generation Methods against PPIs, GPCRs, and Other Difficult Targets

August 28, 2020 | Hilton San Diego Bayfront | San Diego, CA

FRIDAY, APRIL 17

7:30 am **Registration Open and Morning Coffee**

LEVERAGING BIOPHYSICS TO CHARACTERIZE DRUG-TARGET ENGAGEMENT

7:55 **Welcome and Opening Remarks**
Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute
Phillip Schwartz, PhD, Principal Scientist, Biophysics, Frontier Medicines

8:00 **FEATURED PRESENTATION: Label-Free Biosensing for Meeting the Challenges of Increasingly Diverse Chemical Matter**

John Quinn, Biophysical Group, Biochemical and Cellular Pharmacology, Genentech
Increasingly challenging targets have prompted the development of diverse chemical matter supporting many targeting strategies. Typically, routine SAR/SKR provided by biochemical/cell assays requires coupling of complex reporter labels/mechanisms rendering them time consuming to develop and deploy. We show that label-free biosensing allows characterization of on-target binding with acceptable throughput to drive early SAR/SKR for rigorous compound prioritization/optimization over a diverse range of chemical matter.

8:30 **Enabling Drug Discovery with Crude Reaction Mixture Screening**
Ben Davis, PhD, Research Fellow, Vernalis Research
In our experience, gains in potency within a series are largely due to increased residence time. We exploit this feature to assess crude reaction mixtures (CRMs) to identify molecules with slower k-off. We demonstrate that CRMs can be used across a range of important biophysical techniques, thus improving H2L turn-around times, reducing costs and allowing more hit series to be explored. We will demonstrate this approach with examples from a range of targets.

9:00 **Biophysical Techniques to Identify Aggregating Compounds and Select Hits**
Samantha Allen, PhD, Principal Scientist, Discovery Sciences, Janssen R&D
Small-molecule drug discovery can be hindered by aggregating compounds that act as non-selective inhibitors of drug targets. These aggregates appear as false positives in high-throughput screening campaigns and can complicate structure-activity relationships during triage and compound optimization. They can also cause problems in secondary biophysics assays such as SPR. I'll discuss high-throughput microplate-based approaches to identify compound aggregation.

9:30 **Networking Coffee Break**

10:00 Determining Affinity from Irreversible Thermal Shifts

Justin Hall, PhD, Principal Scientist, Structural Biology & Biophysics, Pfizer

We describe here methods and equations to fit ligand affinity from irreversible protein denaturation. Irreversible denaturation occurs for most proteins, particularly in the space of human therapeutics, but equations to fit these data have eluded investigators for many years. These results suggest the kinetic energy barrier for unfolding is similar across proteins; application of these findings should allow investigators to calculate ligand affinity from a single thermal denaturation data point.

10:30 Dissecting the Role of 5'-triphosphate in RNA-induced Conformational Changes of Full Length RIG-I

Justyna Sikorska, PhD, Associate Principal Scientist, Mass Spectrometry & Biophysics, Merck Research Labs

Retinoic inducible gene (RIG)-I senses differences between endogenous and viral RNA for triggering immune response through induction of type I interferons. We present structural biophysical characterization of conformational signatures of 5'-ppp versus 5'-OH dsRNA bound forms of full length RIG-I. Our results were analyzed in the context of the recently published SAXS data, and laid foundation for the hypothesis that motif IVa can be involved in RIG-I activation

11:00 Application of Biophysical and Structure-Based Methods in Membrane Protein Drug Discovery

Sponsored by creoptix sensors

Michael Hennig, PhD, CEO, leadXpro AG

Based on excellence in membrane protein science, leadXpro has established a platform that combines most advanced biophysical assay technologies with high-resolution X-ray and cryo-EM to enable drug design. Expect to see examples of membrane protein targets highlighting the applicability of leadXpro's approach, including binding characterization by grating-coupled interferometry (GCI).

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

12:00 pm Session Break

BIOPHYSICAL TECHNIQUES FOR STUDYING GPCRS

1:00 Chairperson's Remarks

Gottfried Schroeder, PhD, Senior Scientist, Department of Quantitative Biosciences, Merck Research Labs Boston

1:05 Novel Thermo-FRET and BRET-Based Thermostability Assays Applied to GPCRs

Dmitry Veprintsev, PhD, Professor, Molecular and Cellular Pharmacology, University of Nottingham

Sensitive protein stability assays are crucial to structural and biophysical studies. Here, we describe novel high-throughput 384-well FRET and BRET-based thermostability assay allowing for the ultrasensitive determination of GPCR stability. These assays are functional in crude lysates, without any requirement for protein purification enabling the profiling of molecules at orphan GPCRs for which tracers do not currently exist.

1:35 Biophysical Studies of Human GPCR Allosteric Modulators

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

We leverage nuclear magnetic resonance in solution to provide fresh insights into the structural mechanisms of partial agonism in human GPCRs. We also describe NMR studies of endogenous GPCR allosteric modulators (e.g. lipids) and their impact on function-related dynamics.

2:05 Expanding the Domain of Applicability of Structure-Based Drug Design with IFD-MD

Sponsored by SCHRÖDINGER

Cesar de Oliveira, PhD, Principal Scientist II, Applications Science, Schrödinger

Schrödinger's IFD-MD application uses a combination of docking algorithms, water thermodynamics, empirical scoring functions, implicit solvent force field energies and explicit solvent metadynamics trajectories to reliably identify protein-ligand binding poses when the sequence identity between the target protein and template is as low as 40%. In this presentation we'll show some examples of the impact IFD-MD can have on real-world drug discovery programs limited by the availability of high-resolution crystal structures.

2:35 Networking Refreshment Break

LEAD GENERATION CASE STUDIES USING ORTHOGONAL BIOPHYSICAL APPROACHES

3:05 Applying Biophysical Tools for Lead Identification, Validation and Optimization – Case Studies and Lessons Learned

Anup Upadhyay, PhD, Senior Scientist III, Drug Discovery Science & Technology, AbbVie

I will discuss how and when we use different biophysical tools (NMR, SPR, ITC, TSA and MST) to validate HTS hits, understand their binding modes and enable lead optimizations. I will present 2 to 3 different case studies from the papers that we have published recently.

3:35 Targeting the Kringle Domains of Apolipoprotein(a)

Jenny Sandmark, PhD, Associate Principal Scientist, Drug Discovery, AstraZeneca

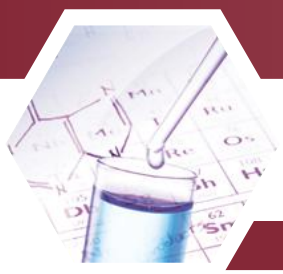
There is a strong link between lipoprotein(a) levels in plasma and cardiovascular disease. Several of the pathological effects associated with lipoprotein(a) are expected to be mediated via kringle domains on apolipoprotein(a). Therefore, we set out to identify inhibitors targeting the small polar lysine binding sites on the kringles. The hit identification campaign followed by structure-based drug design resulted in a compound that specifically bound to kringle IV-10.

4:05 Successes and Challenges in Targeting RNA with Small Molecules

Nathan Baird, PhD, Interim Chair, Department of Chemistry & Biochemistry, Associate Professor of Biochemistry, University of the Sciences

Efforts targeting RNA with small molecules have been deterred by the inherent propensity of structured RNA molecules to adopt multiple conformations. The Baird Lab works to take direct advantage of RNA structural flexibility to discover small molecule inhibitors of RNA by simultaneously evaluating RNA structures and chemical screens. Our results demonstrate that targeting non-functional RNA structures is a challenging yet effective approach for therapeutic development.

4:35 Close of Symposium



Lead Optimization for Drug Metabolism & Safety

Tools and Strategies for Predicting, Optimizing, and Improving PKPD and Safety

August 28, 2020 | Hilton San Diego Bayfront | San Diego, CA

FRIDAY, APRIL 17

7:30 am Registration Open and Morning Coffee

LEVERAGING IN SILICO TOOLS AND MACHINE LEARNING FOR ADME PREDICTIONS

7:55 Welcome and Opening Remarks

Tanuja Koppal, PhD, Senior Conference Director, Cambridge Healthtech Institute

Maria A. Miteva, PhD, Research Director, Molécules Thérapeutiques in silico (MTi), Inserm Institute

8:00 Integration of Structure-Based and Machine Learning Approaches to Predict Inhibition of Drug Metabolizing Enzymes

Maria A. Miteva, PhD, Research Director, Molécules Thérapeutiques in silico (MTi), Inserm Institute

We will present an *in silico* approach to predict inhibition of drug metabolizing enzymes. We focus on Cytochrome P450 (CYP) responsible for the metabolism of 90% drugs and on sulfotransferase (SULT), a conjugate Phase II metabolizing enzyme. We have developed an original *in silico* approach for the prediction of CYP2C9 and SULT1A1 inhibition combining protein structure knowledge, dynamic behaviors in response to ligand binding and modern machine learning modeling.

8:30 Model Informed Human Pharmacokinetics and Dose Prediction: Beyond IVIVE of Compound Enzyme Stability

Yurong Lai, PhD, FAAPS, Senior Director, Drug Metabolism, Gilead Sciences

While *in vitro in vivo* extrapolation (IVIVE) approaches are suitable for drug candidates that are eliminated by metabolizing enzymes, more sophisticated prediction approaches (e.g. PBPK models) are required for drug candidates where transporter-mediated clearance mechanisms are involved. This talk will provide an update on tools for assessing *in vitro* transporter clearance parameters, PBPK model building, curve fitting and verification using preclinical PK data. The presentation will also provide case examples and highlight the gaps in human PK prediction.

9:00 Computational High-Throughput Lead Optimization Using New Free Energy Methods and Quantum Mechanical Force Fields

Darrin York, PhD, Henry Rutgers University Professor, Department of Chemistry and Chemical Biology, Director of the Laboratory for Biomolecular Simulation Research, Rutgers University

Computational lead refinement plays a vital role in drug discovery but has been hampered by the lack of affordable software with state-of-the-art methods that are highly efficient on commodity hardware. These issues have been overcome by the development and implementation of new GPU-accelerated alchemical free energy simulation methods with classical and quantum mechanical force fields in AMBER 2020. These high-throughput features enable new applications including drugs that target metal ion binding sites in metalloenzymes and covalent inhibitors.

9:30 Networking Coffee Break

10:00 Understanding the Applicability and Limitations of *in silico* and *in vitro* Safety Models towards the Design and Selection of the Safest Drug Candidates

Takafumi Takai, PhD, Senior Scientist, Discovery Toxicology, Drug Safety Research & Evaluation, Takeda, Inc.

Many *in silico* and *in vitro* safety models are used during lead optimization to identify safety-related liabilities. A chemistry-based assessment of each model is essential to understand a model's applicability and the relevance of any prediction from them. We will present several case studies of such analyses, including the *in silico* prediction of *in vitro* 3T3 phototoxicity and the use of *in vitro* cytotoxicity to predict *in vivo* toxicity findings.

10:30 FEATURED PRESENTATION: Artificial Intelligence and Small-Molecule Drug Metabolism

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

We have been building artificial intelligence models of metabolism and reactivity. Metabolism can both render toxic molecules safe and safe molecules toxic. The artificial intelligence models we use quantitatively summarize the knowledge from thousands of published studies. The hope is that we could more accurately model the properties of medicines, to determine whether metabolism renders drugs toxic or safe. This is just one of many places where artificial intelligence could give traction on the difficult questions facing the industry.

11:00 Sponsored Presentation *(Opportunity Available)*

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

12:00 pm Session Break

ADME STRATEGIES FOR NEW DRUG MODALITIES

1:00 Chairperson's Remarks

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

1:05 Local Metabolism Leads to Better Understanding of Tissue Drug Concentration for New Modalities

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

For small molecule drugs, liver is the major organ for drug clearance. Liver *in vitro* systems can be used to predict *in vivo* PK. Plasma drug concentration is a good surrogate for tissue concentrations. For new modalities especially drug conjugates, there is a universal lysosomal degradation of proteins for clearance and generation of active drugs. The efficacy and toxicity is supported by the drug in tissue that is released locally in a right form at a proper concentration range from a conjugate. This talk discusses the importance of tissue metabolism.

1:35 *In vitro* ADME Challenges in Assessing New Modalities

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

New modalities such as covalent modulators, macrolides, macrocyclic peptides and antibody-drug conjugates have distinct physicochemical properties, and they pose a variety of unique challenges in assessing various ADME properties including metabolic stability, plasma protein binding and CYP inhibition. As a result, inaccurate *in vitro* ADME data can be reported unnoticeably. This presentation will present some case studies as well as alternative strategies on how to overcome those technical challenges and safeguard data quality.

2:05 Sponsored Presentation *(Opportunity Available)*

2:35 Networking Refreshment Break

REACTIVE METABOLITES, DRUG TRANSPORTERS AND DRUG CLEARANCE

3:00 Chairperson's Remarks
Mark Grillo, PhD, Staff Scientist, Drug Metabolism & Pharmacokinetics, MyoKardia, Inc.

3:05 Reactive Drug Metabolite Assessment in Drug Discovery and Development
Mark Grillo, PhD, Staff Scientist, Drug Metabolism & Pharmacokinetics, MyoKardia, Inc.
Chemically-reactive drug metabolites, formed by enzyme-mediated metabolic activation usually in the liver, are perceived as an unwanted feature of drug candidates. These reactive metabolites may covalently bind to protein nucleophiles *in vivo* leading to subsequent immune-based idiosyncratic toxicities such as hepatotoxicity. The goal is to eliminate or minimize metabolic activation liabilities of drug candidates leading to the increased probability of safer drugs being developed. This talk will review up-to-date risk assessment of reactive drug metabolites.

3:35 Successful Prediction of Hepatic Clearance and Recent Improvements to IVIVE
Jasleen Sodhi, PhD Candidate, Laboratory of Dr. Leslie Benet, University of California San Francisco
Accurate prediction of human pharmacokinetic properties is critically important to progress compounds with favorable PK properties. Of particular importance is the prediction of hepatic clearance, which largely determines drug exposure and contributes to projections of dose, drug half-life and bioavailability. This lecture will cover common *in vitro* techniques used to predict hepatic clearance of new chemical entities, as well as recent advancements and current challenges in IVIVE.

4:05 *In vitro* and *in silico* Tools to Facilitate the Assessment of Transporter-Mediated Drug Interactions
Cen Guo, PhD, Manager, Clinical Pharmacology, Pfizer
Drug-drug interactions (DDIs) mediated by hepatic transporters can have important implications in drug efficacy and safety. However, the accuracy and efficiency for the assessment of transporter mediated DDIs need improvement. This presentation will review some new tools to improve the DDI assessment, including cellular models combined with *in silico* tools to aid data interpretation, *in vitro* assays to characterize transporter probe cocktail and endogenous biomarkers which can be used for *in vivo* DDI assessment.

4:35 ADME Characterization and Challenges on New Biotherapeutic Modalities
Cong Wei, PhD, Senior Scientist and Group Leader, Drug Metabolism and Pharmacokinetics, Biogen Inc.
Over the last decade, an increasing number of new therapeutic modalities such as antibody-drug conjugate, monoclonal antibody, fusion protein, siRNA and oligonucleotide are entering clinical trials for the treatment of various diseases. Different from small molecules, ADME characterization on those new biotherapeutic modalities are focused on bioanalytical and biotransformation studies, and challenges are remaining. This talk will summarize and include some case studies on *in vivo* bioanalysis and biotransformation of the biotherapeutic molecules.

PRESENT A POSTER AND SAVE $50!

Cambridge Healthtech Institute encourages attendees to gain further exposure by presenting their work in the poster sessions. To secure a poster board and inclusion in the conference materials, your abstract must be submitted, approved and your registration paid in full by March 6, 2020.

Reasons you should present your research poster at this conference:

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

Cambridge Healthtech Institute is proud to support and recognize the scientists of tomorrow!

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.

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HOTEL & TRAVEL INFORMATION

Conference Venue and Host Hotel:
Hilton San Diego Bayfront
One Park Boulevard
San Diego, CA 92101
T: 619-564-3333

Discounted Room Rate: $265 s/d
Discounted Room Cut-off Date: March 17, 2020

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

PRICING & REGISTRATION INFORMATION

PREMIUM CONFERENCE PRICING, *BEST VALUE* *(Includes access to two conferences/Training Seminars, two short courses, and one symposium OR two conferences/Training Seminars and four short courses)*	Commercial	Academic, Government, Hospital Affiliated
Advance Registration Discount until June 26, 2020	$3299	$2099
Registrations after June 26 and onsite	$3399	$2199

STANDARD CONFERENCE PRICING *(Includes access to two conferences/Training Seminars, excludes short courses and symposia)*		
Advance Registration Discount until June 26 , 2020	$2499	$1199
Registrations after June 26 and onsite	$2699	$1299

BASIC CONFERENCE PRICING *(Includes access to one conference/Training Seminar, excludes short courses and symposia)*		
Advance Registration Discount until June 26, 2020	$1899	$999
Registrations after June 26 and onsite	$1999	$1099

SHORT COURSE PRICING *(April 13 & 15)*		
One short course	$749	$429
Two short courses	$1049	$729
Three short courses	$1249	$829
Four short courses	$1449	$929

SYMPOSIUM PRICING *(April 17)*		
One Symposium	$1049	$599

Short Courses - April 13
10:00 am to 1:00 pm

SC1: Biochemistry and Pharmacology of the Ubiquitin-Proteasome System

SC2: Immunology Basics for Chemists

SC3: Pharmacology Tricks of the Trade: Identifying Highly Active Compounds and Avoiding Assay Artifacts

2:00 pm to 5:00 pm

SC4: Fragment-Based Drug Design: Tools and Techniques

SC5: Macrocyclic Compounds for Drug Discovery: Opportunities, Challenges, and Strategies

SC6: Emerging Chemical Tools for Phenotypic Screening and Target Deconvolution

6:00 pm to 9:00 pm

SC8: Targeted Protein Degradation Using PROTACs, Molecular Glues, and More

SC9: GPCR Structures and Enabling Biophysical Tools

SC10: Trends in Physical Properties of Drugs

Concurrent Conferences/ Training Seminar *(April 14-15)*	Concurrent Conferences/ Training Seminar *(April 15-16)*	Concurrent Symposia *(April 17)*
C1: Ubiquitin-Induced Targeted Protein Degradation	**C5:** Protein-Protein Interactions	**S1:** RNA as a Small Molecule Target
C2: Fragment-Based Drug Discovery	**C6:** Artificial Intelligence for Early Drug Discovery	**S2:** Biophysical Approaches for Drug Discovery
C3: Kinase Inhibitor Chemistry	**C7:** Small Molecules for Immunology & Oncology	**S3:** Lead Optimization for Drug Metabolism & Safety
C4: Macrocyclics & Constrained Peptides	**C8:** Encoded Libraries for Small Molecule Discovery	
TS1: Targeting GPCRs for Drug Discovery	**TS2:** Introduction to Small Molecule Drug Metabolism and Applications to Discovery and Development	

Dinner Short Courses *(April 15, 6:30 pm to 9:30 pm)*

SC12: DNA-Encoded Libraries & Affinity Selection Methods for Small and Large Molecules

SC13: Principles of Immuno-Oncology

SC14: Ligand-Receptor Molecular Interactions and Drug Design

SC15: Methodologies for Optimizing Drug Clearance and Drug-Drug Interactions

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Poster Submission – Discount ($50 Off): Poster abstracts are due by **March 6, 2020.** Once your registration has been fully processed, we will send an email containing a unique link allowing you to submit your poster abstract. If you do not receive your link within 5 business days, please contact jring@healthtech.com. *CHI reserves the right to publish your poster title and abstract in various marketing materials and products.

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

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

Group Discounts: Discounts are available for multiple attendees from the same organization. For more information on group rates contact Bill Mote at 781-972-5479, bmote@healthtech.com.

ADDITIONAL REGISTRATION DETAILS

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

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

How to Register: DrugDiscoveryChemistry.com

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

Please refer to the Registration Code below:

Cambridge HEALTHTECH Institute
A Division of Cambridge Innovation Institute

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