# Drug Discovery Chemistry

**CAMBRIDGE HEALTHTECH INSTITUTE’S 15th ANNUAL**

**OPTIMIZING SMALL MOLECULES FOR TOMORROW’S THERAPEUTICS**

**APRIL 13 - 17, 2020 | SAN DIEGO, CA | HILTON SAN DIEGO BAYFRONT**

**FINAL AGENDA**

**APRIL 14 – 15**
- Ubiquitin-Induced Protein Degradation
- Fragment-Based Drug Discovery
- Kinase Inhibitor Chemistry
- Macrocyclics & Constrained Peptides
- Training Seminar: GPCR Drug Discovery

**APRIL 15 – 16**
- Protein-Protein Interactions
- Artificial Intelligence for Early Drug Discovery
- Small Molecules for Immunology & Oncology
- Encoded Libraries for Small Molecule Discovery
- Training Seminar: Drug Metabolism

**APRIL 17**
- RNA as a Small Molecule Target
- Biophysical Approaches
- Lead Optimization for Drug Metabolism

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**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](http://DrugDiscoveryChemistry.com)
Conference at-a-Glance

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*Rest Value or separate registration required.

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.

PLENARY KEYNOTES

**TUESDAY, APRIL 14TH | 4:35 - 6:00 PM**

**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.

**THURSDAY, APRIL 16TH | 8:00 - 9:45 AM**

**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

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: Macroyclic 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 macroyclic 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
Robert Kyne, PhD, Senior Scientist, Chemical Biology, Celgene
Hua Xu, PhD, Associate Research Fellow, Medicine Design, Pfizer
- 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
- Additional Instructors to be Announced
- 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
- 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
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**

**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 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 pharmaceutical 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.
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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- Webinars
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For additional information regarding sponsorship and exhibit opportunities, please contact:
Carolyn Cooke | Business Development Manager
ccooke@healthtech.com | 781-972-5412

2019 ATTENDEE DEMOGRAPHICS

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knock-in mice in which PROTAC-dependent recruitment is now rendered active, experimental studies. We report use of Tip60 PROTACs in WT vs. Cereblon makes this possible. However, mice have a single amino acid substitution that important for advances in immuno-oncology, and the PROTAC approach Finding new ways to target histone acetyltransferases, such as Tip60, is Modern drug discovery calls for increased use of phenotypic screens, and novel targets and modalities are being explored in the process. The use of proteolysis targeting chimeras (PROTACs) are bivalent molecules that bring array of ubiquitin enzymes. 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.

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.

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.

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Utilizing Compounds That Are Orally Active in Mouse Xenograft Models
Denise Field, PhD, Senior Scientist, I&I Chemistry and Chemical Biology, Pfizer Inc.

Deconvoluting compound induced degradation, as well as current approaches to validate compound target engagement mechanisms.

Target Engagement and Protein Degradation: Lessons Learned and Future Applications
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Amino Acid-Based Degradation Signal
Hai Rao, 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.
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
(Sponsorship Opportunity Available)

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
Upenдра Dahlal, 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)

“The talks and topics were the best that I’ve been a part of from 20 years of going to conferences.”
Charles W., Novartis
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
Marcel Torrent, PhD, Principal Research Scientist, Molecular Modeling, AbbVie

8:10 Fragment Hits and Leads: More than Meets the Eye
Giordano Fabrizio, 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, Professor, 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
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
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, 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 to be Announced

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 derivate 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 Talk Title to be Announced
Tao Guo, PhD, Vice President, Head, 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 Technology Spotlight Presentation to be Announced
Sponsored by SCHRÖDINGER

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.

8:30 Chairperson’s Remarks
Mary Harner, PhD, Research Investigator II, Mechanistic Biochemistry, Bristol-Myers 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, tumour 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
(Sponsorship Opportunity Available)

10:30 FEATURED PRESENTATION: Fragment-to-Market Discovery of the pan-FGFR inhibitor BalversaTM (Erdafitinib)
Valerio Berdini, PhD, Associate 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)
Erythematosus (SLE) as a Potential Treatment for Systemic Lupus

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.

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.

Phosphoinositide 3-kinase (PI3K) catalytic subunits (PIK3CA) are oncogenes in human cancers. An activating PIK3CA mutation is a common event in certain tumors, such as breast, colorectal, and endometrial carcinomas. PIK3CA-driven cancers arise from somatic gain-of-function mutations of the PIK3CA gene. PROS, 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.

**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 Turismo, 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 Turismo, 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)**
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 (Sponsorship Opportunity Available) or Enjoy Lunch on Your Own**

**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 Kpu. 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 1 and 2 (VRK1 and VRK2) were recently associated with psychiatric morbidities. Current models support the role in cancer and confirm the findings from siRNA or CRISPR/Cas9-based experiments. In this talk, we 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 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 Presentation to be Announced
Sponsored by SCHRODINGER

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 (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 (Sponsorship Opportunity Available)

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.
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 a 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)
Macrocyclics & Constrained Peptides
Discovery and Design of Cell-Penetrating, Middle-Sized Molecules for Oral-Based Meds

April 14-15, 2020 | Hilton San Diego Bayfront | San Diego, CA

**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 Sponsored Presentation (Opportunity Available)

9:40 Networking Coffee Break

10:05 Syrbacltin Proteasome Inhibitors for Oncology and Immune Disorders
Michael Pirrung, PhD, Distinguished Professor of Chemistry, University of California Riverside

Drug candidates based on the syrbacltins, 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 syrbacltin 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, Professor, Biochemistry, Boston University

11:05 Presentation to be Announced

11:35 Session Break

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

12:30 pm Session Break
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 Macro cyclic 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 Macro cyclic 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 macro cyclic 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-likeliness. 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 (Sponsorship Opportunity Available)

10:30 A Macro cyclic Inhibitor of PDL1
Paul Scola, PhD, Senior Scientist, Medicinal Chemistry, Bristol-Myers Squibb

11:00 Design and Development of Repotrectinib, a Next Generation Macro cyclic 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 macrocyclic 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 Presentation to be Announced

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
Covalent Inhibitor of KRAS G12C: Discovery and Early Development of MRTX849, a Selective, in vitro and in vivo as well as structural and functional features of both of these molecules.

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.

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.

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 new lead optimization cycle for KRAS G12C.

Targeting KRAS: Preclinical Compounds

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.

Translating Frontier Oncology Targets to Outsmart Cancer

Adrian Gill, PhD, Vice President, Medicinal Chemistry & CMC, 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(ONF) inhibitors in cancer cell lines bearing KRASG12C mutations and drive dose-dependent tumor regressions in a KRASG12C NSCLC xenograft mouse model.

Presentation to be Announced

10:45 Presentation to be Announced

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

TARGETING KRAS: COMPOUNDS IN THE CLINIC

2:15 Chairperson’s Remarks

Charles Warthcow, 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.

Discovery and Early Development of MRTX849, a Selective, Covalent Inhibitor of KRAS G12C

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

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.

Discovery of First-in-Class 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.

Design of Small Molecule Allosteric Reversible Inhibitors of K-Ras with Antitumor Activity

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.

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.

Close of Conference

5:50 Close of Conference

Enjoy Lunch on Your Own

1:30 Dessert Break in the Exhibit Hall with Poster Awards Announced (Sponsorship Opportunity Available)
2ND ANNUAL

Artificial Intelligence for Early Drug Discovery
AI & Machine Learning for Drug Design and Lead Optimization

April 15-16, 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 Exploring the Latent Space: AI for Generation of de novo Molecules
Qurrat Ul Ain, PhD, Data Scientist Principal, Department of Analytics and AI, Accenture

How might we navigate through the space of chemical and biological data for existing drugs using deep generative AI models and discover new drug-like molecules? This process will hugely impact the number of experiments currently run to test each new formulation in the laboratory. Development of deep generative models and exploration of latent space will help in generating novel and more diverse molecules.

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 Presentation to be Announced

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 FEATURING 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
Speaker to be Announced, LabTwin

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)
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.

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.
TARGETING STING

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 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 Pharmacology, 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 Pesiritidis, 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 minimal single agent efficacy upon intravenous delivery.

3:10 CETSA HT, A Powerful Assay for Small Molecule Drug Discovery
Stina Lundgren, Principal Projects Advisor, Pelago Bioscience

3:25 Sponsored Presentation (Opportunity Available)

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

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 ADMET 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 ‘Immuo’ 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

6:00 Targeting Cell Surface Immuno/Onco-Related Proteins

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
Speaker to be Announced, LabTwin

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.
Small Molecules for Immunology & Oncology | April 15-16, 2020

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
Katerina Leftheris, PhD, Vice President, Chemistry, Pliant

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 Presentation to be Announced

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 (Sponsorship Opportunity Available) or Enjoy Lunch on Your Own

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

NEW INTRACELLULAR 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 Vps34Induces a Proinflammatory Microenvironment Resulting in Tumor Growth Inhibition and Sensitization to PD-1/ PD-L1 Blockade
Jenny Viklund, Director, Protein Science & Drug Design, 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 Disrupting Tumor Metabolism: Targeting the IDO Pathway via Arginase Inhibitors
Emil KuriaKose, PhD, Director, Biology, Calithera
I will provide an overview of the mechanistic rationale for arginase inhibition as an immune activating therapy in the IDO signaling pathway. I also discuss the specific aspects of the compound that provide a viable therapeutic index in the clinical setting. Our arginase inhibitors are in Phase 1 clinical study.

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, SynthexX
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

“I very much appreciated this congress. It was really outstanding and extremely well organized. I liked having the choice of attending numerous sessions in parallel that were of interest.”

Hassan R., Roche
Methods for Estimating Affinity from DEL Primary Selection Data

It is typical to find more candidate binders from DEL selections than is reasonable to pursue. Common practice is to limit synthesis to compounds 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.

INNOVATIONS IN APPROACHES TO SCREENING

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

10:40 Chairperson’s Remarks

Svetlana Belyanskaya, PhD, Encoded Library Technologies, R&D Platform Technology & Science, GlaxoSmithKline Boston
Anokha Ratnayake, PhD, Principal Scientist, Design and Synthesis Sciences, Novartis Pharma AG Institute for Biomedical Research, Chemical Biology & Therapeutics (CBT), Jonas Schaefer, PhD, Laboratory Head, Encoded Library Technologies, Novartis Institutes for Biomedical Research, Chemical Biology & Therapeutics (CBT), WuXi AppTec

Platforms for Drug Discovery
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.

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 Talk Title to be Announced
Letian Kaui, Senior Director, Head, DEL Biology, Research Services Division, WuXi AppTec

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)

INNOVATIONS IN APPROACHES TO SCREENING
2:15 Chairperson's Remarks
Anokha Ratnayake, PhD, Principal Scientist, Design and Synthesis Sciences, DNA Encoded Library Technology (DEL) Group, Pfizer

2:20 mRNA/DNA-Encoding Library of Pseudo-Natural Products and RaPID Screening
Hiroyuki 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 Lactazol A and their library display, allowing for the RaPID discovery of de novo ligands/inhibitors against proteins of interest.

2:50 Talk Title to be Announced
Dean Brown, PhD, formerly Director, External Chemistry, Hit Discovery, Discovery Sciences, IMED Biotech Unit, AstraZeneca

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
Panelists to be Announced
Moderator: Barry Morgan, PhD, CSO, HitGen, Ltd.

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-dioxygenase-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, Synthex
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
**RNA as a Small Molecule Target**

Expanding the Boundaries of Druggable Targets

**April 17, 2020 | Hilton San Diego Bayfront | San Diego, CA**

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

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**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**

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**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.

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

*Jennifer 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.

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**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 of 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.

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**9:30 Networking Coffee Break**

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**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 dystonia, and Huntington's disease.

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**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-administered, 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.

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**11:00 Sponsored Presentation (Opportunity Available)**

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

**12:00 pm Session Break**

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**TARGETING SPLICING MECHANISMS (CONT.)**

**1:00 Chairperson's Remarks**

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

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**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.

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**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.
2:05 Sponsored Presentation (Opportunity Available)
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

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“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.”

Marcel T., Abbvie

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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/SSR 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/SSR 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 Talk Title to be Announced
Payal Sheth, PhD, Executive Director of Mass Spectrometry & Biophysics, Merck Research Labs

11:00 Sponsored Presentation (Opportunity Available)

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 Pharmacology, 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 Presentation to be Announced

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

“The beauty of Drug Discovery Chemistry is that even when clinical stage compounds and clinical results are presented, the talks never lose the science; the presentations stay married to the underlying chemistry.”
Mark P., Cyclenium
model is essential to understand a model's applicability and the relevance to identify safety-related liabilities. A chemistry-based assessment of each will provide an update on tools for assessing where transporter-mediated clearance mechanisms are involved. This talk prediction approaches (e.g. PBPK models) are required for drug candidates that are eliminated by metabolizing enzymes, more sophisticated 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 methods have been used to predict inhibition of drug metabolizing enzymes. We have developed an original approach for the prediction of CYP2C9 and SULT/A1 inhibition combining protein structure knowledge, dynamic behaviors in response to ligand binding and modern machine learning modeling.

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.

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

While in vitro 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.

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.

Networked Coffee Break

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

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 photocytotoxicity and the use of in vitro cytotoxicity to predict in vivo toxicity findings.
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 Close of Symposium

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.
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