22ND Annual

The Industry's Preeminent Event on Novel Drug Targets and Technologies

FINAL AGENDA

Discovery on TARGET

September 30 - October 3, 2024

Boston, MA | SHERATON BOSTON & VIRTUAL

Register by September 6 and Save up to $300

Conference Programs

September 30

- Strategies for Targeting Kinases
- Covalent Chemistries and Induced Proximity NEW
- Emerging Immune Modulation Strategies
- Synthetic Biology for Drug Discovery and Therapy NEW

October 1-2

- Degraders and Molecular Glues – Part 1
- Lead Generation Strategies
- Small Molecules for Cancer Targets
- Antibodies Against Membrane Protein Targets
- Small Molecules Targeting RNA
- AI/ML-Enabled Drug Discovery – Part 1
- Physiologically Relevant Translational Models

- TRAINING SEMINAR GPCR Pharmacodynamics: Kinetics, Allosterism, and Biased Agonism in Pharma Discovery NEW

October 2-3

- Degraders and Molecular Glues – Part 2
- Target Identification Strategies
- GPCR-Based Drug Discovery
- Cancer Antibodies
- Targeting Transcription Factors
- AI/ML-Enabled Drug Discovery – Part 2

- TRAINING SEMINAR Drug Exposure at the Target: The Role of ADME and Pharmacokinetics NEW

Plenary Keynote Program

Discovery of Transformative Rx to Treat Obesity and Related Diseases

Richard DiMarchi, PhD, Distinguished Professor of Chemistry and Chair, Biomolecular Sciences, Indiana University; former Executive, Lilly and Novo Research Labs

Fragment-Based Drug Discovery for Elusive Cancer Targets

Stephen W. Fesik, PhD, Professor of Biochemistry, Pharmacology & Chemistry; Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University

Organized by Cambridge HEALTHTECH Institute

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22ND Annual

About the Event

Discovery on Target (DOT) highlights advances in current and emerging "hot" targets and technologies, as well as target validation strategies for the discovery and development of novel therapeutic agents ranging from biologics to small molecules.

We aim to meet your research needs. Visit numerous concurrent sessions all week for informative presentations, lively dialogue, and meaningful connections with peers. Customize your experience further through focused short courses, training seminars, interactive breakout discussions, and networking options that help you engage with experts and solutions providers.

Our four-day event brings back popular topics like kinases, immunomodulation, and degraders, plus **new coverage** of covalent chemistries and induced proximity, synthetic biology, cancer antibodies, generative AI, and translational models.

Please use keycode **DOT PDF F** when registering!

EVENT AT-A-GLANCE

#BostonDOT24

MONDAY
September 30

- Strategies for Targeting Kinases
- Covalent Chemistries and Induced Proximity NEW
- Emerging Immune Modulation Strategies
- Synthetic Biology for Drug Discovery and Therapy NEW

**Pre-Conference Dinner Short Courses*
MONDAY, September 30**

SC1: Protein Degraders: A Focus on PROTACs from an ADME-Tox Perspective
SC2: Fragment-Based Drug Design: Advancing Tools and Technologies
SC3: DNA-Encoded Libraries
SC4: Best Practices for Targeting GPCRs, Ion Channels, and Transporters with Monoclonal Antibodies
SC5: Developing Physiologically Relevant 3D Models

IN-PERSON ONLY

TUESDAY — WEDNESDAY
October 1 — October 2

- Degraders and Molecular Glues – Part 1
- Lead Generation Strategies
- Small Molecules for Cancer Targets
- Antibodies Against Membrane Protein Targets
- Small Molecules Targeting RNA
- AI/ML-Enabled Drug Discovery – Part 1
- Physiologically Relevant Translational Models

IN-PERSON ONLY

- GPCR Pharmacodynamics: Kinetics, Allosterism, and Biased Agonism in Pharma Discovery NEW

WEDNESDAY — THURSDAY
October 2 — October 3

- Degraders and Molecular Glues – Part 2
- Target Identification Strategies
- GPCR-Based Drug Discovery
- Cancer Antibodies
- Targeting Transcription Factors
- AI/ML-Enabled Drug Discovery – Part 2

IN-PERSON ONLY

- Drug Exposure at the Target: The Role of ADME and Pharmacokinetics NEW

Pre-Conference Symposium*
Conference
Short Course (In-Person Only)*
Training Seminar (In-Person Only)

Premium Package includes access to two short courses and all symposia. Separate registration required for other packages.

**Dinner Short Courses*
WEDNESDAY, October 2**

SC6: Protein Degraders: A Focus on PROTACs from a Beyond Rule of Five Space Perspective
SC7: Chemical Biology for Covalent Discovery, Phenotypic Screening, and Target Deconvolution
SC8: Biophysical Approaches for GPCRs
SC9: Fundamentals of Generative AI for Drug Discovery

IN-PERSON ONLY

**Plenary Keynote Program
WEDNESDAY, October 2**

Become a Sponsor or Exhibitor

SPONSORSHIP PROGRAMS

CHI's comprehensive sponsorship packages allow you to achieve your objectives before, during, and long after the event. Maximize exposure to hard-to-reach decision-makers through the following sponsorship opportunities:

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Sponsors will select their top prospects from the conference preregistration list for an evening of networking at the hotel or at a choice local venue. CHI will extend invitations, conduct follow-up, and confirm attendees. The evening will be customized to meet with your specific objectives.

Corporate Support Exhibit Package

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For more information regarding exhibit and sponsorship, please contact:

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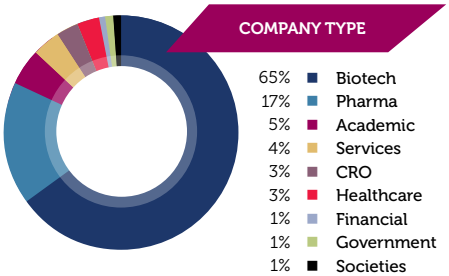
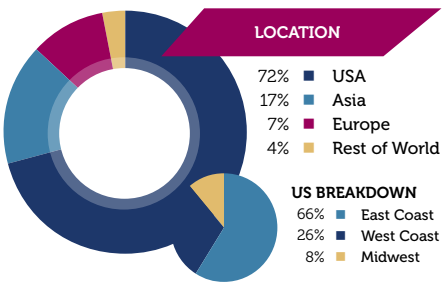
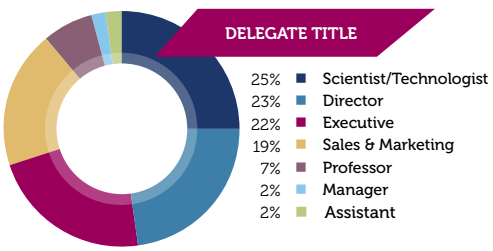
2023 ATTENDEE DEMOGRAPHICS







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Plenary Keynote Program

Join colleagues from around the world for the Discovery on Target Plenary Keynote Program. Bridging both halves of the event, it's the only time our whole community of drug discovery professionals assembles together to learn about big-picture perspectives, innovative technologies, and thought-provoking trends from luminaries in the field.

WEDNESDAY, OCTOBER 2

Discovery of Transformative Rx to Treat Obesity and Related Diseases

Richard DiMarchi, PhD, Distinguished Professor of Chemistry and Chair, Biomolecular Sciences, Indiana University; former Executive, Lilly and Novo Research Labs

Obesity represents a medicinal challenge that warrants broad molecular diversity. We have pioneered the recruitment of endogenous hormones and physiological mechanisms optimized for pharmacological purposes to address it. The discovery of single-molecule, multi-mechanism incretins enables breakthrough efficacy in lowering body weight. The integrated pharmacology of these peptides, with endocrine proteins and nuclear hormones, is providing a library of drug candidates that promises even greater clinical outcomes and therapy for associated diseases that have historically proven as intractable to treat as obesity once constituted.

Professor DiMarchi is a member of the National Academy of Medicine and the National Inventors Hall of Fame. He is a former Group Vice President at Lilly and later Novo. His contributions pertain to the discovery and development of Humalog®, rGlucagon®, Forteo®, and Evista®. His research includes discovery of peptides transforming the treatment of diabetes and obesity. He is co-inventor on >100 U.S. patents and co-author to >250 scientific publications. He was identified as a top-five translation researcher by *Nature Biotechnology*. Since 2003, he has co-founded eight successful biotech companies.

Fragment-Based Drug Discovery for Elusive Cancer Targets

Stephen W. Fesik, PhD, Professor of Biochemistry, Pharmacology & Chemistry; Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University

The most highly validated cancer targets (KRAS, MYC, and WNT) affecting the majority of cancers are thought to be impossible to drug. Using fragment-based methods that I pioneered over 25 years ago, we have discovered mutant selective and pan KRAS inhibitors, potent inhibitors of the MYC cofactor WDR5, and degraders of b-catenin in the WNT pathway. These novel inhibitors/degraders should have a tremendous impact on cancer treatment in the future.

Stephen W. Fesik, PhD is the Orrin H. Ingram II Chair in Cancer Research and a Professor of Biochemistry, Pharmacology, and Chemistry at Vanderbilt University School of Medicine. He is also a member of the Vanderbilt Ingram Cancer Center (VICC), the Vanderbilt Institute of Chemical Biology (VICB), and the Center for Structural Biology (CSB). The focus of his research is on cancer drug discovery using fragment-based approaches and structure-based drug design. Prior to joining Vanderbilt in May 2009, Dr. Fesik was the Divisional Vice President of Cancer Research at Abbott (2000-2009) where he built a pipeline of compounds that are showing promising anti-cancer activities in early-stage clinical trials. In addition, while he was at Abbott, he developed several new NMR methods, determined the three-dimensional structures of several proteins and protein/ligand complexes, pioneered a fragment-based method for drug discovery called SAR by NMR, and applied this method to identify and optimize ligands for binding to many protein drug targets. Dr. Fesik has published more than 295 papers, trained 68 postdoctoral fellows, and has served as a member of the Editorial Boards of many scientific journals, scientific advisory boards, and the Keystone and Bruker Board of Directors. He has also obtained several awards, such as the Lifetime Achievement Award in Nuclear Magnetic Resonance from EAS (2003), the SBS Technology Innovation Award (2010), the NIH Director's Pioneer Award (2010), the AACR Award for Outstanding Achievement in Chemistry in Cancer Research (2012), and 2021 Chester Stock Award from Memorial Sloan Kettering Cancer Center.

In-Person Breakouts

In-Person Breakouts are informal, moderated discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator who keeps the discussion on track and the group engaged. To get the most out of this format, please come prepared to share examples from your work, be a part of a collective, problem-solving session, and participate in active idea sharing. Please visit DiscoveryOnTarget.com/Interactive-Discussions for a complete listing of topics and descriptions.

Dinner Short Courses*

*Premium Pricing or separate registration required

SHORT COURSES AND TRAINING SEMINARS WILL BE OFFERED IN-PERSON ONLY.

MONDAY, SEPTEMBER 30 5:00-7:30 PM

SC1: Protein Degraders: A Focus on PROTACs from an ADME-Tox Perspective

Instructors:

Prasoon Chaturvedi, PhD, Vice President & Head, DMPK, C4 Therapeutics, Inc.

John Erve, PhD, President, Jerve Scientific Consulting

This course focuses on proteolysis targeting chimeras (PROTACs) and will cover topics relevant to developing them as therapeutics. Topics to be covered in this part of the course will include looking at what is known about how PROTACs are metabolized *in vivo* and strategies to deliver them with adequate PK/PD. The unique mechanism of action of PROTACs gives rise to some drug safety issues not seen in small molecules, which will be discussed. Finally, we will explore the possible relevance of circadian rhythm to protein degradation and PROTACs.

SC2: Fragment-Based Drug Design: Advancing Tools and Technologies

Instructors:

Daniel A. Erlanson, PhD, Chief Innovation Officer, Innovation and Discovery, Frontier Medicines Corporation

Ben J. Davis, PhD, Research Fellow, Biology, Vernalis R&D Ltd.

This course aims to introduce the fundamentals of Fragment-Based Lead Discovery (FBLD) to attendees. The first section will focus on the concepts of using fragments for hit generation. Special emphasis will be placed on practical pitfalls and the many ways to advance fragments to leads and drugs. The second part of the course will discuss the variety of fragment screening methods and when they are best applied. The composition of fragment libraries will also be discussed in detail. The attendees should come away from this course with a solid understanding of what FBLD is and how to apply it.

SC3: DNA-Encoded Libraries

Instructors:

Svetlana Belyanskaya, PhD, former Vice President, Biology, Anagenex

Ghotas Evindar, PhD, Drug Discovery Consultant, Former DEL Platform Senior Manager and Group Leader at GlaxoSmithKline

This course provides an overview of DNA-Encoded Library (DEL) screening platforms, discusses common selection strategies for identifying novel hits from DEL campaigns and delves into parameters for building a library collection. The instructors will also cover strategic considerations in using DEL selection data to accelerate hit-to-lead steps in drug discovery.

SC4: Best Practices for Targeting GPCRs, Ion Channels, and Transporters with Monoclonal Antibodies

Instructor:

Joseph Rucker, PhD, Vice President, Research and Development, Integral Molecular, Inc.

Complex membrane proteins represent the majority of protein classes addressed by therapeutic drugs. Significant opportunities exist for targeting complex membrane proteins with antibodies, but it has been challenging. This course will examine emerging technologies and strategies for enabling the successful isolation of specific and functional antibodies against GPCRs, ion channels, and transporters, and highlight progress via case studies.

SC5: Developing Physiologically Relevant 3D Models

Instructors:

Madhu Lal Nag, PhD, CSO, InSphero

Nathan P. Coussens, PhD, Scientific Director, Molecular Pharmacology Laboratory, Frederick National Laboratory for Cancer Research

With the passing of the FDA Modernization Act 2.0, there is a greater interest in the drug discovery community to develop and use physiologically relevant *in vitro* models for drug candidate testing and IND filings. This course will help attendees understand what it takes to design and develop relevant 3D organoid/spheroid models through the various stages of assay development, automation compatibility and data analysis. The utility of these models in answering specific biological questions and the importance of developing a robust, scalable 3D model–based assay for preclinical decision-making will also be demonstrated through case studies.

WEDNESDAY, OCTOBER 2 6:00-8:30 PM

SC6: Protein Degraders: A Focus on PROTACs from a Beyond Rule of Five Space Perspective

Instructors:

John Erve, PhD, President, Jerve Scientific Consulting

Stefanus Steyn, PhD, Research Fellow, Pharmacokinetics Dynamics & Metabolism, Pfizer

This course focuses on proteolysis targeting chimeras (PROTACs) and will cover topics relevant to developing them as oral therapeutics. Topics to be covered in this part of the course will include their physicochemical properties and how these influence solubility and permeability and assays to determine polarity. We will also examine ADME topics focusing on *in vitro* assays including stability assays, transporters, drug-drug interactions (DDIs), Cytochrome P450 (CYP450) inhibition, etc.

SC7: Chemical Biology for Covalent Discovery, Phenotypic Screening, and Target Deconvolution

Instructors:

Paul Brennan, PhD, Professor, Nuffield Department of Medicine, University of Oxford

Brent Martin, PhD, Vice President, Chemical Biology, Scorpion Therapeutics

Angelo Andres, Senior Scientist, Chemical Biology, AstraZeneca Pharmaceuticals

This course is designed to provide an overview and best practices in the use of chemical biology probes and assays that have been developed for applications in early drug discovery. Chemists and biologists working in lead generation, assay development, phenotypic screening, target discovery and deconvolution, target engagement and mechanism-of-action (MoA) studies will all benefit from attending this course. The instructors will share their knowledge and expertise around the use of various technologies and chemistries, and there will be time for open discussion and exchange of ideas.

SC8: Biophysical Approaches for GPCRs

Instructor:

Matthew T. Eddy, PhD, Assistant Professor, Chemistry, University of Florida, Gainesville

This course will cover NMR screening methods for membrane proteins, especially GPCRs; LCP (liquid cubic phase) crystallization applications with a few GPCR examples; and advances in Cryo-EM and nanodiscs. All these biophysical techniques will be discussed in the context of their impact on membrane-protein targeted drug discovery.

SC9: Fundamentals of Generative AI for Drug Discovery

Instructors:

Parthiban Srinivasan, PhD, Professor, Data Science and Engineering, Indian Institute of Science Education and Research, Bhopal

Petrina Kamya, PhD, Global Head of AI Platforms, Vice President Insilico Medicine; President, Insilico Medicine Canada, Insilico

Deep generative modeling is rapidly transforming *de novo* drug discovery, streamlining the entire process. This course aims to explain the potential of AI, machine learning, and generative AI models in creating tailored molecules with specific properties. It explores the fundamentals of Variational Autoencoders, Generative Adversarial Networks, Transformers, Large Language Models (LLMs), BERT, and GPT models in the context of drug discovery, highlighting their crucial role in reshaping the pharmaceutical landscape. Along the way, we'll dissect three pivotal techniques for biopharma specific LLMs: prompt engineering, retrieval augmented generation (RAG), and fine-tuning. This course is designed for medicinal chemists, molecular modeling users, and project managers seeking to harness the capabilities of modern Generative AI concepts and integrate them into their work.

Training SEMINARS

By Cambridge Healthtech Institute

TRAINING SEMINARS WILL BE OFFERED IN-PERSON ONLY.

Cambridge Healthtech Institute Training Seminars offer real-life case studies, problems encountered and solutions applied, along with extensive coverage of the academic theory and background. Each Training Seminar offers a mix of formal lecture and interactive discussions and activities to maximize the learning experience. These Training Seminars are led by experienced instructors who will focus on content applicable to your current research and provide important guidance for those new to their fields.

TUESDAY, OCTOBER 1, 8:00 AM - 6:00 PM | WEDNESDAY, OCTOBER 2, 8:00 - 10:00 AM

TS8A: GPCR Pharmacodynamics: Kinetics, Allosterism, and Biased Agonism in Pharma Discovery

Instructor:

Terrence P. Kenakin, PhD, Professor, Pharmacology, University of North Carolina at Chapel Hill

This training seminar describes models and tools that extend GPCR pharmacology into new therapeutic areas. I review the new data characterizing the allosteric nature of GPCRs and how this can be applied to the discovery of new drugs. Discussion emphasizes characterization of Biased Agonists, Positive Allosteric Modulators (PAMs), and Negative Allosteric Modulators (NAMs) in practical terms for application to drug discovery.

Topics to be Covered:

- The Role of Pharmacology in Drug Discovery / Determining Mechanism of Drug Action / Tools of Pharmacology: Dose-Response Curves, Assays / Pharmacologic Principles: Affinity / Efficacy
- What is Efficacy? / The Black/Leff Operational Model / Biased Signaling / Selecting GPCRs as Drug Targets / Kinetics as a Major Player in GPCR Drug Selection
- Allosteric Protein Function / The 2 Unique Functions of Allosteric Modulators / 'Induced-Bias' and Allosteric Probe Dependence / Quantifying Allosteric Function / NAMs, PAMs, and PAM-Antagonists / Case Studies: 'Know Your Molecule'

INSTRUCTOR BIOGRAPHY

Beginning his career as a synthetic chemist, Terry Kenakin received a PhD in Pharmacology at the University of Alberta in Canada. After a postdoctoral fellowship at University College London, UK, he joined Burroughs-Wellcome as an associate scientist for 7 years. From there, he continued working in drug discovery for 25 years first at Glaxo, Inc., then Glaxo Wellcome, and finally as a Director at GlaxoSmithKline Research and Development laboratories at Research Triangle Park, North Carolina, USA. Dr. Kenakin is now a professor in the Department of Pharmacology, University of North Carolina School of Medicine, Chapel Hill. Currently he is engaged in studies aimed at the optimal design of drug activity assays systems, the discovery and testing of allosteric molecules for therapeutic application, and the quantitative modeling of drug effects. In addition, he is Director of the Pharmacology graduate courses at the UNC School of Medicine. He is a member of numerous editorial boards, as well as Editor-in-Chief of the *Journal of Receptors and Signal Transduction*. He has authored numerous articles and has written 10 books on pharmacology.

WEDNESDAY, OCTOBER 2, 1:45 - 5:15 PM | THURSDAY, OCTOBER 3, 8:00 AM - 4:35 PM

TS7B: Drug Exposure at the Target: The Role of ADME and Pharmacokinetics

Instructor:

Erland Stevens, PhD, James G. Martin Professor, Department of Chemistry, Davidson College

This training seminar describes how pharmacokinetics (PK) affects drug exposure at the intended target. The seminar opens with a foundation of clinical PK including the determination of key PK parameters from Cp-time data. Seminar materials also cover common preclinical ADME assays that allow estimation of a compound's human PK properties. The materials bridge the idea of a compound's PK and its observed pharmacodynamic effects (PD) through coverage of PK/PD modeling. Various drug modalities (e.g., small molecules, antibodies, and peptides) illustrate the concepts of the seminar.

Session 1:

- Drug discovery—typical order of operations
- ADME and key pharmacokinetic parameters
- Modeling Cp-time curves from an IV dose
- Modeling Cp-time curves from an oral dose

Session 2:

- Oral drug space and membrane permeability
- Metabolic stability and intrinsic clearance
- Plasma, PPB, and the free drug hypothesis
- Compartment modeling and PBPK

Session 3:

- Pre-formulation and formulation
- Preclinical species and allometric scaling
- Non-small molecule drug modalities
- PK/PD modeling

INSTRUCTOR BIOGRAPHY

Erland Stevens is formally trained as a synthetic organic chemist, with a PhD from the Department of Chemistry at the University of Michigan at Ann Arbor. He specialized in nitrogen heterocycle synthetic methodology. After completing his postdoctoral research at The Scripps Research Institute in La Jolla, CA, he joined the chemistry faculty at Davidson College in Davidson, NC. In addition to teaching organic chemistry, he created an undergraduate medicinal chemistry course and later published a textbook, *Medicinal Chemistry: The Modern Drug Discovery Process*, with Pearson Education. He then created an online medicinal chemistry course, which has been continuously revised and publicly available for approximately 10 years. He subsequently worked with Novartis to create additional online materials that are used with employees for continuing education purposes. He maintains an interest in the computational prediction of pharmacokinetic parameters based on structural features of drug-like structures.

Pre-Conference Symposia*

Cambridge Healthtech Institute's 15th Annual

Strategies for Targeting Kinases

Novel Chemistries and Techniques for Studying, Modulating, and Degrading Kinases

September 30, 2024

MONDAY, SEPTEMBER 30

8:00 am Pre-Conference Symposium Registration Open and Morning Coffee

NEW KINASE SCREENS & TARGETS

8:50 Welcome Remarks

8:55 Chairperson's Remarks

Rui Wu, PhD, Senior Vice President, Head of Research & Preclinical, Chief CMC Officer, Graviton Bioscience

9:00 Multi-Modal Machine Learning to Screen for Novel, Conformation-Specific Inhibitors of Dark Kinases

Rayees Rahman, PhD, Co-Founder & CEO, Harmonic Discovery

Dark kinases are a group of 160 proteins with poorly understood biological functions, resulting in a scarcity of tool compounds that could serve as starting points for drug discovery. We employ a multi-model deep learning approach to screen for novel inhibitors targeting dark kinases. We demonstrate that our method identifies molecules that engage these kinases across various active-site conformational states, thereby broadening the exploration of the kinase inhibitor chemical space.

9:30 Dark Kinase Allostery Atlas

Dima Kozakov, PhD, Associate Professor, Applied Mathematics & Statistics, SUNY Stony Brook

The inhibition of kinases has been pursued by the pharmaceutical industry for over 20 years. We report Dark Kinase Allostery Atlas which is a systematic collection of binding hot spots located at sites on the entire human kinome, with the focus on dark kinases. The hot spots are identified by FTMap, a computational analogue of experimental fragment screening. The ensemble is sampled by a combination of physics and AlphaFold-based sampling.

10:00 FEATURED PRESENTATION: Targeting Kinase Scaffolds in Disease

Arvin Dar, PhD, Professor, Chemical Biology, Memorial Sloan Kettering Cancer Center

I will present structural and *in vivo* binding data demonstrating how interactions on wild-type and mutant kinases impact pathway inhibition and adaptive feedback mediated by rebound signaling. I will further present structure-based approaches for developing next-generation inhibitors and molecular glues with the goal of improving target engagement and combinatorial activity to mitigate the emergence of drug resistance.

10:30 Pocket-Specific Fragment Hits for RIPK1 and their Evolution into Long Residence Time Inhibitors

PROTEROS
REACH RIGHT FASTER

Lars Neumann, Co-Head - Discovery Solutions, Proteros Biostructures GmbH

Proteros offers generation of Qualified Hits for challenging targets to enable demanding drug discovery projects. We present the identification of pocket-specific fragments for RIPK1 and their development into long residence time inhibitors as performed for the UT MD Anderson Center. A Proteros fragment library was screened with site-specific binding assay techniques, hits were kinetically profiled and binding modes were verified by protein crystallography all in-house.

11:00 Enjoy Lunch on Your Own

NOVEL KINASE MODULATORS

12:25 pm Chairperson's Remarks

Ken Hsu, PhD, Stephen F. and Fay Evans Martin Endowed Associate Professor, Department of Chemistry, The University of Texas at Austin

12:30 Nephroprotective Effects of a ROCK2 Inhibitor in Model of Hypertension-Accelerated Chronic and Diabetic Kidney Disease

Rui Wu, PhD, Senior Vice President, Head of Research & Preclinical, Chief CMC Officer, Graviton Bioscience

Graviton's GV101 is a potent, selective and best-in-class ROCK2 inhibitor. Our data in a hypertension-accelerated animal model demonstrate that GV101 treatment improves insulin sensitivity and reduces the plasma glucose and HbA1c levels. GV101 also reversed kidney fibrosis, especially glomerulosclerosis. This was illustrated with AI-powered pathological analysis of PAS-stained kidney sections. In addition, GV101 reduced macrophage infiltration and prevented the buildup of kidney injury molecules.

1:00 Allosteric Modulation of NEK7 to Inhibit the NLRP3 Inflammasome

David Bearss, PhD, Co-Founder & CEO, Halia Therapeutics

We have developed a groundbreaking approach by identifying a new allosteric modulation mechanism of NEK7. This modulation interrupts the vital interaction between NEK7 and NLRP3, effectively preventing the formation and function of the NLRP3 inflammasome, a major contributor to inflammatory and autoimmune diseases. These findings present a promising therapeutic strategy for effectively managing complex immune responses and inflammation.

1:30 Discovery of Novel Degrader Targeting PTK6 Kinase-Independent Functions

Yan Xiong, PhD, Instructor, Laboratory of Dr. Jian Jin, Pharmacological Sciences, Icahn School of Medicine at Mount Sinai

PTK6/Brk was reported as an oncogenic driver in several tumor types and in some cancer types; PTK6 non-catalytic functions play key roles in oncogenic activities. We present the discovery of novel PROTAC degrader, MS105, which potently downregulates PTK6 level, induces expression of Bim, and apoptosis of cancer cells. Taken together, our studies suggest PTK6 degrader could provide a preferred approach to clinically targeting PTK6 in cancer.

2:00 In-Person Brainstorming Session

This informal session will be led by the speakers, allowing participants to ask questions and exchange ideas around topics related to the symposium. To get the most out of this session, please come prepared to share your ideas and participate in collective problem-solving.

2:45 Networking Refreshment Break

3:15 Covalent Strategies for Targeting the Kinome

Ken Hsu, PhD, Stephen F. and Fay Evans Martin Endowed Associate Professor, Department of Chemistry, The University of Texas at Austin

I will describe the synthesis of sulfonyl-triazoles as a new phenol-reactive group for covalent modification of tyrosine and lysine residues on proteins through sulfur-triazole exchange (SuTEx) chemistry. The reactivity of SuTEx chemistry is highly tunable, which can facilitate optimization of potent and selective binders to orthosteric and allosteric sites on kinases. I will conclude my talk by describing efforts to use lead SuTEx inhibitors for modulating kinase function in cells.

**Premium Package includes access to two short courses and all symposia. Separate registration required for other packages.*

Cambridge Healthtech Institute's 15th Annual

Strategies for Targeting Kinases

Novel Chemistries and Techniques for Studying, Modulating, and Degrading Kinases

September 30, 2024

3:45 E3 Warhead Meets Small Molecule: Evaluating Kinome Binding between Therapeutic Modalities with Reverse Competition

Fiona Pachl, PhD, Associate Principal Scientist, Chemical Biology and Proteomics, AstraZeneca Pharmaceuticals

Proteolysis-targeting chimeras (PROTACs) offer the ability to drive degradation of kinases more selectively and efficaciously, relative to conventional small molecules. Discerning compound engagement with the kinome is challenging due to low expression levels of kinases but is necessary to compare the effects of PROTACs to corresponding small molecules. We present a kinase enrichment strategy implementing reverse competition to differentiate between small molecule binding and PROTAC binding on the kinome.

4:15 Close of Symposium

5:00 Dinner Short Courses*

**Premium Pricing or separate registration required. See Short Courses page for details.*

7:30 Close of Day

Pre-Conference Symposia*

NEW

Cambridge Healthtech Institute's Inaugural

Covalent Chemistries and Induced Proximity

Strategies to Modulate Cellular Interactions and Drive New Therapies

September 30, 2024

MONDAY, SEPTEMBER 30

8:00 am Pre-Conference Symposium Registration Open and Morning Coffee

EMERGING COVALENT STRATEGIES

8:50 Welcome Remarks

8:55 Chairperson's Remarks

Kay Ahn, PhD, CSO & Co-Founder, ReAx Biotechnologies

9:00 Covalent Drug Discovery Strategies to Tackle Challenging Cancer Targets

Brent Martin, PhD, Vice President, Chemical Biology, Scorpion Therapeutics

Recent chemoproteomics advances have enabled covalent ligand discovery across a broad range of new targets. Here, we discuss the expanding role of chemical biology and chemoproteomics to support covalent lead discovery efforts, from early hit-finding to late lead optimization.

9:30 Discovery, Optimization, and Characterization of a Covalent Small Molecule Inhibitor against an Anti-Apoptotic Protein Target

Brooke Brauer, PhD, Senior Research Scientist, Mass Spectrometry, AstraZeneca Pharmaceuticals

In this talk, I will discuss the biochemical and biophysical assays used to optimize and characterize a covalent small molecule inhibitor against an anti-apoptotic protein. I will then discuss how targeted proteomics was used to monitor the impact of compound treatment on target half-life and to determine target occupancy.

10:00 Chemoproteomic Profiling in Multiple Cell Types to Assess Pharmacological Targets and Off-Target Safety Risks

Doug Johnson, PhD, Senior Director, Chemical Biology & Proteomics, Biogen

This presentation will describe our utilization of clickable chemical biology probes to assess target engagement and conduct selectivity profiling to identify off-targets in two drug discovery endeavors featuring covalent inhibitors. In both instances, thorough selectivity profiling across multiple cell types was pivotal, allowing for a more comprehensive identification of potential off-targets that could pose safety concerns.

enzymlogic

10:30 Kinetic Profiling of Covalent Inhibitors using COVALfinder®

Patricia Alfonso San-Segundo, Co Founder & CSO, Enzymlogic

We will present case studies illustrating how Enzymlogic's COVALfinder platform provides a detailed understanding of inactivation kinetic parameters KI, kinact, kinact/KI, T1/2∞ for determination of Kinetic Selectivity in covalent drug design. Enzymlogic serves an international client base with kinetic screening of reversible & irreversible inhibitors in early discovery to iterate Medicinal Chemistry, understand PK PD disconnects and build better models to define therapeutic windows.

11:00 Enjoy Lunch on Your Own

NOVEL APPROACHES FOR INDUCING PROXIMITY

12:25 pm Chairperson's Remarks

Philip E. Brandish, PhD, Senior Vice President, Immuno-Oncology, Bicycle Therapeutics

12:30 Constrained Bicyclic Peptide Conjugates as Novel Therapeutics in Cancer

Philip E. Brandish, PhD, Senior Vice President, Immuno-Oncology, Bicycle Therapeutics

Constrained bicyclic peptides that embody the minimal pharmacophore of an antibody without the protein scaffold are well-suited to induced proximity applications because of their small size, high ligand efficiency, and ease of conjugation. At Bicycle Therapeutics, we are exploring how conjugation of Bicycle molecules to afford simultaneous binding and pharmacology at more than one target or site can access novel biology and lead to impactful new medicines.

1:00 Strategies to Chemically Control Protein Stability and Activity

Behnam Nabet, PhD, Assistant Professor, Human Biology Division, Fred Hutchinson Cancer Center

Small molecules that chemically induce proximity are powerful approaches to rewire the circuitry of the cell. My talk will describe our recent advances in the development of chemical-genetic tag-based platforms to precisely modulate protein levels, stability, and activity. I will also describe our work to apply these approaches for biological investigation and pre-clinical target discovery and validation.

1:30 Covalent Proximity-Induction Strategies to Modulate Ligand-Receptor Interactions for Immuno-Oncology

Anthony Rullo, PhD, Associate Professor, Department of Medicine, Chemistry and Chemical Biology, McMaster University

A major class of tumor immunotherapeutics function by bridging immune machinery with tumor antigens, highly expressed on cancer cells compared to normal tissue. In this talk, we describe the development of chimeric molecules that use covalency to induce cell-cell proximity. Covalent stabilization of ternary complexes significantly enhances tumoricidal immune function, and may find special utility for induced proximity in the absence of positive co-operativity.

2:00 In-Person Brainstorming Session

This informal session will be led by the speakers, allowing participants to ask questions and exchange ideas around topics related to the symposium. To get the most out of this session, please come prepared to share your ideas and participate in collective problem-solving.

2:45 Networking Refreshment Break

3:15 Specific Covalent Targeting of Histidine, Tyrosine, and Lysine to Expand the Druggable Proteome

Andrea Zuhl, PhD, Vice President, Chemical Biology & Proteomics, Hyku Biosciences, Inc.

The integration of covalent chemistry with chemoproteomics has catalyzed the identification of novel small molecule binding pockets across the proteome. This talk will describe key features of the HYKU platform including warhead development for covalent screening of histidine, tyrosine, and lysine

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(HYK) residues; optimizing mass spectrometry-based chemoproteomics for non-cysteine amino acids; and integration of structural information to prioritize novel binding pockets for further development of covalent or non-covalent compounds.

3:45 Mini-PROTACs

Hai Rao, PhD, Professor and Chair, Department of Biochemistry, Southern University of Science and Technology, China

Proteolysis-targeting chimera (PROTAC) that selectively eliminates detrimental proteins represents a promising therapeutic strategy for various diseases. We have developed a set of PROTACs with the short and interchangeable degradation signals that attract several distinct E3 ubiquitin ligases. We demonstrate the utility and efficacy of these mini-PROTACs *in vitro* and *in vivo*, expanding the repertoire of limited ligands and degradation pathways available for PROTACs.

4:15 Close of Symposium

5:00 Dinner Short Courses*

**Premium Pricing or separate registration required. See Short Courses page for details.*

7:30 Close of Day

Pre-Conference Symposia*

Cambridge Healthtech Institute's 3rd Annual

Emerging Immune Modulation Strategies

Assays and Techniques for Identifying, Understanding, and Predicting Immune Responses

September 30, 2024

MONDAY, SEPTEMBER 30

8:00 am Pre-Conference Symposium Registration Open and Morning Coffee

EXPLORING DIVERSE MODALITIES

8:50 Welcome Remarks

8:55 Chairperson's Remarks

Rakesh Dixit, PhD, DABT, President & Founder, Bionavigen Oncology, LLC and Regio Biosciences

9:00 Challenges and Opportunities in the Development of Antibody-Immune Agonist Conjugates (AIC)

Rakesh Dixit, PhD, DABT, President & Founder, Bionavigen Oncology, LLC and Regio Biosciences

AICs are a new generation of tumor antigen-targeting antibody-immune agonists conjugates that stimulate innate and adaptive immunity, providing dual therapeutic MOAs in eliminating cancers. While providing great promises, many early AICs were terminated in clinical development due to poorly manageable toxicities, immunogenicity, poor PK, and limited clinical efficacy. The presentation will comprehensively review ISACs' composition and function, lessons learned from failed AICs, and opportunities of developing the next generation of AICs.

9:30 Bivalent Agonist Antibodies as a Next-Generation Immunological Platform

Andy Sullivan, MS, Associate Director, Biology and Pharmacology, Diagonal Therapeutics

The use of cytokine muteins to target and activate the immune system is a promising approach to treating cancer, but several challenges are affecting its applicability—as the discovery process can be time-consuming and restrictive due to the limitations of the natural cytokine. Bivalent agonist antibodies possess distinct developability features that present the opportunity to selectively address unmet needs that were not druggable with conventional muteins.

10:00 Anti-Tumor Immunity Induced by Precision-Guided Bicycle Therapeutics

Anne-Sophie Dugast, PhD, Director Oncology, Discovery Research, Bicycle Therapeutics

Small bicyclic peptides constrained by a central scaffold can have pharmacologic and pharmacodynamic properties that fit very well with the design goals and are therefore ideally positioned to deliver immune agonists in a way not practically feasible with traditional antibodies. We will demonstrate that Bicycle TICAs (tumor-targeted immune cell agonists) can potently activate anti-tumor immunity in cancer, in particular via the activating receptors CD137 and NKp46 in a tumor-targeted manner.

10:30 Sponsored Presentation *(Opportunity Available)*

11:00 Enjoy Lunch on Your Own

TARGETING TUMOR CELLS

12:25 pm Chairperson's Remarks

Peng Wu, PhD, Professor, Chemical Physiology, Scripps Research Institute

12:30 Developing Small-Molecule Modulators to Alleviate T Cell Exhaustion

Peng Wu, PhD, Professor, Chemical Physiology, Scripps Research Institute

Adoptive cell transfer therapy is a new paradigm in cancer treatment. However, during the *ex vivo* expansion process, T cells undergo exhaustion—as a result they lose the ability to persist after adoptive transfer. In this talk, I will discuss small molecule modulators discovered in my lab which can facilitate T cell proliferation and generate T cells with stem cell-like properties. Upon transfer, they confer excellent tumor control.

1:00 RNAi Conjugates for Cancer Immunotherapy

Shanthi Ganesh, PhD Director, Pharmacology, Global Nucleic Acid Therapies, Novo Nordisk

Refractory malignant solid tumors create an immunosuppressive tumor microenvironment (TME), which renders them resistant to standard-of-care immune checkpoint inhibitors. We developed RNAi agents to silence STAT3 or PD-L1 targets in tumor-associated immune cells, which mediate immune suppression in the TME. Silencing these genes remodeled the TME and increased cytotoxic T-cell infiltration into the tumor. Human active STAT3 and PDL1 RNAi conjugates are currently in Phase 1 trials for immunotherapy-refractory cancers.

1:30 Precision Immunotherapy for Oncogenic Driver Mutations

Gary Shapiro, PhD, VP, Discovery Biology, Affini-T Therapeutics Inc.

Affini-T, a precision immunotherapy company, develops potentially curative therapies for solid tumors by targeting oncogenic driver mutations, beginning with KRAS. We are advancing two distinct therapeutic modalities, adoptive cellular therapies and bispecific T cell engagers, designed to harness T cell immunity with unprecedented precision and potency. Our TCR-T cell therapy-enabling platforms utilize state-of-the-art TCR discovery, synthetic biology, and gene editing to modify the tumor microenvironment and optimize T cell functions.

2:00 In-Person Brainstorming Session

This informal session will be led by the speakers, allowing participants to ask questions and exchange ideas around topics related to the symposium. To get the most out of this session, please come prepared to share your ideas and participate in collective problem-solving.

2:45 Networking Refreshment Break

TOOLS FOR IMMUNE MODULATION

3:15 Analysis Platforms to Quantify Tumor-Immune Interactions through Multiplexed Spatial Profiling Technologies

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

Spatial profiling technologies have the potential to enable multi-factorial, multi-modal characterization of the tissue microenvironment. Scalable, quantitative methods to analyze and interpret spatial patterns of protein staining and gene expression are required to understand cell-cell relationships in the context of local variations in tissue structure. We will discuss elements of spatial profiling from multiple studies as well as paradigms from statistics and machine learning in the context of these problems.

3:45 Developing and Applying a Novel Chemoproteomics Platform for Immune Cell Transcription Factors

Olesya Ulanovskaya, PhD, Senior Director, Biology, Belharra Therapeutics

Belharra Therapeutics is the next wave in chemoproteomics focused on applying a novel chemistry enabled non-covalent probe library and quantitative mass spectrometry to identify chemical probes that selectively

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bind any pocket, on any protein, in live cells. Most proteins identified as being selectively engaged by our probe library do not have a reported ligand, demonstrating the ability to identify novel pockets and potential chemical probe starting points for these targets.

4:15 Close of Symposium

5:00 Dinner Short Courses*

**Premium Pricing or separate registration required. See Short Courses page for details.*

7:30 Close of Day

Pre-Conference Symposia*

NEW

Cambridge Healthtech Institute's Inaugural

Synthetic Biology for Drug Discovery and Therapy

Novel Cellular Engineering and Predictive Modeling for Regulating Diverse Systems

September 30, 2024

MONDAY, SEPTEMBER 30

8:00 am Pre-Conference Symposium Registration Open and Morning Coffee

8:50 Welcome Remarks

8:55 Chairperson's Remarks

Ron Weiss, PhD, Professor, Biological Engineering, Massachusetts Institute of Technology

9:00 FEATURED PRESENTATION: Mammalian Synthetic Biology and Programmable Organoids

Ron Weiss, PhD, Professor, Biological Engineering, Massachusetts Institute of Technology

Programmable Organoids is a new platform for drug discovery that enables rapid and effective drug screening. Based on programmed differentiation into synthetic mammalian tissues having multiple cell type architectures similar to human organs, Programmable Organoids mimic the response of a target organ to both positive and negative effects of drug candidates. Organoids programmed with both general and disease-specific sensors can be used to identify candidates for further analysis.

10:00 Programming mRNA for Cancer Immunotherapy

Jaspreet Khurana, PhD, Senior Director, mRNA Programming, Strand Therapeutics Inc.

We have developed a platform in which we design RNA-encoded programmable genetic "circuits" that detect molecular cues in a cell to specifically express a payload protein in cells that exhibit a particular molecular signature. We applied this platform to the development of our program which entails systemic delivery of lipid nanoparticle (LNP)-encapsulated mRNA-bearing programmable genetic circuitry that selectively expresses a therapeutic payload within target cells.

10:30 Protein-in-hand in 48 hours: Multiplexing Protein Expression and Purification Screen on a Digital Microfluidic Device

nuclera

Michael Chen, CEO & Co Founder, Nuclera UK

The eProtein Discovery™ System can screen multiple protein expression and purification profiles and deliver reliable proteins in-hand in less than 48 hours. eProtein Discovery reduces the timelines and costs associated with protein production through 24 customizable expression conditions and subsequent identification of optimal conditions for scale-up. Integrating cell-free protein synthesis and digital microfluidics on smart cartridges, Nuclera's eProtein Discovery enables rapid access to even challenging proteins at high quality.

11:00 Enjoy Lunch on Your Own

PROGRAMMING CELLULAR PATHWAYS

12:25 pm Chairperson's Remarks

Akos Nyerges, PhD, Research Fellow, Laboratory of Dr. George Church, Department of Genetics, Harvard Medical School

12:30 Programming Mammalian Gene Expression with Synthetic Promoters

William Chen, MD, PhD, Assistant Professor, Sanford School of Medicine, University of South Dakota

Constitutive mammalian gene expression relies on a limited collection of natural promoters that drive discrete levels of transcription. The activities of many natural promoters are unpredictable in different species and cell types, making it difficult to precisely control transgene expression. To address these obstacles, using synthetic biology toolkits, we have developed versatile, scalable synthetic promoter platforms and programmable genetic components to transform the regulation of mammalian transcription and transgene expression.

1:00 Synthetic Gene Circuits for Cancer Immunotherapy: Turning Cancer Cells against Themselves

Ming-Ru Wu, MD, PhD, Assistant Professor, Department of Cancer Immunology and Virology, Dana-Farber Cancer Institute, Harvard Medical School

We have developed synthetic cancer-targeting gene circuits that specifically target cancer cells. Once the circuits enter cells, they will sense the activity of several cancer-associated transcription factors and get activated in tumor cells to trigger tumor-localized combinatorial immunotherapy. Circuits mediate robust therapeutic efficacy in ovarian cancer mouse models. This platform can be adjusted to treat multiple cancer types and can potentially trigger any genetically-encodable immunomodulators as therapeutic outputs.

1:30 Talk Title to be Announced

Farren Isaacs, PhD, Professor, Department of Molecular & Cellular & Developmental Biology, Yale University

2:00 In-Person Brainstorming Session

This informal session will be led by the speakers, allowing participants to ask questions and exchange ideas around topics related to the symposium. To get the most out of this session, please come prepared to share your ideas and participate in collective problem-solving.

2:45 Networking Refreshment Break

3:15 Engineering High-Precision, Dynamic Genetic Control Systems for Cellular Engineering

Katie Galloway, PhD, W. M. Keck Career Development Professor, Biomedical Engineering and Chemical Engineering, Massachusetts Institute of Technology

Integrating synthetic circuitry into larger transcriptional networks to mediate predictable cellular behaviors remains a challenge. To accelerate high-efficiency cellular engineering, we've developed physiochemical models of gene regulation to guide the design of highly-compact genetic tools with improved performance across cell lines and primary cells. In this talk, I will share how these models have improved engineered cells and opened opportunities for phenotypic screening, disease modeling, and gene and cell therapies.

3:45 Multiplexed *in vivo* Screening of Tissue-Specific Targeting Protein Therapies

Alex Reis, PhD, Principal Scientist, Computation, Manifold Biotechnologies Inc.

Manifold has developed an *in vivo* protein multiplexing platform, using a proprietary protein barcoding technology (mCodes), and is now leveraging it to engineer tissue-specific biologics with optimal profiles. We share several case studies using our platform across diverse therapeutic areas, including

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neuro and metabolic disease. We have applied this platform to screen 1000s of shuttle candidates *in vivo*, resulting in shuttles against novel receptors for brain and tissue uptake.

4:15 Close of Symposium

5:00 Dinner Short Courses*

**Premium Pricing or separate registration required. See Short Courses page for details.*

7:30 Close of Day

TUESDAY, OCTOBER 1

7:00 am Registration Open and Morning Coffee

STRUCTURAL & MECHANISTIC CHARACTERIZATION

7:55 Welcome Remarks

8:00 Chairperson's Remarks

Ralph Mazitschek, PhD, Assistant Professor, Harvard Medical School; Co-Director of the Chemical Biology Platform, Center for Systems Biology, Massachusetts General Hospital

8:05 CoraFluor-Enabled TR-FRET Assay Strategies for Facile PROTAC Profiling

Ralph Mazitschek, PhD, Assistant Professor, Harvard Medical School; Co-Director of the Chemical Biology Platform, Center for Systems Biology, Massachusetts General Hospital

Building on our CoraFluor TR-FFRET technology, we have established a versatile assay platform for the comprehensive characterization of PROTACs and molecular glue degraders, including (a) detailed kinetic and thermodynamic analyses of ligand binding to both endogenous and recombinant proteins, (b) accurate quantification of ternary complex cooperativity, (c) facile measurements of cellular protein levels. This advancement provides a robust toolset for enhancing the understanding and development of targeted protein degradation technologies.

8:35 Leveraging High-Throughput Targeted Proteomics to Impact a Protein Degrader

Wankyu Lee, PhD, Senior Research Scientist, AstraZeneca Pharmaceuticals

Targeted proteomics through parallel reaction monitoring (PRM) leverages high precision and quantitative accuracy for target protein(s), affording higher throughput as opposed to discovery proteomics. For degrader projects, targeted proteomics is invaluable for quantitatively understanding degradation in cells and *in vivo*. Here, we describe a case study where targeted proteomics impacted a protein degrader project at AstraZeneca, by providing a key orthogonal method to understand accurate DC50 and Dmax values.

9:05 Computational Structural Modeling of PROTACs and Molecular Glues

Dima Kozakov, PhD, Associate Professor, Applied Mathematics & Statistics, SUNY Stony Brook

The design of PROteolysis-TArgeting Chimeras (PROTACs) requires bringing an E3 ligase into proximity with a target protein to modulate the concentration of the latter through its ubiquitination and degradation. Here, we present a combination of physics and machine learning methods for generating high-accuracy structural models of E3 ligase-PROTAC-target protein ternary complexes. We will discuss the generalization of the approach for other TACs and ligases, and principles of molecular glue discovery.

9:35 Networking Coffee Break

10:05 Parkin Ligase and PINK1 Signaling, Molecular Glue and its Role in Neurodegenerative Diseases and Aging

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

Parkinson's disease (PD) and Alzheimer's Disease (AD) share common neurodegenerative traits, inability to correct protein misfolding or remove aggregated proteins. Progenra has discovered a molecular glue that activates parkin ligase and phospho-poly-ubiquitinate target proteins in cells and animal models. Blood-based levels of phospho-ubiquitin are important biomarkers for neurodegeneration. Discovery and development of molecular glue for parkin ubiquitin ligase that induces mitophagy and improves neuronal health will be discussed.

10:35 Preclinical Characterization of a Selective and CNS-Penetrant BTK Degrader

Bekim Bajrami, PhD, Senior Scientist, Chemical Biology and Proteomics, Biogen, Inc.

Multiple sclerosis (MS) is characterized by inflammation and demyelination in the central nervous system, lacking effective treatments despite advancements. Bruton's tyrosine kinase (BTK) is crucial in B cell activation and MS autoimmunity. BTK degraders offer a fresh therapeutic path by specifically degrading BTK protein. This talk discusses the rationale for targeting BTK in MS and elucidates the mechanism of BTK degraders through preclinical characterization of selective and CNS-penetrant degraders.

11:05 Small Molecule Lysosome-Targeting Chimeras (SMaLTACs): Receptor Mimetics Targeting Extracellular Proteins for Degradation

Angelo Andres, Senior Scientist, Chemical Biology, AstraZeneca Pharmaceuticals

The targeted degradation of extracellular and membrane proteins via lysosome targeting chimeras (LYTACs) requires the engineering of bispecifics or targeting antibodies functionalized with multivalent carbohydrates to deliver targets for degradation. We have developed a small molecule-based platform termed small molecule lysosome targeting chimeras (SMaLTACs). Using a modular chemical approach we demonstrate how SMaLTACs are rapidly deployed to degrade cell surface receptors and they may how compare mechanistically to existing approaches.

11:35 Presentation to be Announced

11:50 Presentation to be Announced

12:05 pm Transition to Lunch

12:10 LUNCHEON PRESENTATION: Identification and Validation of Novel Target Binders for Protein Degraders and Molecular Glues

Katherine Jones, Associate Science Director, Charles River Labs

This presentation will describe diverse hit identification strategies, such as SAMDI-ASMS and DNA-encoded library screening, and their use to discover small molecule binders to novel targets. We will then describe how these hit molecules can be validated and progressed through degrader optimisation projects, including assay methodologies to measure molecular glue-like properties.

12:40 Session Break

DEGRADATION STRATEGIES FOR CANCER

1:15 Chairperson's Remarks

John Brognard, PhD, Senior Investigator, Laboratory of Cellular & Developmental Signaling, National Cancer Institute, National Institutes of Health

1:20 PIM1 Targeted Degradation Prevents the Emergence of Chemoresistance in Prostate Cancer

John Brognard, PhD, Senior Investigator, Laboratory of Cellular & Developmental Signaling, National Cancer Institute, National Institutes of Health

PIM kinases have pro-tumorigenic roles and mediate several oncogenic traits, including cell proliferation and survival. We found that inhibition of PIM kinase activity stabilizes PIM protein levels and this promotes resistance to PIM inhibitors. We designed PIM PROTACs to target PIM for degradation. PIM PROTACs downmodulated PIM levels through the ubiquitin-proteasome pathway. Degradation of PIM kinases was more potent than inhibition of catalytic activity at inducing apoptosis in prostate cancer.

1:50 Degradation of Siglec 7/9 to Reshape the Tumor Microenvironment for Cancer Immunotherapy

Peng Wu, PhD, Professor, Chemical Physiology, Scripps Research Institute

Many patients fail to respond to anti-CTLA-4 and anti-PD-1-based checkpoint blockade, suggesting that orthogonal immune checkpoints exist. Myeloid cell-associated Siglecs-7 and -9 have recently been identified as glycoimmune checkpoints. However, there is currently no antibody that can target both Siglecs. We have developed a degrader that induces efficient degradation of both Siglecs, which showed excellent tumor control in several murine solid tumor models when used alone or combined with anti-CTLA-4.

2:20 Sponsored Presentation *(Opportunity Available)*

2:50 In-Person Breakouts

In-Person Breakouts are informal, moderated discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator who keeps the discussion on track and the group engaged. To get the most out of this format, please come prepared to share examples from your work, be a part of a collective, problem-solving session, and participate in active idea sharing. Please visit the Breakouts page on the conference website for a complete listing of topics and descriptions.

IN-PERSON BREAKOUT: Structural and Mechanistic Characterization of Degraders and Glues

Ralph Mazitschek, PhD, Assistant Professor, Harvard Medical School; Co-Director of the Chemical Biology Platform, Center for Systems Biology, Massachusetts General Hospital

Hua Xu, PhD, Director, Mechanistic Biology & Profiling, AstraZeneca

IN-PERSON BREAKOUT: Tackling Transcription Factors and Other Difficult-to-Drug Targets

John Brognard, PhD, Senior Investigator, Laboratory of Cellular & Developmental Signaling, National Cancer Institute, National Institutes of Health

Wankyu Lee, PhD, Senior Research Scientist, AstraZeneca Pharmaceuticals

Peng Wu, PhD, Professor, Chemical Physiology, Scripps Research Institute

3:35 Grand Opening Refreshment Break in the Exhibit Hall with Poster Viewing and Best of Show Voting Begins

4:35 FEATURED PRESENTATION: Targeting the PI3K Pathway in Cancers

Anwesha Dey, PhD, Director & Distinguished Scientist, Discovery Oncology, Genentech Inc.

PIK3CA is one of the most frequently mutated oncogenes; the p110α protein it encodes plays a central role in tumor cell proliferation. Inavolisib is a potent and selective p110α inhibitor that promotes the degradation of mutated p110α. The significance of this unique mechanism to trigger specific degradation of mutant p110α without significant change in wild-type p110α protein may result in improved therapeutic index in PIK3CA-mutant tumors.

5:05 The Evolving Chemical Space of Bi-functional Degraders Targeting the CNS

Wylie S. Palmer, PhD, Senior Director, Nurix Therapeutics, Inc.

Description:Bi-functional degraders occupy beyond-rule-of-five chemical space where established rules for drug-likeness cannot easily be applied. In contrast to approved CNS drugs, bi-functional degraders violate most metrics, particularly molecular weight, yet we routinely observe brain penetrance in our programs. For example, NX-5948, a clinical stage orally bioavailable BTK degrader shows CNS exposure and activity both preclinically and clinically. This presentation will explore our evolving understanding of targeting the CNS using degraders.

5:35 IKZF2 Degrader Discovery

Kevin D. Freeman-Cook, PhD, Vice President & Head, Medicinal & Computational Chemistry, Plexium Inc.

The zinc finger transcription factor Helios (IKZF2) is highly expressed in Tregs and plays an important role in helping tumors evade a normal immune response. IKZF2 is a transcription factor that had been considered "undruggable." Here we disclose the discovery and preclinical evaluation of a selective molecular glue degrader of IKZF2 (PLX-4545) which reverses Treg suppression and is currently being evaluated in a Phase 1 trial of healthy volunteers.

6:05 Welcome Reception in the Exhibit Hall with Poster Viewing

7:05 Close of Day

WEDNESDAY, OCTOBER 2

7:30 am Registration Open and Morning Coffee

TARGETING TRANSCRIPTION

7:55 Chairperson's Remarks

Danette Daniels, PhD, Vice President, Degrader Platform, Foghorn Therapeutics

8:00 FEATURED PRESENTATION: Attenuating Oncogenic Transcription

Angela Koehler, PhD, Associate Professor, Biological Engineering, Massachusetts Institute of Technology

Outside of nuclear receptors, transcription factors have traditionally been considered "undruggable" by small molecules due to significant structural disorder and lack of defined binding pockets. I will review successful targeting strategies, including discussion of compounds that modulate MYC-driven transcription via mechanisms involving the MAX partner protein or the transcriptional kinase CDK9. New directions for cancer target classes beyond transcription factors will be discussed, including RNA-binding proteins and cytokines.

9:00 The Discovery and Characterization of Selective CREB-Binding Protein (CBP) Degraders

Darshan Sappal, Director, Biology, Foghorn Therapeutics

Leveraging our expertise in targeted protein degradation at Foghorn Therapeutics, we will describe our efforts at successfully identifying and characterizing potent, highly selective CBP heterobifunctional degraders with biological activity in CBP-dependent cancer lines.

9:30 Targeted Protein Degradation (TPD): A New Frontier in Drug Discovery

Alessandro Cinti, Principal Investigator Proposal, Axxam

Targeted Protein Degradation (TPD) offers a novel approach to modulate the intracellular levels of disease-causing proteins. Here, we will delve into the practical aspects of TPD, focusing on the development and implementation of cell-based assays aimed at monitoring target protein levels, and will discuss how complementary cell-based and cell-free assays support the discrimination of unspecifically interfering compounds and detailed characterization and further development of hit compounds.

10:00 Coffee Break in the Exhibit Hall with Poster Viewing

PLENARY KEYNOTE PROGRAM

10:50 Plenary Keynote Chairperson's Remarks
An-Dinh Nguyen, Team Lead, Discovery on Target, Cambridge Healthtech Institute

10:55 PLENARY KEYNOTE: Discovery of Transformative Rx to Treat Obesity and Related Diseases
Richard DiMarchi, PhD, Distinguished Professor of Chemistry and Chair, Biomolecular Sciences, Indiana University; former Executive, Lilly and Novo Research Labs
To address obesity, a medicinal challenge that warrants broad molecular diversity, we pioneered the pharmacological strategy of recruiting endogenous hormones to optimize physiological mechanisms. Our discovery of single-molecule, multi-mechanism incretins enabled breakthrough efficacy in lowering body weight. The integrated pharmacology of these endocrine proteins and nuclear hormones is providing a library of drug candidates that promises great clinical outcomes for obesity and associated diseases that have historically been intractable.

11:40 PLENARY KEYNOTE: Fragment-Based Drug Discovery for Elusive Cancer Targets
Stephen W. Fesik, PhD, Professor of Biochemistry, Pharmacology & Chemistry; Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University
The most highly validated cancer targets (KRAS, MYC, and WNT) affecting the majority of cancers are thought to be impossible to drug. Using fragment-based methods that I pioneered over 25 years ago, we have discovered mutant selective and pan KRAS inhibitors, potent inhibitors of the MYC cofactor WDR5, and degraders of b-catenin in the WNT pathway. These novel inhibitors/degraders should have a tremendous impact on cancer treatment in the future.

12:25 pm Close of Degraders and Molecular Glues – Part 1 Conference

WEDNESDAY, OCTOBER 2

PLENARY KEYNOTE PROGRAM

10:50 am Plenary Keynote Chairperson's Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target, Cambridge Healthtech Institute

10:55 PLENARY KEYNOTE: Discovery of Transformative Rx to Treat Obesity and Related Diseases

Richard DiMarchi, PhD, Distinguished Professor of Chemistry and Chair, Biomolecular Sciences, Indiana University; former Executive, Lilly and Novo Research Labs

To address obesity, a medicinal challenge that warrants broad molecular diversity, we pioneered the pharmacological strategy of recruiting endogenous hormones to optimize physiological mechanisms. Our discovery of single-molecule, multi-mechanism incretins enabled breakthrough efficacy in lowering body weight. The integrated pharmacology of these endocrine proteins and nuclear hormones is providing a library of drug candidates that promises great clinical outcomes for obesity and associated diseases that have historically been intractable.

11:40 PLENARY KEYNOTE: Fragment-Based Drug Discovery for Elusive Cancer Targets

Stephen W. Fesik, PhD, Professor of Biochemistry, Pharmacology & Chemistry; Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University

The most highly validated cancer targets (KRAS, MYC, and WNT) affecting the majority of cancers are thought to be impossible to drug. Using fragment-based methods that I pioneered over 25 years ago, we have discovered mutant selective and pan KRAS inhibitors, potent inhibitors of the MYC cofactor WDR5, and degraders of b-catenin in the WNT pathway. These novel inhibitors/degraders should have a tremendous impact on cancer treatment in the future.

12:25 pm Enjoy Lunch on Your Own

PROXIMITY-INDUCED THERAPEUTICS

1:45 Welcome Remarks

1:50 Chairperson's Remarks

Adam Gilbert, PhD, Executive Director, Medicine Design, Pfizer Inc.

1:55 FEATURED PRESENTATION: Discovery of Molecular Glues from Degraders to Stabilizers

Ryan Potts, PhD, Executive Director and Head, Induced Proximity Platform, Amgen, Inc.

Induced proximity is a novel strategy for targeting the highly intractable proteins that are involved in many human diseases. By bringing together disease targets and biological effectors, such as enzymes, ubiquitin ligases, or transcription factors, proximity-based therapeutics can modulate the function, stability, or localization of the target proteins. My talk will cover new approaches for molecular glue discovery for both degraders (beyond CRBN) and stabilizers of protein-protein and protein-metabolite interactions.

2:25 FEATURED PRESENTATION: Ubiquitin-Independent Protein Degradation

Thomas Kodadek, PhD, Professor, Department of Chemistry, University of Florida, Scripps Biomedical Research

Targeted protein degradation is usually achieved by bringing into proximity a target protein and an E3 ubiquitin ligase. An alternative strategy is to deliver the target directly to the proteasome and bypass the requirement for poly-ubiquitylation. We present an engineered cell line that allows the strengths and weaknesses of ubiquitin-independent degraders (UIDs) to be evaluated, as well as progress towards the discovery of proteasome ligands for the development of UIDs.

2:55 Proximity Biosensor Assay for PROTAC Ternary Complex Analysis

dynamic BIOSENSORS

Ulrich Rant, Professor/Director, TU Dresden/Kurt-Schwabe-Institute for Bioanalytical Systems

Ternary complexes present challenges in analyzing molecular interactions due to their reliance on cooperativity and avidity, beyond binary affinities. We introduce a proximity binding assay that simultaneously measures binary and ternary interaction kinetics on a biosensor surface, using a Y-shaped DNA scaffold and fluorescence methods. This assay is applied to CRBN, VHL, and various PROTACs, revealing insights into ternary complex stability and binding kinetics.

3:25 Refreshment Break in the Exhibit Hall with Poster Viewing

4:15 FIRESIDE CHAT: What Does the Future of Induced Proximity-based Therapeutics Look Like?

Moderator: Adam Gilbert, PhD, Executive Director, Medicine Design, Pfizer Inc.

Panelists:

Danette Daniels, PhD, Vice President, Degrader Platform, Foghorn Therapeutics

Thomas Kodadek, PhD, Professor, Department of Chemistry, University of Florida, Scripps Biomedical Research

Ryan Potts, PhD, Executive Director and Head, Induced Proximity Platform, Amgen, Inc.

5:15 Dinner Short Course Registration*

**Premium Pricing or separate registration required. See Short Courses page for details.*

5:15 Diversity Discussion *(Sponsorship Opportunity Available)*

IN-PERSON DISCUSSION: Fostering Diversity through Mentoring

Naytia Byrd, Manager, Human Resources, Ovid Therapeutics, Inc.

Saudat Fadeyi, PhD, MBA, Director, Business Development, Ovid Therapeutics, Inc.

Fred Manby, DPhil, Co-Founder & CTO, Iambic Therapeutics

Joel Omage, Research Scientist II, CVM Disease Area, Novartis Institutes for BioMedical Research, Inc.

Andrew Zhang, PhD, Director, Chemical Biology, AstraZeneca

Topics for discussion will include, but certainly not be limited to:

- How to increase awareness and address hidden barriers and biases in life sciences
- How to motivate early-career scientists to seek out mentors and resources
- How to convince senior leadership to take time for coaching the next generation of leaders and support DEI initiatives
- How to create simple and impactful opportunities for mentors and mentees to connect and collaborate

6:00 Dinner Short Courses*

**Premium Pricing or separate registration required. See Short Courses page for details.*

8:30 Close of Day

THURSDAY, OCTOBER 3

7:30 am Registration Open and Morning Coffee

INSIGHTS FROM VENTURE CAPITALISTS

8:00 PANEL DISCUSSION: Trends in Drug Discovery

Moderator: Daniel A. Erlanson, PhD, Chief Innovation Officer, Innovation and Discovery, Frontier Medicines Corporation

Panelists:

Jernej Godec, PhD, Principal, Atlas Venture

Jenna Hebert, PhD, Senior Associate, RA Capital Management

Jamie Kasuboski, PhD, Partner, Luma Group

Jasmina Marjanovic, PhD, Partner, Takeda Ventures

Swetha Murali, PhD, Vice President, OMX Ventures

EXPLORING NOVEL MOLECULAR GLUES

8:45 Chairperson's Remarks

Yong Cang, PhD, Professor, ShanghaiTech University; Co-Founder & CSO, Degron Therapeutics

8:50 Non-Degrading Molecular Glues—A Novel Platform for Unlocking the Undruggable Genome

Rick Ewing, PhD, Vice President and Head of Chemistry, Rapafusyn Pharmaceuticals

Non-degrading Type I molecular glues, FK506, Cyclosporin, and Rapamycin, have delivered marketed therapies. The complex structures of these molecules have limited application to only a limited number of protein targets. The presentation will describe construction of DEL and array libraries of non-degrading molecular glues used for finding chemical starting points for a wide range of intracellular targets. Concepts of topological diversity, cell permeability, and molecular glue characterization will be described.

9:20 NST-628 Is a Novel, Potent, Fully Brain-Penetrant MAPK Pathway Molecular Glue That Inhibits RAS- and RAF-Driven Cancers

Klaus Hoeflich, PhD, CSO, Nested Therapeutics Inc.

Although targeting the RAS-MAPK has been the heartland of cancer research, high unmet clinical need remains. NST-628 is a molecular glue acting as an induced stabilizer of key nodes in the RAS-MAPK pathway. With its differentiated mechanism and superior drug-like properties, NST-628 has the potential to provide transformative clinical benefit as both monotherapy and vertical combination anchor for RAS-MAPK-driven cancers.

9:50 Degrading the RNA Binding Protein HuR to Treat BRAF Mutant Cancer

Yong Cang, PhD, Professor, ShanghaiTech University; Co-Founder & CSO, Degron Therapeutics

Human Antigen R (HuR), encoding by ELAVL1, binds and stabilizes mRNAs encoding oncogenic drivers and proinflammatory cytokines. Using our GlueXplorer discovery platform, we have identified novel CRBN-based molecular glue degraders of HuR, a previously undruggable target, and determined BRAF mRNA as one of its major direct targets in cancer cells. A preclinical candidate has been selected for development, and this first-in-class program is moving to clinical testing.

10:20 In-Person Breakouts

In-Person Breakouts are informal, moderated discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator who keeps the discussion on track and the group engaged. To get the most out of this format, please come prepared to share examples from your work, be a part of a collective, problem-solving session, and participate in active idea sharing. Please visit the Breakouts page on the conference website for a complete listing of topics and descriptions.

IN-PERSON BREAKOUT: Novel Modalities, E3 Ligases and Ligands for Induced Proximity

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

Rick Ewing, PhD, Vice President and Head of Chemistry, Rapafusyn Pharmaceuticals

IN-PERSON BREAKOUT: Discovery and Optimization of Molecular Glues

Yong Cang, PhD, Professor, ShanghaiTech University; Co-Founder & CSO, Degron Therapeutics

Susanta Samajdar, PhD, CSO, Aurigene Discovery Technologies Ltd.

11:05 Coffee Break in the Exhibit Hall with Poster Viewing and Best of Show Awards Announced

11:45 Efficacy of a First-in-Class Polymerase Theta Degrader in Preclinical Cancer Models

Susanta Samajdar, PhD, CSO, Aurigene Discovery Technologies Ltd.

Targeting PolΘ through degradation (glue or PROTAC) may provide the opportunity to ablate PolΘ entirely, which mimics the biological consequences of a PolΘ genetic knockout. We shall present *in vitro* and *in vivo* data of our first-in-class degrader of PolΘ for the first time.

12:15 pm A Molecular Glue Degrader of the WIZ Transcription Factor for Fetal Hemoglobin Induction

Pamela Ting, PhD, Associate Director, Hematology, Novartis Institutes for BioMedical Research

Sickle cell disease affects millions of people worldwide, disproportionately in resource-limited regions. The development of a widely-accessible, oral fetal hemoglobin (HbF) inducer has long been a goal. Here we leveraged a chemical library of CRBN-biased molecular glues to explore HbF reactivation. Phenotypic screening identified the transcription factor WIZ as a previously unrecognized repressor of HbF. Chemical optimization generated potent WIZ degraders, which were well-tolerated and induced HbF in preclinical models.

12:45 Sponsored Presentation *(Opportunity Available)*

1:15 Transition to Lunch

1:20 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:50 Dessert Break in the Exhibit Hall with Last Chance for Poster Viewing

DEGRADING TRANSCRIPTION FACTORS

2:30 Chairperson's Remarks

Kristy Stengel, PhD, Assistant Professor, Department of Cell Biology, Albert Einstein College of Medicine

2:35 Targeted Transcription Factor Degradation Reveals Therapeutic Vulnerabilities and Mechanisms of Regulation

Kristy Stengel, PhD, Assistant Professor, Department of Cell Biology, Albert Einstein College of Medicine

Transcription factors (TFs) are among the most frequently mutated and/or translocated genes in cancer, suggesting that a detailed understanding of their mechanism-of-action could better define disease etiology and help identify novel nodes for therapeutic intervention. Recently, our lab has employed novel degron technologies to rapidly degrade TF proteins. This technology, when combined with nascent transcript sequencing and multiomic readouts, allows us to identify direct mechanisms of TF action.

3:05 Discovery of Highly Potent, Selective, and Efficacious STAT3 PROTAC Degraders Capable of Achieving Long-Lasting Tumor Regression

Haibin Zhou, PhD, Associate Research Scientist, Laboratory of Dr. Shaomeng Wang, Department of Hematology & Oncology, University of Michigan

STAT3 is a transcription factor and a promising therapeutic target for cancer and other human diseases. We have discovered a highly potent, selective, and efficacious STAT3 degrader UM-STAT3-1218. UM-STAT3-1218 is a highly promising STAT3 degrader for the treatment of human cancers and other human diseases in which STAT3 plays a key role.

3:35 Novel Heterobifunctional Modalities for Targeted Protein Degradation and Stabilization

H. Ümit Kaniskan, PhD, Associate Professor, Laboratory of Dr. Jian Jin, Department of Pharmacological Sciences, Icahn School of Medicine at Mt. Sinai

The Jian Jin Laboratory at Icahn School of Medicine at Mount Sinai is a leader in discovering novel degraders targeting oncogenic proteins and developing new technologies for advancing targeted protein degradation and stabilization. Our lab's recent progress will be presented featuring our latest studies such as Methyl-PROTAC, Z-PROTAC, and more.

4:05 Degradation of Nuclear Receptors for Oncology: AR Degrader HP518 and ER Degrader HP568

Wu Du, PhD, Senior Vice President, Department of Medicinal Chemistry, Hinova Pharmaceuticals, Inc.

Hinova discovered highly potent and orally available AR degrader HP518 and ER-targeting degrader HP568. HP518 demonstrated an excellent preclinical profile and is currently in Phase I/II clinical trial. Thus far, HP518 has showed a satisfactory safety profile and encouraging efficacy signals in heavily pretreated prostate cancer patients. HP568 showed oral PK and preclinical efficacy superior to current leading AR degraders. Both compounds are promising best-in-class AR and ER degraders.

4:35 Close of Conference

TUESDAY, OCTOBER 1

7:00 am Registration Open and Morning Coffee

DNA-ENCODED LIBRARY INNOVATIONS

7:55 Welcome Remarks

8:00 Chairperson's Remarks
Rachael Jetson, PhD, Senior Director, Lead Discovery, Valo Health

8:05 First-in-Class PiK3 Inhibitor from DEL Selection
Ching-Hsuan Tsai, PhD, Director, Discovery Technologies, Relay Therapeutics, Inc.
Treatments for PIK3CA-mutant cancers are limited by toxicities associated with the inhibition of WT PI3Ka. I will describe how Relay Therapeutics integrates our Dynamo Platform with DEL screening to identify mutant-selective chemical starting points. From these starting points came the development of RLY-2608, a first-in-class inhibitor demonstrating mutant selectivity in patients.

8:35 The Role of on-DNA Hit Confirmation in DNA-Encoded Library Screening
Karanbir Pahil, PhD, Investigator, Affinity Selections & Biophysics, GlaxoSmithKline
DNA-encoded libraries enable us to identify thousands of hits from screens using billions of molecules, producing a vast array of potential chemical matter that needs to be triaged efficiently. Here, we show how we leverage the facility of resynthesizing screening hits on-DNA to enable biophysical follow-up. Ultimately, this enables us to make decisions on chemistry resource investments, including synthesis of compounds that may not have been obvious during data analysis.

9:05 Phenotypic DEL in Droplets for TPD and Beyond
Ken Yamada, PhD, Associate Director, Global Discovery Chemistry, Novartis BioMedical Research
This talk will describe microfluidics-enabled cellular phenotypic DEL workflow—MicDrop. We will introduce molecular glue degrader concept with an example and its potential implications, how we overcame the challenges to perform cellular DEL screen in droplets, followed by results from a cellular protein degradation screen with a validation library. Our results show how this new paradigm of DEL screen can accelerate the field of molecular glue discovery, and beyond.

9:35 Networking Coffee Break

PPI LEAD GENERATION CASE STUDIES

10:05 FEATURED PRESENTATION: High-Dimensional Biology and AI/ML to Accelerate Lead Identification and Optimization
Samantha J. Allen, PhD, Scientific Director, High Dimensional Biology & Cellular Pharmacology, Janssen R&D LLC
High-dimensional approaches and AI/ML hold great promise in drug discovery from target identification to candidate selection. At Johnson & Johnson we've built capabilities to drive a data paradigm shift and accelerate small molecule discovery through the large-scale generation and integration of unbiased high-dimensional data with AI/ML. In this presentation I'll describe our platform along with portfolio applications from lead identification to lead optimization.

10:35 New Leads against HIV Targets: Invention of the HIV-1 Maturation Inhibitor VH3739937 (VH-937)
Alicia Regueiro-Ren, PhD, Scientific Senior Director, Medicinal Chemistry, Bristol Myers Squibb Co.
GSK-3532795/BMS-955176, an inhibitor of HIV-1 maturation was an effective antiviral agent in HIV-1 infected substrates including those with the preexisting polymorphisms that hadn't responded to the first-generation maturation inhibitor (MI) bevirimat. An optimization campaign identified GSK3640254 and VH3739937 (VH-937) as MIs with enhanced antiviral and safety profiles. Both compounds demonstrated efficacy in the clinic, GSK3640254 as a QD oral agent and VH-937 as an agent with potential for infrequent dosing.

11:05 Case-Studies of Delivering First-in-Class Targets with DEL
Timothy L. Foley, PhD, Senior Principal Scientist & Lab Head, DNA Encoded Library Selection & Pharmacology, Pfizer Global R&D Groton Labs
Identifying small molecule ligands to unprecedented targets is a significant hurdle in drug discovery. DNA-encoded library (DEL) technology is an important component of our Hit ID toolbox. Through a series of case-studies I will discuss lessons learned in the use of DEL to discover hits for emerging targets that represented first-in-class opportunities within our global portfolio.

11:35 Talk Title to be Announced
Fangchao Liu, , HitGen Inc.

12:05 pm Transition to Lunch

12:10 LUNCHEON PRESENTATION: Recent Trends, Limitations, and New Opportunities in Covalent Drug Discovery
Daniel St-Cyr, Associate Principal Scientist, X-Chem, Inc.
As demonstrated by the approval of more than 30 covalent drugs, the growth in covalent drug discovery has changed the pharmaceutical landscape. We can now target a wider variety of amino acid residues with an ever-increasing diversity of warheads. From an analysis of recent covalent patents, the focus on KRAS, EGFR, BTK, and FGFR with acrylamide warheads is evident. GSH half-life to gauge intrinsic reactivity remains popular, but a clear consensus on the exact boundary between desirable and excessive reactivity is missing. There are also debates on whether traditional methods to describe covalent inhibitor potency are valid, which time-independent constants are most useful, and whether reversible complex formation or reactivity rate determine efficacy. This field is rapidly evolving with new warheads, new mechanistic and kinetic understanding, and novel opportunities. This presentation will focus on recent trends in the covalent patent literature, expanded DEL covalent libraries that incorporate recently validated warheads, and improved methods to assess nonspecific warhead reactivity.

12:40 Session Break

BIOPHYSICAL TOOLS AND FRAGMENT-BASED APPROACHES FOR HIT-FINDING

1:15 Chairperson's Remarks
Daniel A. Erlanson, PhD, Chief Innovation Officer, Innovation and Discovery, Frontier Medicines Corporation

1:20 Beyond Isotopic Labeling: Measuring Small Molecule Affinities to Proteins Using 1D-Diffusion Filtered NMR
Thomas E. Frederick, PhD, Senior Scientist II, Biophysics & Fragment Screening, Abbvie

Protein-detect NMR is widely used in lead discovery campaigns for measuring small molecule interactions with proteins and provides a robust measure of weak affinities. This approach generally requires isotopic labeling. Here, I will discuss an approach for measuring affinities of small molecule ligands to unlabeled proteins that uses a 1D-diffusion filter and ECHOS analysis. This enables protein-detect NMR as a method to characterize ligand-protein interactions for most protein targets.

1:50 Fab-Induced Stabilization of an Ion Channel Enables Biosensor-Based Mechanistic Characterization for Early Development of Small Molecule Therapeutics

Soo Ro, PhD, Senior Scientist I, Biophysics, Genentech Inc.

SPR characterization of interactions between small molecule (SM) therapeutics and membrane proteins is extremely challenging, due to loss of protein activity on the sensing surface and signal interference from detergent micelles. Here, we report SPR characterization of interactions between SMs and an ion channel stabilized in complex with antigen-binding fragments in conditions with low micelle interference, progressing SM therapeutic development of an ion channel target.

2:20 Chemoproteomic Discovery of Covalent Binders to Undruggable Targets in Living Cells

Nan Chen, CEO, ChomiX Biotech Co., Ltd.

In this presentation, I will describe our self-designed automated chemical proteomic workstation. Utilizing a meticulously crafted cysteine-targeted covalent library, we aim to leverage ChomiX's automated platform for the identification of specific binders to a series of undruggable targets, such membrane proteins and E3 ligases within living cells.

2:35 Sponsored Opportunity

2:50 In-Person Breakouts

In-Person Breakouts are informal, moderated discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator who keeps the discussion on track and the group engaged. To get the most out of this format, please come prepared to share examples from your work, be a part of a collective, problem-solving session, and participate in active idea sharing. Please visit the Breakouts page on the conference website for a complete listing of topics and descriptions.

IN-PERSON BREAKOUT: Affinity Selection-Mass Spectrometry (AS-MS) for *de novo* Hit Generation and DEL Hit Verification

Allen Annis, PhD, Independent Consultant, former SVP Research, Aileron Therapeutics

Hans-Peter N. Biemann, PhD, Distinguished Scientist, Integrated Drug Discovery, Sanofi

- AS-MS and DEL as synergistic tools for hit generation and verification of on- and off-DNA hit structures
- Where does AS-MS fit in the HTS toolbox vs. DEL and other biophysical/biochemical screening technologies?
- How do we access AS-MS for hit-finding and verification? Outsourcing options vs. in-house platform development

IN-PERSON BREAKOUT: Hit Validation Strategies

Mitchell H. Keylor, PhD, Associate Principal Scientist, Merck

- Eliminating false positives
- Data analysis formats
- Binding methods: How important is it? Favorite biophysical tools?

3:35 Grand Opening Refreshment Break in the Exhibit Hall with Poster Viewing and Best of Show Voting Begins

4:35 FEATURED PRESENTATION: Covalent Fragments

Kate Carroll, PhD, Associate Professor, Chemistry, Florida Atlantic University

Chemoproteomics reveals a vast expanse of ligandable cysteine sulfenic acids in the human proteome highlighting the utility of small molecules in the fragment-based, covalent-based ligand discovery pipeline.

5:05 Structure-Based Approach to Screen and Characterize RNA-Targeted Small Molecules

Yaqiang Wang, PhD, Principal Scientist, Chemical Sciences & Structural Biology, Arrakis Therapeutics

RNA plays a ubiquitous role in every facet of the cell life cycle, and its dysregulation frequently underlies various diseases. Arrakis's mission is to solve very broadly the problem of how to drug RNA with small molecules. This presentation covers RNA structure identification, screening, and hit characterization. We utilize an integrative structural biology approach to decipher RNA/ligand interactions and accelerate ligand optimization.

5:35 High-Throughput Crystallography and Structure-Based Design for CDK7

Manjeet Mukherjee, PhD, Senior Research Associate, Astex Pharmaceuticals, Ltd.

I will highlight how we enabled a structural system for cancer target CDK7 to perform structure-based drug design. I will show examples of liganded complexes with clinical stage compounds in both covalent and non-covalent modalities and discuss how that impacted our drug lead design.

6:05 Welcome Reception in the Exhibit Hall with Poster Viewing

7:05 Close of Day

WEDNESDAY, OCTOBER 2

7:30 am Registration Open and Morning Coffee

SMALL MOLECULE REGULATORS OF MEMBRANE PROTEINS

7:55 Chairperson's Remarks

Samantha J. Allen, PhD, Scientific Director, High Dimensional Biology & Cellular Pharmacology, Janssen R&D LLC

8:00 Discovery and Characterization of JNT-517, an Inhibitor of SLC6A19 for the Treatment of Phenylketonuria

Dean G. Brown, PhD, Vice President & Head, Chemistry, Jnana Therapeutics

The discovery efforts using our RAPID (Reactive Affinity Probe Interaction Discovery) chemoproteomics platform will be described that led to small molecules that inhibited transporter SLC6A19 and demonstrated *in vivo* activity in the Pahenu2 model. This work led to the identification of JNT-517, a potential first-in-class clinical candidate for the treatment of phenylketonuria which has demonstrated positive POC in a Ph1b clinical trial.

8:30 Optimization of Allosteric Regulators of the NaV1.7 Sodium Channel for Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Se In Son, PhD, Research Scientist, Chemistry, NIH NCATS

NCATS and Regulonix developed NaV1.7 channel regulators by targeting CRMP2 sumoylation, which is an allosteric regulator of the channel. Regulonix discovered that surface expression of the channels can be decreased due to loss of CRMP2 sumoylation. Through virtual screening and hit search, lead compound AZ194 was discovered. The NCATS team expanded the library of inhibitors from AZ194 to more than 450 analogs, with novel structures, improved potency, and ADME properties.

9:00 TREM2 Molecular Glues to Treat Neurodegenerative Diseases

Bhaumik A. Pandya, PhD, Director, Chemistry Vigil Neuroscience

Triggering receptor expressed in myeloid cells 2 (TREM2) is a lipid-sensing receptor that promotes the growth, migration, and anti-inflammatory effects of microglia that are upregulated within pathological microenvironments. Loss-of-function TREM2 variants impose genetic risk for Alzheimer's disease (AD). Herein we highlight the activity and profile of Vigil's first-in-class small molecule TREM2 agonists for treatment of neurodegenerative diseases.

9:30 Using High-Content Imaging to Drive Small Molecule Protein Degraders from Hit to Lead

Clark Driscoll, Sr. Research Scientist , Curia

Using High-Content Imaging to Drive Small Molecule Protein Degraders from Hit to Lead: While PROTACs and targeted degrader programs have proven to be successful, small molecule degrader screening remains a viable approach when coupled with a well-developed screening platform. In this case study we describe the development of a high content screening and lead optimization platform for small molecule degraders. By front-loading data across multiple targets, this approach accelerated the discovery pipeline and enabled classification of compounds with unique phenotypic profiles.

10:00 Coffee Break in the Exhibit Hall with Poster Viewing

PLENARY KEYNOTE PROGRAM

10:50 Plenary Keynote Chairperson's Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target, Cambridge Healthtech Institute

10:55 PLENARY KEYNOTE: Discovery of Transformative Rx to Treat Obesity and Related Diseases

Richard DiMarchi, PhD, Distinguished Professor of Chemistry and Chair, Biomolecular Sciences, Indiana University; former Executive, Lilly and Novo Research Labs

To address obesity, a medicinal challenge that warrants broad molecular diversity, we pioneered the pharmacological strategy of recruiting endogenous hormones to optimize physiological mechanisms. Our discovery of single-molecule, multi-mechanism incretins enabled breakthrough efficacy in lowering body weight. The integrated pharmacology of these endocrine proteins and nuclear hormones is providing a library of drug candidates that promises great clinical outcomes for obesity and associated diseases that have historically been intractable.

11:40 PLENARY KEYNOTE: Fragment-Based Drug Discovery for Elusive Cancer Targets

Stephen W. Fesik, PhD, Professor of Biochemistry, Pharmacology & Chemistry; Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University

The most highly validated cancer targets (KRAS, MYC, and WNT) affecting the majority of cancers are thought to be impossible to drug. Using fragment-based methods that I pioneered over 25 years ago, we have discovered mutant selective and pan KRAS inhibitors, potent inhibitors of the MYC cofactor WDR5, and degraders of b-catenin in the WNT pathway. These novel inhibitors/degraders should have a tremendous impact on cancer treatment in the future.

12:25 pm Close of Lead Generation Strategies Conference

WEDNESDAY, OCTOBER 2

PLENARY KEYNOTE PROGRAM

10:50 am Plenary Keynote Chairperson's Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target, Cambridge Healthtech Institute

10:55 PLENARY KEYNOTE: Discovery of Transformative Rx to Treat Obesity and Related Diseases

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12:25 pm Enjoy Lunch on Your Own

PROTEOMICS-DRIVEN TARGET DECONVOLUTION

1:45 Welcome Remarks

1:50 Chairperson's Remarks

Christopher am Ende, PhD, Associate Research Fellow, Internal Medicine Medicinal Chemistry, Pfizer Inc.

1:55 Developing and Applying a Novel Chemoproteomics Platform for Transcription Factor Drug Discovery

Sherry Niessen, PhD, Vice President, Proteomics, Belharra Therapeutics

applying a novel chemistry enabled non-covalent probe library and quantitative mass spectrometry to identify chemical probes that selectively bind any pocket, on any protein, in live cells. The platform is identifying chemical probes that selectively engage diverse protein classes. Most proteins identified by our probe library do not have a reported ligand in drug bank demonstrating the ability of the platform to identify novel pockets and starting points for probes.

2:25 FEATURED PRESENTATION: Combining Sample Multiplexing and Targeted Proteomics to Screen Electrophilic Fragment Libraries

Steve Gygi, PhD, Professor, Department of Cell Biology, Harvard Medical School

Covalent modification of cysteines by libraries of fragment electrophiles can be assessed proteome-wide using chemoproteomics techniques. In this talk, I will present the CysDig strategy which exploits the direct targeting of a few hundred cysteines for quantification. Importantly, this approach is flexible such that biotin enrichment is optional and the protein's expression levels can also be assessed. An example targeted library screen for E3 ligase binders identified a Huwe1 inhibitor.

2:55 Sponsored Presentation *(Opportunity Available)*

3:25 Refreshment Break in the Exhibit Hall with Poster Viewing

4:15 Advancing Chemical Biology through Innovative Chemistry

Christopher am Ende, PhD, Associate Research Fellow, Internal Medicine Medicinal Chemistry, Pfizer Inc.

This presentation explores new reactive moieties for protein labeling through a series of vignettes. It focuses on the mechanistic analysis and proteome-wide labeling capabilities of cyclobutyl diazirine probes and the large-scale proteomic analysis of diazirine photoaffinity probes—as well as the broad utility of tetrazines as bioorthogonal handles, in addition to protein labeling applications.

4:45 Systematic Identification of Condensate Targets and Development of Condensate-Modifying Drugs (c-mods) across Therapeutic Areas

Ann Boija, PhD, Vice President, Head of Cancer Biology, Dewpoint Therapeutics

Condensates regulate cellular processes by concentrating and organizing biomolecules within communities with distinct microenvironments. Condensate aberrations serve as central nodes of dysfunction in many diseases. Viewing condensates as drug targets opens untapped opportunities to influence high value, "undruggable" drug targets. Our AI-powered discovery platform supports identification of condensate-drivers of diseases, development of disease-faithful models, and discovery & development of c-mods, fueling programs across multiple therapeutic areas, including oncology and neurodegeneration.

5:15 Dinner Short Course Registration*

**Premium Pricing or separate registration required. See Short Courses page for details.*

5:15 Diversity Discussion *(Sponsorship Opportunity Available)*

IN-PERSON DISCUSSION: Fostering Diversity through Mentoring

Naytia Byrd, Manager, Human Resources, Ovid Therapeutics, Inc.
Saudat Fadeyi, PhD, MBA, Director, Business Development, Ovid Therapeutics, Inc.
Fred Manby, DPhil, Co-Founder & CTO, Iambic Therapeutics
Joel Omage, Research Scientist II, CVM Disease Area, Novartis Institutes for BioMedical Research, Inc.
Andrew Zhang, PhD, Director, Chemical Biology, AstraZeneca

Topics for discussion will include, but certainly not be limited to:

- How to increase awareness and address hidden barriers and biases in life sciences
- How to motivate early-career scientists to seek out mentors and resources
- How to convince senior leadership to take time for coaching the next generation of leaders and support DEI initiatives

• How to create simple and impactful opportunities for mentors and mentees to connect and collaborate

6:00 Dinner Short Courses*

**Premium Pricing or separate registration required. See Short Courses page for details.*

8:30 Close of Day

THURSDAY, OCTOBER 3

7:30 am Registration Open and Morning Coffee

INSIGHTS FROM VENTURE CAPITALISTS

8:00 PANEL DISCUSSION: Trends in Drug Discovery

Moderator: Daniel A. Erlanson, PhD, Chief Innovation Officer, Innovation and Discovery, Frontier Medicines Corporation
Panelists:
Jernej Godec, PhD, Principal, Atlas Venture
Jenna Hebert, PhD, Senior Associate, RA Capital Management
Jamie Kasuboski, PhD, Partner, Luma Group
Jasmina Marjanovic, PhD, Partner, Takeda Ventures
Swetha Murali, PhD, Vice President, OMX Ventures

FUNCTIONAL SCREENING FOR TARGET ID

8:45 Chairperson's Remarks

Sujatha Gopalakrishnan, Director, Research Fellow, Head of HTS & Molecular Characterization, AbbVie

8:50 Uncovering Potential Anti-Coronavirus Agents: Phenotypic Screening and Target Identification of Compounds Targeting Nucleocapsid N Protein

Sujatha Gopalakrishnan, Director, Research Fellow, Head of HTS & Molecular Characterization, AbbVie

The urgent need for effective therapeutics against coronaviruses has prompted the development of innovative drug discovery approaches. In this study, we established a robust high-content screening platform to identify small molecules capable of modulating the condensation of the SARS-CoV-2 Nucleocapsid (N) protein. Our promising results demonstrate that perturbing viral condensate dynamics can generate effective antiviral drugs for multiple viral species, including SARS-CoV-2.

9:20 QUANTROseq: A Transcriptomic Platform Matching Drugs to Their Targets

Arianna Sabo, PhD, Head, Research & Discovery, Quantro Therapeutics GmbH

QUANTRO developed QUANTROseq, an innovative platform able to map small molecules to their targets by matching transcriptional fingerprints produced by drug candidates with the ones obtained by controlled acute degradation of the target-of-interest. Using this technology at-scale, QUANTRO demonstrated that time-resolved transcriptional profiling reveals drugs´ mode-of-action with unprecedent precision and sensitivity and enables discovery of NCE against previously undruggable targets.

9:50 Toward a Universal Toolbox of Valuable Building Blocks for Chemical Biology Probe Synthesis

David Lapinsky, PhD, Associate Professor, Medicinal Chemistry, Duquesne University School of Pharmacy and Graduate School of Pharmaceutical Sciences

Clickable covalent compounds are some of the most valuable small-molecules one could pursue, given their numerous applications. However, merging a ligand/protein-recognition element, a protein-reactive functional group, and a bioorthogonal chemistry reporter group into a single chemical probe is non-trivial. This talk will highlight some of our work toward a universal toolbox of valuable building blocks researchers can use to synthesize clickable covalent probes for chemical biology-mediated drug discovery and development.

10:20 In-Person Breakouts

In-Person Breakouts are informal, moderated discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator who keeps the discussion on track and the group engaged. To get the most out of this format, please come prepared to share examples from your work, be a part of a collective, problem-solving session, and participate in active idea sharing. Please visit the Breakouts page on the conference website for a complete listing of topics and descriptions.

IN-PERSON BREAKOUT: Leveraging Covalent Chemistries, Phenotypic Screening, Chemoproteomics Tools

Alexander Federation, PhD, Co-Founder & CEO, Talus Bioscience
Denise Field, PhD, Senior Principal Scientist, Chemical Biology and Proteomics, Pfizer
Andrew Zhang, PhD, Director, Chemical Biology, AstraZeneca

11:05 Coffee Break in the Exhibit Hall with Poster Viewing and Best of Show Awards Announced

11:45 Utilizing CRISPR-Suppressor Scanning to Functionally Map Chromatin Complexes

Hui Si Kwok, PhD, Postdoctoral Fellow, Laboratory of Dr. Brian Liau, Department of Chemistry and Chemical Biology, Harvard University

Genes encoding chromatin proteins are among the top mutated cancer genes. Interpreting the functional significance for every cancer mutation remains a major obstacle for advancing cancer research. Using Polycomb repressive complex 2 (PRC2) as a case study, I will showcase the utility of pooled tiling base-editing screens to define regulatory regions and understand the functional significance of cancer-associated mutations in their endogenous context.

12:00 pm Systems-Wide Approaches for Mapping Substrates to E3 Ligases

Elijah Mena, PhD, Post-Doctoral Researcher, Laboratory of Dr. Stephen Elledge, Department of Genetics, Harvard University Medical School

The complexity of the ubiquitin-proteasome system makes it challenging to systematically pair proteasomal substrates to their cognate E3 ubiquitin ligases. We have developed new technologies that are able to identify ubiquitin-proteasome targets on a genome-wide scale and can pair these substrates to E3s using multiplex CRISPR screening. Additionally, saturating mutagenesis and computational approaches allow us to define the molecular basis for many degradative pathways at scale.

12:15 Application of High-Density CRISPR Screens for Mutational Scanning of Endogenous Elements

Ganna Reint, PhD, Postdoctoral Fellow, Broad Institute of Harvard and MIT

Assessment of the functional effects of DNA sequence variation is crucial for an understanding of the genetic basis of human disease. We applied the newest versions of base editors, coupled with the PAM-flexible Cas9, for high-throughput interrogation of genetic variation at endogenous loci. High-

coverage tiling enabled mapping of the functional regions in the proteins and discovering potential gain-of-function mutations across a panel of genes with strong cancer dependencies.

12:30 Continuous Evolution of Compact Protein Degradation Tags Regulated by Selective Molecular Glues

Stephan John DeCarlo, PhD Student, Laboratory of David Liu, Harvard University

Shourya Roy Burman, PhD, Scientist, Cancer Biology, Dana-Farber Cancer Institute

Conditional degron tags are >100 amino acids long or are triggered by compounds with off-target effects, thwarting their use as specific modulators of endogenous protein levels. We evolved a 36-amino acid degron, SD40, that binds cereblon in complex with an otherwise inert compound, PT-179. Endogenous proteins tagged in-frame with SD40 using prime editing are degraded by PT-179. Cryo-EM structures of SD40 in complex with ligand-bound cereblon reveal molecular basis of SD40's activity.

12:45 Sponsored Presentation *(Opportunity Available)*

1:15 Transition to Lunch

1:20 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:50 Dessert Break in the Exhibit Hall with Last Chance for Poster Viewing

AI-DRIVEN TARGET DISCOVERY

2:30 Chairperson's Remarks

Harpreet Saini, PhD, Senior Director, Informatics, Astex Pharmaceuticals Ltd.

2:35 Integrative Computational Genetics Approach for Target Discovery of ALS

Harpreet Saini, PhD, Senior Director, Informatics, Astex Pharmaceuticals Ltd.

We have developed a computational, genetics-based approach which integrates functional data from GWAS, ontologies, and biological networks to predict potential drug targets with evidence for disease association. We obtained a list of target genes associated with ALS and prioritized potential target genes by integrating structural information and cell-type transcriptomics data.

3:05 FEATURED PRESENTATION: Target Discovery Using AI—The Story behind Insilico Medicine's Discovery and Validation of MYT1 as a Target Implicated in Breast Cancer

Petrina Kamya, PhD, Global Head of AI Platforms, Vice President Insilico Medicine; President, Insilico Medicine Canada, Insilico

Using PandaOmics, we identified MYT1 as a promising new therapeutic target for breast and gynecological cancer. PandaOmics is Insilico Medicine's AI-driven target discovery platform that leverages multi-modal data to discover targets implicated in a disease. To further validate the selection of MYT1, we leveraged Chemistry42 to design and optimize a lead compound that exhibits remarkable selectivity over WEE1 and has promising *in vivo* antitumor efficacy.

3:35 Interaction-Based Hit Discovery Platform to Orphan Targets

Dmitri Kireev, PhD, Professor, Department of Chemistry, University of Missouri

Interaction-based screening and design are promising novel strategies for hit finding and lead optimization. The key information unit in the interaction realm is a thin interface between the interacting ligand and protein. When fed to deep neural networks, interaction signatures may infer SAR for unliganded proteins by exploiting structural data across ligands and proteins. We give an overview of the approach and describe its successful applications to several challenging targets.

4:05 Assessment of Target Druggability Enabled by Machine Learning

Diane M. Joseph-McCarthy, PhD, Professor of the Practice, Biomedical Engineering, Boston University

Identification of hot spots on the surface of macromolecules is key to evaluating the druggability of novel targets and the likelihood of finding new chemical entities. Computational hot-spot mapping was performed across a set of drug targets, and a machine learning approach was employed to select the top druggable sites. Within this context, the utility of AI-generated protein models obtained using AlphaFold, including ensembles of structural models, was assessed.

4:35 Close of Conference

TUESDAY, OCTOBER 1

7:00 am Registration Open and Morning Coffee

COVALENT OR DEGRADER APPROACHES FOR RAS OR WRN

7:55 Welcome Remarks

8:00 Chairperson's Remarks

Mellissa Nixon, PhD, Senior Scientist, Merck Research Labs

8:05 Discovery of FMC-376 a Potent Dual Inhibitor of 'ON' and 'OFF' States of KRASG12C Broadly Active in PDX Models of Resistance

Snahel Patel, Vice President, Head, Medicinal & Platform Chemistry, Frontier Medicines Corp.

Once viewed undruggable, frequently mutated oncogene KRAS has led to the recent approval of two $KRAS^{G12C}$ small molecule covalent inhibitors targeting the inactive GDP-bound (OFF) state. Patient benefit has fallen short with these first-generation inhibitors due to innate or acquired resistance driven by upregulation of the activated GTP-bound (ON) state of $KRAS^{G12C}$. We present the discovery of potent dual inhibitor FMC-376 targeting both active and inactive forms of $KRAS^{G12C}$.

8:35 Tyrosine-Targeted Covalent Fragments for KRAS

Samy O. Meroueh, PhD, Professor, Biochemistry, Member of Cancer Center Drug Discovery Program, University of Illinois Urbana-Champaign

I present my Ras GTPases (mainly Ral and KRAS) work where I used fragment-screening to develop covalent inhibitors that react with tyrosines. A tyrosine-based covalent approach expands the number of KRAS-origin cancers that can be targeted because only 10% of KRAS genes have the G12C mutation. I also discuss our progress with covalent inhibition of Ral GPTase using tyrosine and will present a unique KRAS structure that I recently published.

9:05 FEATURED PRESENTATION: Identification of VVD-214/RO7589831, a Clinical-Stage, Covalent Allosteric Inhibitor of WRN Helicase for the Treatment of MSI-High Cancers

Shota Kikuchi, PhD, Director, Chemistry, Vividion Therapeutics

WRN helicase is a promising target for treating cancers with microsatellite instability (MSI), due to its essential role in resolving deleterious non-canonical DNA structures that accumulate in cells with faulty mismatch repair mechanisms. Here we describe the medicinal chemistry optimization of potency, ADME, and PK properties of chemoproteomic screening hits, which resulted in identification of VVD-214/RO7589831 (Vividion/Roche), a clinical-stage, covalent allosteric inhibitor of WRN.

9:35 Networking Coffee Break

PROTEIN-STABILIZING STRATEGIES FOR CANCER

10:05 Rational Discovery of a Small Molecule Intramolecular Glue Inhibitor of CBL-B that Enhances T-cell Function

Stefan Gajewski, PhD, Structural Biologist, Early Drug Discovery, Nurix Therapeutics Inc

Casitas B lymphoma-b (CBL-B) is a RING-type E3 ubiquitin ligase that plays an important role in regulating T cell function. Loss of CBL-B is associated with enhanced T and NK cell activity which makes it an interesting target for immuno-oncology drug development. We present a rational approach to discover and optimize small molecule inhibitors for CBL-B that elicit a potent T cell activation and antitumor activity.

10:35 Inhibiting CBL-B: An E3 Ligase Immuno-Oncology Target

Michael Lambrecht, PhD, Principal Scientist, Drug Discovery, Genentech

Knockout of the ubiquitin ligase cbl-b causes tumor rejection in murine models and represents a promising target for cancer immunotherapy. We screened a DNA-encoded library and discovered a xanthene-containing lead molecule that bound to and inhibited cbl-b. An x-ray co-crystal structure showed this lead molecule bound to the SH2 domain of cbl-b. Here we describe these studies and a medicinal chemistry campaign that provided an inhibitor with measurable cell activity.

11:05 Accelerating Inhibitor Discovery for Deubiquitinating Enzymes

Wai Cheung Adrian Chan, PhD, Principal Scientist, Enabling Sciences, Odyssey Therapeutics

Deubiquitinating enzymes (DUBs) are a class of ~100 cysteine proteases, of interest as emerging drug targets and for application in targeted protein stabilization. Pairing a bespoke library with activity-based protein profiling as a high-density primary screen, we identify and validate a multitude of promising chemical starting points and a direct path to tool compounds that can be used to decipher DUB function, substrates, and signaling pathways.

11:35 Exploring the Power of Structural Biology on Degrader Discovery BIORTUS

JIAQUAN WU, General Manager, Biortus

The emerging of protein degradation as a novel therapeutic modality has attracted interest in broad drug discovery community. Unlike conventional small molecular drug discovery, where SBDD has been widely adopted for rational design of hit and lead molecules, the application of structural biology to degrader discovery is only limited to the elucidation of the binding mode of selected lead PROTAC or molecular glue molecules so far. This is largely due to two reasons: one being the lack of robust protocols to assemble stable degradation complexes, and the other being the less than desired resolution of the complex structures solved by ether crystallography or cryoEM. At Biortus, we strive to help the community to evolve degrader discovery from experience-based design to SBDD by exploring our expertise in both protein chemistry and structural biology. We have now established robust methodologies for PROTAC and molecular glue complex structure determination using both crystallography and cryoEM, and are working towards solutions to improve resolution for SBDD.

12:05 pm Transition to Lunch

12:10 LUNCHEON PRESENTATION: Biortus's Protein Focused Discovery Services: Protein Production, Assay and Screening, Crystallography, and CryoEM BIORTUS

Larry Jin, COO, Biortus

Biortus is a global leading service provider of target protein and structural biology. Biortus implements AI-powered construct design for protein expression in *E. coli*, insect cells, mammalian cells, yeast, CFS, and silkworm systems. Accumulatively, Biortus has over 50,000 plasmids in stock, from which over 3,000 unique target proteins have been expressed and purified, with over 300 being membrane proteins. Biortus's hit finding capabilities cover biochemical, biophysical, and cellular assay and screening, with several internal fragment libraries for easy access and flexible screening schedule. Biortus's crystallography has delivered more than 7,000 xtal structures for over 600 unique targets, some of them being first-to-the-world structures. Biortus's cryoEM platform is the largest service facility so far, with 8 units of ThermoFisher electron microscopes and over 60 structural biologists working

exclusively on SPA, MicroED, and LNP/AAV characterization.
Biortus offers catalog proteins via VWR, Cayman, FisherSci, and several other partners. Biortus is a regular contributor to the PDB and EMDD database.

12:40 Session Break

DEGRADERS & CANCER

1:15 Chairperson's Remarks
Philip N. Collier, PhD, Director, Medicinal Chemistry, Kymera Therapeutics

1:20 Abbapolin PLK1 Degraders in Prostate Cancer
Campbell McInnes, PhD, Professor, Drug Discovery & Biomedical Sciences, University of South Carolina
Inhibition of PLK1 may be key to overcoming resistance to androgen blocking treatments that result in Castration Resistant Prostate Cancer (CRPC) providing new therapeutic options. Using the REPLACE strategy, we found compounds that bind tightly to PLK1 and induce its degradation. Through our hit to lead conversion studies we identified an abbapolin with potent on target cellular engagement of PLK1, good oral pharmacokinetics and antitumor efficacy in prostate xenografts.

1:50 Discovery and Development of pan-KRAS Degraders for Cancer Therapy
Murali Ramachandra, PhD, CEO, Aurigene Discovery Technologies, Ltd.
Despite recent advances in KRAS inhibitors for cancer therapy, a majority of KRAS alterations remain unaddressed. The rapid emergence of resistance where inhibitors are available underscores the need for novel approaches. We will discuss our focus on targeted protein degradation to eliminate mutant KRAS as a promising avenue for superior and durable efficacy.

2:20 Presentation to be Announced

PELAGO BIOSCIENCE

2:35 Presentation to be Announced

ICE Bioscience

3:05 In-Person Breakouts
In-Person Breakouts are informal, moderated discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator who keeps the discussion on track and the group engaged. To get the most out of this format, please come prepared to share examples from your work, be a part of a collective, problem-solving session, and participate in active idea sharing. Please visit the Breakouts page on the conference website for a complete listing of topics and descriptions.

IN-PERSON BREAKOUT: Covalent Approaches for Drug Discovery
Paul E. Gormisky, PhD, Senior Director, Enabling Sciences Chemistry, Odyssey Therapeutics
- Strategies to prioritize targets for covalent drug discovery
- Assessing if a covalent ligand or fragment for a novel target can be progressed to a drug (e.g., sufficient pocket, supportive biology)
- Role of covalency in other new modalities (degraders, macrocycles)

3:35 Grand Opening Refreshment Break in the Exhibit Hall with Poster Viewing and Best of Show Voting Begins

4:35 FEATURED PRESENTATION: Targeting the PI3K Pathway in Cancers
Anwesha Dey, PhD, Director & Distinguished Scientist, Discovery Oncology, Genentech Inc.
PIK3CA is one of the most frequently mutated oncogenes; the p110α protein it encodes plays a central role in tumor cell proliferation. Inavolisib is a potent and selective p110α inhibitor that promotes the degradation of mutated p110α. The significance of this unique mechanism to trigger specific degradation of mutant p110α without significant change in wild-type p110α protein may result in improved therapeutic index in PIK3CA-mutant tumors.

5:05 The Evolving Chemical Space of Bi-functional Degraders Targeting the CNS
Wylie S. Palmer, PhD, Senior Director, Nurix Therapeutics, Inc.
Description:Bi-functional degraders occupy beyond-rule-of-five chemical space where established rules for drug-likeness cannot easily be applied. In contrast to approved CNS drugs, bi-functional degraders violate most metrics, particularly molecular weight, yet we routinely observe brain penetrance in our programs. For example, NX-5948, a clinical stage orally bioavailable BTK degrader shows CNS exposure and activity both preclinically and clinically. This presentation will explore our evolving understanding of targeting the CNS using degraders.

5:35 IKZF2 Degrader Discovery
Kevin D. Freeman-Cook, PhD, Vice President & Head, Medicinal & Computational Chemistry, Plexium Inc.
The zinc finger transcription factor Helios (IKZF2) is highly expressed in Tregs and plays an important role in helping tumors evade a normal immune response. IKZF2 is a transcription factor that had been considered "undruggable." Here we disclose the discovery and preclinical evaluation of a selective molecular glue degrader of IKZF2 (PLX-4545) which reverses Treg suppression and is currently being evaluated in a Phase 1 trial of healthy volunteers.

6:05 Welcome Reception in the Exhibit Hall with Poster Viewing

7:05 Close of Day

WEDNESDAY, OCTOBER 2

7:30 am Registration Open and Morning Coffee

SMALL MOLECULE IMMUNO-ONCOLOGY TARGETS

7:55 Chairperson's Remarks
Jenny Chengyi Shu, PhD, Senior Director, Biology Immunology, Life Mine Therapeutics

8:00 Structure-Based Design of DHODH Inhibitors for the Treatment of Acute Myelogenous Leukemia
Justin Cisar, PhD, Principal Scientist, Medicinal Chemistry, Janssen Pharmaceuticals Inc.

8:30 Identification of a Novel Linker Enabling Bioconjugation of a Cyclic Dinucleotide for the STING Antibody-Drug Conjugate TAK-500
Hong Myung Lee, PhD, Senior Scientist, Medicinal Chemistry, Takeda Pharmaceuticals Inc.
The chemistry strategy was established to enable targeted delivery of a cyclic dinucleotide STING agonist TAK-676 to CCR2+ myeloid cells through an antibody-drug conjugate approach. A self-immolative spacer between the adenine of TAK-676 and the cleavable dipeptide linker rendered a linker payload with enhanced plasma stability. Stochastic cysteine conjugation of the linkers provided immune cell-stimulating ADC TAK-500. In mouse models, mTAK-500 showed antitumor activity driven by immune cell activation.

9:00 GPCRs of the Tumor Microenvironment as Novel Immuno-Oncology Drug Targets

Stephan Schann, PhD, CSO, Domain Therapeutics SA

Immunotherapy has revolutionized cancer treatment, including metastatic disease cures. However, many patients do not benefit from immunotherapy due to multiple resistance mechanisms. At Domain, our innovative approach focuses on precision. Our unique pipeline of GPCR targeting drug candidates targets immunosuppressive mechanisms, unlocking new therapeutic possibilities in cancer. In this presentation, we'll explore the identification of novel immunosuppressive GPCRs and small molecule drug discovery, emphasizing Domain's precision research approach.

9:30 Quantification of Small Molecule and Phosphopeptide Binding Affinity Selectivity Across Human SH2 Domains Assays

Jean Bernatchez, Sr Scientist & R&D Grp Leader, Eurofins Discovery

SH2 domains are an emerging target class for the development of small molecules which disrupt protein-protein interactions, as well as for the development of targeted protein degraders. We present screening validation data against a panel of 95 wild type and 7 mutant SH2 domain assays for a collection of reported small molecules and peptides which bind to this protein-protein interaction module.

10:00 Coffee Break in the Exhibit Hall with Poster Viewing

PLENARY KEYNOTE PROGRAM

10:50 Plenary Keynote Chairperson's Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target, Cambridge Healthtech Institute

10:55 PLENARY KEYNOTE: Discovery of Transformative Rx to Treat Obesity and Related Diseases

Richard DiMarchi, PhD, Distinguished Professor of Chemistry and Chair, Biomolecular Sciences, Indiana University; former Executive, Lilly and Novo Research Labs

To address obesity, a medicinal challenge that warrants broad molecular diversity, we pioneered the pharmacological strategy of recruiting endogenous hormones to optimize physiological mechanisms. Our discovery of single-molecule, multi-mechanism incretins enabled breakthrough efficacy in lowering body weight. The integrated pharmacology of these endocrine proteins and nuclear hormones is providing a library of drug candidates that promises great clinical outcomes for obesity and associated diseases that have historically been intractable.

11:40 PLENARY KEYNOTE: Fragment-Based Drug Discovery for Elusive Cancer Targets

Stephen W. Fesik, PhD, Professor of Biochemistry, Pharmacology & Chemistry; Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University

The most highly validated cancer targets (KRAS, MYC, and WNT) affecting the majority of cancers are thought to be impossible to drug. Using fragment-based methods that I pioneered over 25 years ago, we have discovered mutant selective and pan KRAS inhibitors, potent inhibitors of the MYC cofactor WDR5, and degraders of b-catenin in the WNT pathway. These novel inhibitors/degraders should have a tremendous impact on cancer treatment in the future.

12:25 pm Close of Small Molecules for Cancer Targets Conference

WEDNESDAY, OCTOBER 2

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12:25 pm Enjoy Lunch on Your Own

NMR, FRAGMENTS & OTHER NEW TOOLS FOR GPCR DRUG DISCOVERY

1:45 Welcome Remarks

1:50 Chairperson's Remarks

Florence Brunel, PhD, Senior Principal Scientist, Novo Nordisk Inc

1:55 New NMR Applications for Quantitative Determination of GPCR Drug Efficacy and Lead Compound Identification

Matthew T. Eddy, PhD, Assistant Professor, Chemistry, University of Florida, Gainesville

We present a new application of NMR spectroscopy to quantitatively determine GPCR drug efficacy. NMR data quantitatively correlate with results from cellular signaling assays. We highlight examples where the NMR method proves particularly advantageous, especially in accurately quantifying efficacy for compounds with lower potency. Additionally, we present a new approach that leverages NMR to identify weakly interacting small molecule fragments for GPCR drug discovery.

2:25 Bioorthogonal Tethering of Drug Fragments to Engineered GPCRs

Jordan Mattheisen, PhD, Postdoctoral Fellow, Chemical Biology, AstraZeneca

Despite the increasing availability of high-resolution GPCR structures, finding allosteric modulators remains challenging due to the dynamic nature of GPCRs in native membranes. I present a novel strategy to site-specifically covalently tether drug fragments adjacent to allosteric sites in engineered GPCRs harboring noncanonical reactive amino acids. This approach enhances compound potency, enabling fragment-based drug screening and the discovery of new functional allosteric binding sites using live-cell assays.

2:55 Accelerate the Development of Therapeutics for Obesity and Diabetes with Functional Cell-based Assays

Venkatesh Chari, Scientific Market Development Manager, Eurofins DiscoverX

GPCR-based peptide therapeutics have shown promise in treating obesity and diabetes. The development of innovator drugs, biosimilars and small molecules for these globally prevalent conditions require demonstration of accurate mechanism of action and pharmacology crucial to characterize their true therapeutic potential. Here, we present fit-for-purpose assays for evaluating therapeutics targeting GLP-1, GIP, glucagon, TSH, PYY, amylin, GPR10, and GPR75 receptors to accelerate global programs for screening, characterization, and potency testing.

3:25 Refreshment Break in the Exhibit Hall with Poster Viewing

4:15 FEATURED PRESENTATION: SPR-Microscopy for Detecting GPCR Target Engagement

Kris A. Borzilleri, Principal Scientist, Structural Biology & Molecular Sciences, Pfizer Global R&D, Groton Labs

Measuring direct binding and kinetics to membrane proteins has long been a challenge due to poor behavior of these targets when purified out of their native environments. Surface Plasmon Resonance Microscopy (SPRm), which combines optical microscopy with label-free SPR, allows for detection of binding in the whole cell environment. Using SPRm, we measured binding affinities on several targets that are in excellent agreement with radioligand binding and functional IC50 assays.

4:45 DNA-Encoded Library Approaches for GPCR-Ligand Discovery

Casey J. Krusemark, PhD, Associate Professor, Medicinal Chemistry & Molecular Pharmacology, Purdue University

We present novel approaches for the selection of molecules from DNA-encoded libraries (DEL) using enzymatic tags on target proteins. We apply these assays for DEL discovery with GPCRs in live cells for both the discovery of ligands and for specific discovery of biased agonists.

5:15 Dinner Short Course Registration*

**Premium Pricing or separate registration required. See Short Courses page for details.*

5:15 Diversity Discussion *(Sponsorship Opportunity Available)*

IN-PERSON DISCUSSION: Fostering Diversity through Mentoring

Naytia Byrd, Manager, Human Resources, Ovid Therapeutics, Inc.
Saudat Fadeyi, PhD, MBA, Director, Business Development, Ovid Therapeutics, Inc.
Fred Manby, DPhil, Co-Founder & CTO, Iambic Therapeutics
Joel Omage, Research Scientist II, CVM Disease Area, Novartis Institutes for BioMedical Research, Inc.
Andrew Zhang, PhD, Director, Chemical Biology, AstraZeneca

Topics for discussion will include, but certainly not be limited to:

- How to increase awareness and address hidden barriers and biases in life sciences
- How to motivate early-career scientists to seek out mentors and resources
- How to convince senior leadership to take time for coaching the next generation of leaders and support DEI initiatives

• How to create simple and impactful opportunities for mentors and mentees to connect and collaborate

6:00 Dinner Short Courses*

**Premium Pricing or separate registration required. See Short Courses page for details.*

8:30 Close of Day

THURSDAY, OCTOBER 3

7:30 am Registration Open and Morning Coffee

INSIGHTS FROM VENTURE CAPITALISTS

8:00 PANEL DISCUSSION: Trends in Drug Discovery

Moderator: Daniel A. Erlanson, PhD, Chief Innovation Officer, Innovation and Discovery, Frontier Medicines Corporation

Panelists:

Jernej Godec, PhD, Principal, Atlas Venture

Jenna Hebert, PhD, Senior Associate, RA Capital Management

Jamie Kasuboski, PhD, Partner, Luma Group

Jasmina Marjanovic, PhD, Partner, Takeda Ventures

Swetha Murali, PhD, Vice President, OMX Ventures

STRUCTURE-BASED DRUG DESIGN FOR GPCRs

8:45 Chairperson's Remarks

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

8:50 Structure, Function, and Pharmacology of Delta Opioid Receptor Ligands for the Development of Better Chronic Pain Therapeutics

Sarah Bernhard, Laboratory of Susrata Majumdar, Center for Clinical Pharmacology, Washington University School of Medicine

Therapeutic options for treating chronic pain are limited by low efficacy and adverse effects. Delta opioid receptor (DOR) agonists show potential in relieving chronic pain symptoms; however, they can exhibit adverse effects like seizures and tolerance. Our studies aim to understand pharmacological and behavioral profiles of DOR full agonists, partial agonists, and allosteric modulators to develop a structural platform for designing the next generation of pain relievers.

9:20 Discovery and Mechanism of Opioid Receptor Allosteric Modulators

Evan O'Brien, PhD, Assistant Professor, Biophysics & Biophysical Chemistry, The Johns Hopkins University School of Medicine

The mu-opioid receptor (MOR) is a well-established GPCR target for analgesia, yet conventional orthosteric opioid agonists suffer from serious adverse effects, notably respiratory depression and addiction. We screened a large DNA-encoded chemical library and discovered new positive and negative allosteric modulators of the receptor. We then used cryoEM to determine detailed structural mechanisms of allosteric modulation and demonstrated *in vivo* efficacy for a new class of "Narcan-boosters."

9:50 Developing Small Molecule Agonists of GLP-1R and other Peptide-Binding GPCRs

Yingli Y Ma, PhD, CTO, Platform Technology, Structure Therapeutics Shanghai Basecamp Biotechnology Co

This presentation will focus on the development of small molecule agonist versions of peptide-binding GPCRs such as GLP-1R.

10:20 In-Person Breakouts

In-Person Breakouts are informal, moderated discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator who keeps the discussion on track and the group engaged. To get the most out of this format, please come prepared to share examples from your work, be a part of a collective, problem-solving session, and participate in active idea sharing. Please visit the Breakouts page on the conference website for a complete listing of topics and descriptions.

IN-PERSON BREAKOUT: Peptide Agonists for GPCRs

Florence Brunel, PhD, Senior Principal Scientist, Novo Nordisk Inc

• How will small molecule GPCR agonists compete with peptides?
• What are the next GPCRs to be blockbusters?
• What is the limitation to developing more peptide GPCR agonists? What are the new techniques to help solve these issues?

IN-PERSON BREAKOUT: Innovations in GPCR-Hit Discovery

Evan O'Brien, PhD, Assistant Professor, Biophysics & Biophysical Chemistry, The Johns Hopkins University School of Medicine

• Role of cryoEM
• Impact of AI
• DNA-Encoded Libraries (DEL) & GPCRs
• New biophysical tools: SPR microscopy, single-molecule FRET

11:05 Coffee Break in the Exhibit Hall with Poster Viewing and Best of Show Awards Announced

GPCR-TARGETED DRUG CANDIDATES

11:45 FEATURED PRESENTATION: Discovery of Clinical Candidate AZD5462, an Allosteric Oral Small Molecule RXFP1 Agonist for the Treatment of Heart Failure

Niklas Larsson, PhD, Principal Scientist, AstraZeneca R&D

The relaxin H2 hormone is a clinically relevant peptide agonist for the G protein-coupled receptor RXFP1, but the short half-life and need for injectable delivery limits its therapeutic potential. AZD5462 is the first clinical candidate, small-molecule RXFP1 agonist that mimics the signaling pharmacology of relaxin H2. AZD5462 is a promising potential therapeutic treatment for patients with heart failure and other conditions where physiological effects of chronic RXFP1 agonism are desirable.

12:15 pm Discovering the Next-Generation of GPCR-targeted Therapeutics to Address Metabolic Diseases with Unmet Patient Needs

Oliver Hartley, PhD, Vice President, Drug Discovery, Orion Biotechnology

I present how we leveraged a novel drug modality and proprietary discovery platform to unlock metabolic GPCRs.This enabled us to advance a pipeline of differentiated therapeutics for obesity and metabolic disorders. We strive to capture the untapped potential of novel metabolic targets with innovative monotherapy & combination approaches.

12:45 Enjoy Lunch on Your Own

1:50 Dessert Break in the Exhibit Hall with Last Chance for Poster Viewing

GPCR-TARGETED DRUG CANDIDATES (CONT'D)

2:30 Chairperson's Remarks

Yamina A. Berchiche, PhD, Founder, Dr. GPCR

2:35 Selecting a Clinical Candidate Based on GPCR Signaling Profiles: Discovery of FPR2 Agonist BMS-986331

Nicholas R. Wurtz, PhD, Associate Director, Discovery Chemistry, Bristol Myers Squibb Co.

Formyl Peptide Receptor 2 (FPR2) agonists with biased GPCR signaling profiles were discovered through a combination of screening and rational design. A detailed evaluation of these agonists demonstrated that a specific profile afforded efficacy in rodent heart failure models. Optimization of an arylpiperidinone chemotype with the preferred GPCR agonist profile led to the identification of BMS-986331, which was progressed into Phase I clinical trials.

3:05 Methodological Toolbox to Characterise Allosteric Modulators at CB1R

Dmitry Veprintsev, Professor of Molecular & Cellular Pharmacology, University of Nottingham; Co-Founder and CEO, Z7 Biotech Ltd.

Allosteric ligands modulate receptor responses without completely blocking their functions, an attractive property for drug development. However characterizing allosteric modulators is challenging. We developed a fluorescent allosteric probe which differentiated effects of orthosteric and allosteric ligands binding to the CB1 receptor. We further performed G protein recruitment and ModuMelt™ assays to understand the pharmacological activity and cooperativity of orthosteric and allosteric ligand binding. This toolbox is applicable to other GPCRs

3:35 Structure-Based Drug Discovery on OX2R

Pieter Claes, PhD, Principal Scientist, Medicinal Chemistry, Confo Therapeutics

Agonism of the Orexin type 2 receptor has emerged as an attractive approach for the treatment of narcolepsy. Here, we describe the identification of an agonist series [PC1] using a new screening assay based on ConfoBodies, the elaboration of the chemical series and its puzzling structure-activity relationship. Determination of the active-state structure with a series representative revealed the cause of these unexpected activity cliffs.

4:05 Presentation to be Announced

4:35 Close of Conference

Antibodies Against Membrane Protein Targets

New Strategies and Technologies to Accelerate the Development of Biotherapeutics Against Complex GPCR and Ion Channel Targets

OCTOBER 1-2, 2024

TUESDAY, OCTOBER 1

7:00 am Registration Open and Morning Coffee

EMERGING MODALITIES

7:55 Welcome Remarks

8:00 Chairperson's Remarks
Robbins Puthenveetil, PhD, Senior Scientist, AstraZeneca

8:05 Overcoming the Challenges with Raising Antibodies against STEAP2 Extracellular Domains for Targeted CAR T Cell Therapy
Dewald van Dyk, PhD, Associate Director, Biologics Engineering, AstraZeneca Pharmaceuticals LP
Six-transmembrane epithelial antigen of prostate-2 (STEAP2) is a complex membrane protein that is highly expressed on prostate cancer cells with limited distal normal tissue expression. High species homology and small extracellular domains make STEAP2 a very challenging protein to target. I will share reflections on the multifaceted discovery campaigns that enabled the isolation of STEAP2-specific antibodies for the development of an armored STEAP2 chimeric antigen receptor T cell therapy.

8:35 Transferrin Receptor Targeting Chimeras (TransTACs) for Targeted Depletion of Complex Membrane Targets
Kaitlin Rhee, Researcher, Xin Zhou Lab, Biological Chemistry & Molecular Pharmacology, Dana-Farber Cancer Institute, Harvard Medical School
GPCRs play critical roles in nearly all aspects of cancer progression, including growth and survival, invasion and metastasis, and drug resistance. However, signaling inhibition can be complicated by ligand-independent signaling, oligomerization with coreceptors, multiple ligand and receptor pairings, and the challenge of developing selective high-affinity antagonists. Thus, we propose an induced proximity/bispecific antibody-based approach to selectively deplete GPCRs for sustained signaling inhibition, by co-opting cancer cell-surface recycling and lysosome-targeting receptors.

9:05 Antibody-Drug Conjugates Targeting GPCRs and Combination Strategies to Enhance Efficacy in Colorectal Cancer
Kendra Carmon, PhD, Associate Professor, Center for Translational Cancer Research, University of Texas Health Science Center at Houston
Our group has generated antibody-drug conjugates (ADCs) directed against G protein-coupled receptor (GPCR) targets highly expressed in colorectal and other cancer types. These GPCR-targeted ADCs were generally well-tolerated and show promising efficacy in preclinical models of colorectal cancer, yet tumors were not completely eliminated. Currently, we are evaluating ADCs in combination with FDA-approved therapies to enhance efficacy and overcome resistance and relapse.

9:35 Networking Coffee Break

10:05 Discovery and Engineering of Bispecific Anti-CD3 Heavy Chain-Only Antibodies
Noel T. Pauli, PhD, Group Leader, Antibody Engineering, Adimab LLC
T cell engagers utilizing CD3 are an increasingly validated class of multispecific antibodies, but are inherently complicated to generate. Reducing engineering complexity through a CD3-specific heavy chain–only antibody (HCAb) would be beneficial. Using a yeast-based platform, we demonstrate the discovery and engineering of a panel of high-affinity, CD3-specific, HCAbs from immunized camelids, and validate their use in functional bispecific molecules.

10:35 SPECIAL PRESENTATION: Insights from Current Pipelines of Antibody-Based Therapeutics against GPCR, Ion-Channel, and Transporter Targets
Catherine Hutchings, PhD, Independent Consultant
Complex multi-pass transmembrane proteins represent some of the most important drug target classes across a wide range of therapeutic areas. An annual update on antibody-based therapeutics in the GPCR, ion channel, and transporter R&D pipeline will be provided, outlining the breadth and diversity of the target landscape.

11:05 KEYNOTE PRESENTATION: Insights from Alphafold2 Antibody Screening against High-Value GPCRs
Jeffrey Skolnick, PhD, Professor, Biology, Director, Center for the Study of Systems Biology, Georgia Institute of Technology
Alphafold2Complex, a generalization of Alphafold2, can predict if proteins interact, and if so, their quaternary structure. AF2Complex has provided insights into important pathways such as the outer membrane biogenesis pathway in *E. coli*. Here, it is applied to the antibody modulation of GPCR signaling associated with breast cancer cell migration. Following modeling the activation of GPCRs that initiate breast cancer cell migration, we suggest antibodies that could inhibit this process.

11:35 Structure-Based Charge Calculations for Predicting Properties and Profiling Antibody Therapeutics
Philippe Archambault, Application Scientist, Chemical Computing Group
We present a method for modeling antibodies and performing pH-dependent conformational sampling, which can enhance property calculations. Structure-based charge descriptors are evaluated for their predictive performance on recently published antibody pI, viscosity, and clearance data. From this, we devised four rules for therapeutic antibody profiling which address developability issues arising from hydrophobicity and charged-based solution behavior, and PK.

12:05 pm Transition to Lunch

12:10 LUNCHEON PRESENTATION: Advanced Antigen Design Strategies for Shaping Human Antibody Repertoires in OmniAb Animals
Devendra Srivastava, Director, OmniAb
OmniAb antibody discovery campaigns leverage advanced immunization strategies tailored for high-value, challenging targets, including ion channels, GPCRs, and multi-pass transmembrane proteins. To shape robust immune repertoires, we have developed proprietary mRNA-LNP production methods and engineered vector libraries for rapid high-quality production of membrane proteins.

12:40 Session Break

DISCOVERY TOOLS AND TECHNOLOGIES

1:15 Chairperson's Remarks
Catherine Hutchings, PhD, Independent Consultant

1:20 bioSens-All: A Multiparametric BRET-Based Platform for Comprehensive Profiling of GPCR Signaling and Pharmacology-Enabling Drug Discovery
Laurent Sabbagh, PhD, Scientific Director, Domain Therapeutics

The 3rd-generation bioSens-All platform combines BRET-based biosensors that are highly adaptable to the needs of discovery projects for small molecules, peptides, and antibodies. The platform has been successfully used internally to identify biased small molecule negative allosteric modulators for protease-activated receptor 2 (PAR2). In addition, the platform was used to develop assays for high-throughput screening for the challenging adhesion GPCR, ADGRE5.

1:50 Application of Synthetic Libraries against Membrane Targets for Antibody Generation

Jeffrey Barker, PhD, Principal Research Scientist, AbbVie

Discovery of biotherapeutics against challenging targets such as integral membrane proteins, membrane protein complexes, and heavily glycosylated surface proteins using display technologies remains a challenge. We have utilized therapeutic-ready phage- and yeast-display platforms expressing a diversity of formats to pan against both cells and virus-like particles. Using these novel reagents and protocols, we have managed to discover biotherapeutics to traditionally display "unfriendly" targets.

2:20 Accelerating Biotherapeutics Development against Membrane Proteins Using Next-Generation Polymers-Based Nanodiscs

Cube Biotech

Jan Kubicek, CSO & Co Founder, Cube Biotech GmbH

Detergent solubilization is one of the biggest roadblocks against therapeutic development for membrane proteins as they provide poor protein stabilization and interfere with many downstream applications. I will discuss how co-polymers can efficiently solubilize membrane proteins into native nanodiscs which, unlike detergents, preserves the protein's environment and function. I will illustrate how co-polymer stabilization outperforms classical detergents in display and drug discovery techniques.

2:50 In-Person Breakouts

In-Person Breakouts are informal, moderated discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator who keeps the discussion on track and the group engaged. To get the most out of this format, please come prepared to share examples from your work, be a part of a collective, problem-solving session, and participate in active idea sharing. Please visit the Breakouts page on the conference website for a complete listing of topics and descriptions.

IN-PERSON BREAKOUT: Avoiding Roadblocks: Maneuvering the Challenges of Difficult Targets

Joseph Rucker, PhD, Vice President, Research and Development, Integral Molecular, Inc.

3:35 Grand Opening Refreshment Break in the Exhibit Hall with Poster Viewing and Best of Show Voting Begins

4:35 Leveraging Structural Biology to Address Discovery Challenges with Complex Membrane Proteins

Robbins Puthenveetil, PhD, Senior Scientist, AstraZeneca

Cryo-electron microscopy has revolutionized structural characterization of complex membrane proteins, leading to improved design of powerful biologics. With the advent of cryo-EM, significant strides made through structure-based drug design approaches have augmented the specificity and efficacy of therapeutic interventions. In this presentation, we will explore the obstacles encountered by a multi-pass transmembrane protein target, illustrating how cryo-EM can help overcome these challenges and instruct remediation of liabilities though protein engineering.

5:05 Engineering a New Class of Therapeutic Proteins with Antibody-Like Properties

Mahmoud Nasr, PhD, RPh, Assistant Professor, Medicine, Brigham and Women's Hospital, Harvard Medical School

We will introduce a new class of therapeutic proteins. Our newly engineered proteins offer great advantages over the conventional antibodies and nanobodies. We will discuss their properties, their production, and finally, show their use to target membrane proteins implicated in various diseases.

5:35 Biology-Based ML Model for Targeting GPCR-Biased Signaling Cascades

Aurelien Rizk, PhD, CSO & Co-Founder, InterAx Biotech AG

InterAx combines real-time cellular assays and mathematical pathway modelling to define novel pharmacodynamic parameters. These parameters quantify signaling and kinetic biases, allowing to (1) determine the optimal signaling profile for therapeutic efficacy and safety and (2) apply machine learning methods to efficiently select and optimize drugs. We will show how we use this approach to discover diabetes and obesity drugs that minimize nausea without compromising effectiveness.

6:05 Welcome Reception in the Exhibit Hall with Poster Viewing

7:05 Close of Day

WEDNESDAY, OCTOBER 2

7:30 am Registration Open and Morning Coffee

MACHINE LEARNING FOR GPCR BIOTHERAPEUTICS

7:55 Chairperson's Remarks

Noel T. Pauli, PhD, Group Leader, Antibody Engineering, Adimab LLC

8:00 *De novo* Design and Engineering of Novel GLP1R Agonist Miniprotein

Ben Meinen, PhD, Head, Protein Design, AI Proteins

De novo–designed miniproteins represent a groundbreaking new modality, offering unprecedented flexibility in engineering biologics with an array of desirable features tailored for specific applications. We developed a novel GLP1R-agonist miniprotein designed *de novo* to exhibit improved biased signaling with a strong emphasis on G protein-coupled signaling, while significantly reducing ß-arrestin signaling.

8:30 Rapid Screening for GPCR Active Ligands Using Machine Learning

Jianing Li, PhD, Assistant Professor, Medicinal Chemistry and Molecular Pharmacology, Purdue University

Molecules with bioactivity towards GPCRs represent a subset of the vast space of small drug-like molecules. Machine learning models, including dilated graph convolutional networks, have been created and validated for binary classification to quickly identify active molecules towards GPCRs. As proof of principle, the incorporation of our best model into a high-throughput virtual screening workflow is demonstrated for several class A and class B receptors.

9:00 GPCR-BERT: Interpreting Sequential Design of G Protein-Coupled Receptors Using Protein Language Models

Amir Barati Farimani, PhD, Associate Professor, Machine Learning, Carnegie Mellon University

We developed GPCR-BERT, a transformer-based model, to understand the sequential design of G protein-coupled receptors (GPCRs). By fine-tuning the model with prediction tasks on conserved motifs, we elucidated relationships between binding pocket residues and motifs. Attention weights and hidden states were analyzed to determine amino acid contributions. Embedding analysis over 3D structures revealed higher-order interactions within receptor conformations. GPCR-BERT demonstrates the potential of language models in therapeutic design.

9:30 Sponsored Presentation *(Opportunity Available)*

10:00 Coffee Break in the Exhibit Hall with Poster Viewing

PLENARY KEYNOTE PROGRAM

10:50 Plenary Keynote Chairperson's Remarks
An-Dinh Nguyen, Team Lead, Discovery on Target, Cambridge Healthtech Institute

10:55 PLENARY KEYNOTE: Discovery of Transformative Rx to Treat Obesity and Related Diseases
Richard DiMarchi, PhD, Distinguished Professor of Chemistry and Chair, Biomolecular Sciences, Indiana University; former Executive, Lilly and Novo Research Labs
To address obesity, a medicinal challenge that warrants broad molecular diversity, we pioneered the pharmacological strategy of recruiting endogenous hormones to optimize physiological mechanisms. Our discovery of single-molecule, multi-mechanism incretins enabled breakthrough efficacy in lowering body weight. The integrated pharmacology of these endocrine proteins and nuclear hormones is providing a library of drug candidates that promises great clinical outcomes for obesity and associated diseases that have historically been intractable.

11:40 PLENARY KEYNOTE: Fragment-Based Drug Discovery for Elusive Cancer Targets
Stephen W. Fesik, PhD, Professor of Biochemistry, Pharmacology & Chemistry; Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University
The most highly validated cancer targets (KRAS, MYC, and WNT) affecting the majority of cancers are thought to be impossible to drug. Using fragment-based methods that I pioneered over 25 years ago, we have discovered mutant selective and pan KRAS inhibitors, potent inhibitors of the MYC cofactor WDR5, and degraders of b-catenin in the WNT pathway. These novel inhibitors/degraders should have a tremendous impact on cancer treatment in the future.

12:25 pm Close of Antibodies Against Membrane Protein Targets Conference

WEDNESDAY, OCTOBER 2

PLENARY KEYNOTE PROGRAM

10:50 am Plenary Keynote Chairperson's Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target, Cambridge Healthtech Institute

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12:25 pm Enjoy Lunch on Your Own

ENGINEERING ANTIBODIES FOR PRECISION IO

1:45 Welcome Remarks

1:50 Chairperson's Opening Remarks

Anjali Shenoy, PhD, Post Doctoral Researcher, Molecular Biology & Immunology, John Hopkins University

1:55 Selective Targeting of Oncogenic Hotspot Mutations of the HER2 Extracellular Region

Injin Bang, PhD, Postdoctoral Researcher, Infectious Diseases & Immunology, New York University

We developed antibodies exquisitely selective to HER2 S310F/Y, two of the most common oncogenic mutations in the HER2 extracellular region. Cryo-EM structures reveal that these antibodies mimic the dimerization arm of HER and inhibit dimerization. As T cell engagers, they selectively killed a HER2 S310F-driven cancer cell line *in vitro* and in a mouse xenograft model. Overall, these antibodies appear to be promising candidates for clinical development.

2:25 A Robust Heterodimeric Fc Platform Engineered for Efficient Development of Bispecific Antibodies of Multiple Formats

John R. Desjarlais, PhD, CSO, Xencor

Xencor has developed a robust bispecific antibody platform based on a novel set of Fc domain substitutions that promote high heterodimer yield and facile purification. We'll discuss application of this platform to the development of classic CD3 bispecific antibodies and CD28 costimulatory bispecifics. The XmAb 2+1 format—enabling bivalent targeting of a tumor-associated antigen and monovalent engagement of CD3—promotes higher tumor/normal selectivity with growing clinical validation.

2:55 Sponsored Presentation *(Opportunity Available)*

3:25 Refreshment Break in the Exhibit Hall with Poster Viewing

4:15 Engineering a Novel IL-2-Based Immunocytokine with Enhanced Effector and Memory Function

Anjali Shenoy, PhD, Post Doctoral Researcher, Molecular Biology & Immunology, John Hopkins University

We have previously developed therapeutic immunocytokines (IC) which link interleukin-2 (IL-2) to anti-cytokine antibodies that bias IL-2 towards potentiating immune effector cells and promote tumor clearance. Here, we engineered a novel immunocytokine which replaces IL-2 with a variant that elicits memory-biased immune responses. The resulting molecule induces both effector cell responses for tumor elimination and memory responses to prevent cancer reoccurrence, representing a powerful new strategy for cancer treatment.

4:45 Optimizing Delivery and Half-Life of Small Antibodies

Vince Kelly, PhD, Graduate Research Assistant, Biochemistry, University of Illinois

Here, we demonstrate that rational swapping of surface-exposed cationic residues with anionic restudies, in combination with fusion to a homotrimeric peptide domain, significantly extends half-life and delays renal filtration of single-domain antibodies. Further, we combine these modifications with FcRn-binding peptide fusions to facilitate transmembrane transport in a mouse model. These rational modifications may improve the suitability of nanobodies for use as therapeutics, particularly in combination with alternative delivery systems.

5:15 Dinner Short Course Registration*

**Premium Pricing or separate registration required. See Short Courses page for details.*

5:15 Diversity Discussion *(Sponsorship Opportunity Available)*

IN-PERSON DISCUSSION: Fostering Diversity through Mentoring

Naytia Byrd, Manager, Human Resources, Ovid Therapeutics, Inc.
Saudat Fadeyi, PhD, MBA, Director, Business Development, Ovid Therapeutics, Inc.
Fred Manby, DPhil, Co-Founder & CTO, Iambic Therapeutics
Joel Omage, Research Scientist II, CVM Disease Area, Novartis Institutes for BioMedical Research, Inc.
Andrew Zhang, PhD, Director, Chemical Biology, AstraZeneca

Topics for discussion will include, but certainly not be limited to:

- How to increase awareness and address hidden barriers and biases in life sciences
- How to motivate early-career scientists to seek out mentors and resources
- How to convince senior leadership to take time for coaching the next generation of leaders and support DEI initiatives
- How to create simple and impactful opportunities for mentors and mentees to connect and collaborate

6:00 Dinner Short Courses*

**Premium Pricing or separate registration required. See Short Courses page for details.*

8:30 Close of Day

THURSDAY, OCTOBER 3

7:30 am Registration Open and Morning Coffee

ENGINEERING ANTIBODIES FOR PRECISION IO

8:00 Chairperson's Remarks

Francis Gaudreault, PhD, Research Officer, Human Health Therapeutics, National Research Council Canada

8:05 Maleimides in Site-Specific Antibody Conjugations Creating Two Carbon-Carbon Bonds Using an Enzyme and a 100-Year-Old Reaction

Thomas Nittoli, PhD, Senior Director, Therapeutic Proteins, R&D Chemistry, Regeneron Pharmaceuticals, Inc.

We present a two-step sequential conjugation approach that marries the site specificity of the bacterial transglutaminase (TG) reaction with the robustness of Diels-Alder (DA) chemistry to generate stable antibody conjugates. In addition, we show strong potency of antibody conjugates, prepared via TG-DA chemistry, in both cell-based assays and a mouse model. Overall, our conjugation approach is site specific, versatile, and stable.

FROM SEQUENCING TO STRUCTURE: CUTTING-EDGE COMPUTATIONAL TOOLS

8:50 Rapid Discovery of High-Affinity Antibodies via Massively Parallel Sequencing, Ribosome Display, and Affinity Screening

Christopher Wassif, PhD, Director, Molecular Engineering & Antibody Technologies, AstraZeneca

This presentation will focus on the convergence of a new high-throughput antibody discovery platform capable of screening 100s of millions of antibodies with machine learning to accelerate the full discovery process. This work is resulting in the identification of high-affinity, developable modalities fit for therapeutic use in accelerated time frames, while generating significant amounts of data and further refining our algorithms and models.

9:20 Structural Basis of Antibody Conformation and Stability Modulation by Framework Somatic Hypermutation

Zizhang Sheng, PhD, Assistant professor, Aaron Diamond AIDS Research Center, Columbia University

Accumulation of somatic hypermutation (SHM) is the primary mechanism to enhance the binding affinity of antibodies to antigens *in vivo*. Here, we built a high-throughput structural bioinformatics pipeline to study the effects of SHMs on antibody conformation, flexibility, stability, and affinity. Our study revealed a common mechanism of antibody conformation and stability modulation by framework mutations and epistatic effects between framework SHMs.

9:50 KEYNOTE PRESENTATION: Antibody-Antigen Structure Prediction from Deep Learning-Generated Models

Francis Gaudreault, PhD, Research Officer, Human Health Therapeutics, National Research Council Canada

The prediction of the structure of antibody-antigen complexes *in silico* would provide a lot of value for medical applications. Recent deep learning technologies have enabled the production of antibody models with significantly better quality than traditional tools. We evaluated if such quality is sufficient for successful antibody-antigen structure prediction, using traditional molecular docking tools that normally fall short in real applications where the antibody structure is unknown.

10:20 In-Person Breakouts

In-Person Breakouts are informal, moderated discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator who keeps the discussion on track and the group engaged. To get the most out of this format, please come prepared to share examples from your work, be a part of a collective, problem-solving session, and participate in active idea sharing. Please visit the Breakouts page on the conference website for a complete listing of topics and descriptions.

IN-PERSON BREAKOUT: Strategies for Enhancing Antibody Efficiency and Selectivity

Thomas Nittoli, PhD, Senior Director, Therapeutic Proteins, R&D Chemistry, Regeneron Pharmaceuticals, Inc.

- Improving tissue penetration and targeting
- Reducing immunogenicity and off-target effects
- Optimizing antibody-drug conjugate design and development

11:05 Coffee Break in the Exhibit Hall with Poster Viewing and Best of Show Awards Announced

11:45 Antibody Mutations Favoring pH-Dependent Binding in Solid Tumor Microenvironments: Insights from Large-Scale Structure-Based Calculations

Wanlei Wei, PhD, Research Associate, Computer-Aided Drug Discovery, National Research Council Canada

In recent years, engineering of pH-sensitive therapeutic antibodies has gained traction, for endosomal recycling and enhanced specificity in acidic solid-tumor microenvironments. While there is a need for pH-dependent immunotherapies, current engineering techniques are tedious and laborious, requiring repeated rounds of experiments under different pH conditions. Here, we developed a sequence-based method for engineering pH-dependent antibody binders, called SIpHAB, which could circumvent the lack of structural details.

BRINGING TARGETED DELIVERY TO THE CLINIC

12:15 pm Harnessing Modular E3 Ligase and Cytokine Receptor Targeting Chimeras to Degrade Cell-Surface and Extracellular Proteins

Josef Gramespacher, PhD, Co-Founder, EpiBiologics

By ablating all disease-associated functions of a given protein at once, targeted protein degradation has emerged as a promising therapeutic strategy to overcome limitations of traditional occupancy-based inhibitors. To this end, at EpiBiologics we are developing antibody-based PROTACs (AbTACs) and cytokine receptor-targeting chimeras (KineTACs). These are fully recombinant and modular bispecific antibodies capable of recruiting membrane-bound E3 ligases or cytokine receptors to mediate degradation of cell-surface and extracellular proteins.

12:45 Sponsored Presentation *(Opportunity Available)*

1:15 Transition to Lunch

1:20 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:50 Dessert Break in the Exhibit Hall with Last Chance for Poster Viewing

BRINGING TARGETED DELIVERY TO THE CLINIC (CONT.)

2:30 Chairperson's Remarks
John R. Desjarlais, PhD, CSO, Xencor

2:35 Delivery of a Therapeutic Bispecific T Cell Engager Using a pH-Sensitive Nanoparticle Platform
Tian Zhao, PhD, Vice President, R&D, OncoNano Medicine
Spatially and temporally precise delivery of therapeutic macromolecules—such as bispecific T cell engagers—to tumors, while avoiding systemic toxicity, remains a challenge in transforming cancer treatment. OncoNano is developing the ON-BOARD ultra-pH sensitive micelle delivery platform to surmount these constraints. Herein, we report the efficacious masked delivery of a bispecific T cell engager to tumors in mice using ON-BOARD, demonstrating an improved safety profile and potential for clinical translation.

3:05 Tumor-Activated, Fc-Enhanced CTLA-4 Antibody XTX101 Demonstrated Potent Tumor-Growth Inhibition and Tumor-Selective Pharmacodynamics *in Vivo*
Kurt Jenkins, PhD, Director, Xilio Therapeutics
The clinical benefit of CTLA-4 blocking antibodies has been well established but treatment-related toxicities remain a limiting factor. XTX101 is an investigational tumor-activated, Fc-enhanced, high affinity binding anti-CTLA-4 monoclonal antibody designed to maximize activity in the tumor microenvironment and improve tolerability compared with systemically active anti-CTLA-4 antibodies. This talk will cover design and preclinical characterization of XTX101, including demonstration of tumor regressions and tumor-specific pharmacodynamic changes *in vivo*.

3:35 Discovery and Development of DYP688
John W. Blankenship, PhD, Executive Director and Head, Biologics Discovery and Automation, Novartis Biomedical Research
GNAQ/11 mutations occur in up to 95% of uveal melanomas and are considered genetic drivers of the disease. PMEL17 (gp100) is a melanocytic lineage gene that is highly and broadly expressed in melanomas. DYP688 is a novel antibody-drug conjugate that binds to PMEL17 on target cells to deliver the payload SDZ475, a targeted inhibitor of Gq/11 oncogenic signaling. Preclinical and early clinical development of DYP688 will be discussed.

4:05 PANEL DISCUSSION: Delivering Cancer Antibodies to the Clinic
Moderator: John W. Blankenship, PhD, Executive Director and Head, Biologics Discovery and Automation, Novartis Biomedical Research
Panelists:
Josef Gramespacher, PhD, Co-Founder, EpiBiologics
Kurt Jenkins, PhD, Director, Xilio Therapeutics
Tian Zhao, PhD, Vice President, R&D, OncoNano Medicine

4:35 Close of Conference

TUESDAY, OCTOBER 1

7:00 am Registration Open and Morning Coffee

CHEMICAL BIOLOGY STRATEGIES FOR MODULATING RNA

7:55 Welcome Remarks

8:00 Chairperson's Remarks

Ken Hsu, PhD, Stephen F. and Fay Evans Martin Endowed Associate Professor, Department of Chemistry, The University of Texas at Austin

8:05 Strategies to Modulate the Conformation and Function of RNA with Small Molecules

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

The Hargrove Lab leverages fundamental discoveries of the drivers of small molecule : RNA recognition to develop new strategies for RNA targeting. These methods account for differences in RNA chemical and conformational space to yield functional RNA-targeting small molecules and allow rational optimization without high-resolution structure.

8:35 Chemical Approaches to Study and Target Post-transcriptional RNA Regulatory Mechanisms

Ralph Kleiner, PhD, Assistant Professor, Department of Chemistry, Princeton University

The Kleiner lab develops chemical approaches to study RNA modifying enzymes and RNA-protein interactions. Here we will describe RNA-mediated activity-based protein profiling (RNABPP), a chemoproteomic strategy for profiling and inhibiting RNA modifying enzymes using mechanism-based modified nucleotide probes. We will also discuss TRIBE-ID, an RNA editing-based platform for studying RNA-protein interactions with temporal resolution.

9:05 Targeted Post-Translational Lysine Acetylation Modulates Viral RNA-Host Protein Interactions

Mikail Abbasov, PhD, Assistant Professor, Chemistry and Chemical Biology, Cornell University

The Abbasov laboratory exploits reactivity of lysines at RNA-protein interaction interfaces by leveraging activity-based proteomics and lysine-reactive natural products and small molecules. We developed activity-based acylome profiling, a chemoproteomic strategy that exploits elaborate acylating agents and lysine-centric probes for site-specific introduction and proteome-wide mapping of posttranslational lysine acylations in live cells. We identified paralog-selective chemical probes that acetylate lysines in interferon-stimulated antiviral RNA-binding proteins, generating proteoforms with obstructed RNA interactions.

9:35 Networking Coffee Break

10:05 Covalent Targeting of Disease-Relevant RNA-Binding Proteins

Brahma Ghosh, PhD, Senior Principal Scientist & Head, Chemical Biology, Global Discovery Chemistry, Johnson & Johnson

Here, I will present our efforts that led to the identification of covalent ligands that alter RNA-protein complexes in human cells. The talk will focus on the discovery of novel chemotypes that stereo-selectively i) engage the RNA-binding protein NONO to decrease the expression of transcripts encoding the androgen receptor and its splice variants in prostate cancer cells, and ii) those that functionally remodel the spliceosome to perturb mRNA splicing.

10:35 PANEL DISCUSSION: Finding the Right Tools and Assays to Study RNA Structure and Function

Moderator: Ken Hsu, PhD, Stephen F. and Fay Evans Martin Endowed Associate Professor, Department of Chemistry, The University of Texas at Austin

Panelists:

Mikail Abbasov, PhD, Assistant Professor, Chemistry and Chemical Biology, Cornell University

Brahma Ghosh, PhD, Senior Principal Scientist & Head, Chemical Biology, Global Discovery Chemistry, Johnson & Johnson

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

Ralph Kleiner, PhD, Assistant Professor, Department of Chemistry, Princeton University

11:35 Sponsored Presentation *(Opportunity Available)*

12:05 pm Transition to Lunch

12:10 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

12:40 Session Break

AI FOR RNA DRUG DISCOVERY

1:15 Chairperson's Remarks

1:20 Combining NMR Transverse Relaxation Times (T2) and Computational Chemistry to Target RNA

Barak Akabayov, PhD, Professor, Department of Chemistry, Ben Gurion University of the Negev

Using a unique combination of NMR and computational chemistry, we have developed novel antibacterial small molecules by targeting an RNA hairpin within the ribosomal PTC. The optimization models used a dataset of small molecules, and their docking scores were crucial in establishing design principles for new small molecules with improved bioactivity. We synthesized molecules, tested their ability to inhibit the ribosome, and demonstrated the binding mechanism to the RNA hairpin.

1:50 LightON mRNA: Anima's mRNA Lightning Brings AI to mRNA Biology

Generoso Ianniciello, Chief Business Officer, Anima Biotech

Using high-content, high-throughput imaging, we have generated over 2 billion visualizations to train our mRNA image neural network to identify disease signatures. Our massively parallel automated mRNA lab tests thousands of molecules, identifying active ones that visually restore diseased cells to their healthy state. MOAi technology utilizes the mRNA knowledge graph, our LLM, and the Lightning co-pilot, rapidly pinpointing mechanisms of action and molecular targets, through a unified, scalable interface.

2:20 Presentation to be Announced

药明康德 WuXi AppTec

2:50 In-Person Breakouts

In-Person Breakouts are informal, moderated discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator who keeps the discussion on track and the group engaged. To get the most out of this format, please come prepared to share examples from

your work, be a part of a collective, problem-solving session, and participate in active idea sharing. Please visit the Breakouts page on the conference website for a complete listing of topics and descriptions.

IN-PERSON BREAKOUT: Challenges and Opportunities in Pursuing RNA as a Drug Target
Generoso Ianniciello, Chief Business Officer, Anima Biotech
Karthik Iyer, PhD, Director, Head of Medicinal Chemistry, Arrakis Therapeutics
Marla Weetall, PhD, Senior Vice President, Pharmacology and Biomarkers, PTC Therapeutics

3:35 Grand Opening Refreshment Break in the Exhibit Hall with Poster Viewing and Best of Show Voting Begins

4:35 Recent Advances in the Discovery of RNA-Targeted Small Molecules
Karthik Iyer, PhD, Director, Head of Medicinal Chemistry, Arrakis Therapeutics
Our mission at Arrakis is to solve very broadly the problem of how to drug RNA with small molecules. This presentation will provide an update on the platform we have built to achieve that mission and provide early data on specific mRNA targets.

5:05 Developing RNA-Targeted Oral Small Molecules to Treat Incurable Diseases
Chris M. Yates, Executive Director, Head, Medicinal Chemistry, Rgenta Therapeutics
Rgenta Therapeutics is leveraging our proprietary, integrative RNA-targeting small molecule discovery platform to pioneer the development of first-in-class oral therapies. Rgenta is pursuing oncology and neurological disease targets, exemplified by the oncogenic transcription factor target c-MYB and the *PMS1* gene. *PMS1* is a key component of the DNA mismatch repair pathway, implicated in the pathological somatic trinucleotide repeat expansion observed in Huntington's Disease (HD) and other trinucleotide repeat expansion disorders.

5:35 Targeting Pre-mRNA with Small Molecules
Marla Weetall, PhD, Senior Vice President, Pharmacology and Biomarkers, PTC Therapeutics
Utilizing small molecules to modulate splicing is a successful therapeutic approach to regulate protein expression. Evrysdi™ (risdiplam) was recently approved for the treatment of Spinal Muscular Atrophy. PTC518 is in clinical development for Huntington's disease. The learnings from the SMA and HD programs have helped PTC Therapeutics find other molecules for other diseases. Here, we discuss discovery, preclinical, and clinical development of small molecules that modulate pre-mRNA.

6:05 Welcome Reception in the Exhibit Hall with Poster Viewing

7:05 Close of Day

WEDNESDAY, OCTOBER 2

7:30 am Registration Open and Morning Coffee

EXPLOITING EMERGING RNA BIOLOGY

7:55 Chairperson's Remarks
Donny Licatalosi, PhD, Head, RNA Biology, Takeda Pharmaceutical Company

8:00 Pancreatic Cancer Cells Are Addicted to Expression of the PLAC8 mRNA, but Not the Encoded Protein
Malte Buchholz, PhD, Head of Basic Research, Clinic for Gastroenterology, Philipps University Marburg
The PLAC8 gene is strongly ectopically expressed in pancreatic ductal adenocarcinoma (PDAC), and inhibition of PLAC8 expression significantly impairs cell proliferation and viability. Surprisingly, the functional entity mediating the cell-intrinsic pro-tumorigenic effects is not the PLAC8 protein, but instead the PLAC8 mRNA itself. Functionally, the PLAC8 mRNA, but not the protein, is centrally important for maintenance of genome integrity (and hence cell viability) via regulation of the MRN complex.

8:30 Targeting an Oncogenic Long Noncoding RNA with Small Molecule Compounds
Tao Liu, PhD, Associate Professor and Research Group Leader, Gene Dysregulation Group, Children's Cancer Institute Australia, University of New South Wales
We have identified a novel long noncoding RNA, lncNB1, as a critical driver of neuroblastoma progression in mouse models and identified the oncogenic RNA-binding protein MSI2 as a functional partner binding protein of lncNB1. Small molecule compound library screening identified SM2023 as an efficient inhibitor of lncNB1 RNA and MSI2 protein interaction. Treatment with SM2023 blocked lncNB1 and MSI2 function and induced neuroblastoma cell growth inhibition and apoptosis.

9:00 Small Molecule-regulated Gene Therapy Using an Engineered Small Molecule-binding Splice Site
Samie Jaffrey, MD, PhD, Professor, Department of Pharmacology, Weill Cornell Medicine; Co-Founder, Gotham Therapeutics
We present Cyclone, a novel acyclovir-controlled poison exon system designed for small molecule control of endogenous gene expression. By engineering the exon 7 hairpin structure from SMN1 to include an acyclovir-binding aptamer, we enable tunable, reversible, and dynamic regulation of both transgenes and endogenous genes. Cyclone offers a streamlined approach to controlling gene expression, harnessing naturally occurring RNA structures for efficient small molecule modulation.

9:30 Presentation to be Announced

Depixus

9:45 Sponsored Presentation *(Opportunity Available)*

10:00 Coffee Break in the Exhibit Hall with Poster Viewing

PLENARY KEYNOTE PROGRAM

10:50 Plenary Keynote Chairperson's Remarks
An-Dinh Nguyen, Team Lead, Discovery on Target, Cambridge Healthtech Institute

10:55 PLENARY KEYNOTE: Discovery of Transformative Rx to Treat Obesity and Related Diseases
Richard DiMarchi, PhD, Distinguished Professor of Chemistry and Chair, Biomolecular Sciences, Indiana University; former Executive, Lilly and Novo Research Labs
To address obesity, a medicinal challenge that warrants broad molecular diversity, we pioneered the pharmacological strategy of recruiting endogenous hormones to optimize physiological mechanisms. Our discovery of single-molecule, multi-mechanism incretins enabled breakthrough efficacy in lowering body weight. The integrated pharmacology of these endocrine proteins and nuclear hormones

is providing a library of drug candidates that promises great clinical outcomes for obesity and associated diseases that have historically been intractable.

11:40 **PLENARY KEYNOTE: Fragment-Based Drug Discovery for Elusive Cancer Targets**

Stephen W. Fesik, PhD, Professor of Biochemistry, Pharmacology & Chemistry; Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University

The most highly validated cancer targets (KRAS, MYC, and WNT) affecting the majority of cancers are thought to be impossible to drug. Using fragment-based methods that I pioneered over 25 years ago, we have discovered mutant selective and pan KRAS inhibitors, potent inhibitors of the MYC cofactor WDR5, and degraders of b-catenin in the WNT pathway. These novel inhibitors/degraders should have a tremendous impact on cancer treatment in the future.

12:25 pm **Close of Small Molecules Targeting RNA Conference**

WEDNESDAY, OCTOBER 2

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An-Dinh Nguyen, Team Lead, Discovery on Target, Cambridge Healthtech Institute

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12:25 pm Enjoy Lunch on Your Own

1:45 Welcome Remarks

TRANSCRIPTIONAL CROSSTALK

1:50 Chairperson's Remarks

Asad Taherbhoy, PhD, Director, Drug Discovery, Foghorn Therapeutics

1:55 FEATURED PRESENTATION: Biochemical and Functional Interplay Between Cancer-associated mSWI/SNF Chromatin Remodeling Complexes and Transcription Factors

Cigall Kadoch, PhD, Associate Professor, Pediatric Oncology, Dana-Farber Cancer Institute/Harvard Medical School; Scientific Founder, Foghorn Therapeutics

ATP-dependent chromatin remodeling complexes are multi-component molecular machines that govern genomic accessibility and gene expression and are among the most frequently implicated cellular entities in human cancer. This presentation highlights biochemical and structural advances that have enabled the mechanistic understanding of mSWI/SNF complex activities in normal and disease states, opening new opportunities for therapeutic intervention.

2:25 FEATURED PRESENTATION: An 'Omics Approach to Drug Discovery'

Liron Bar-Peled, PhD, Associate Professor, Medicine, Harvard Medical School and Massachusetts General Hospital Cancer Center

How different oncogenic contexts influence cysteine targeting remains unknown. To address this question, we have developed DrugMap, an atlas of cysteine ligandability compiled across 416 cancer cell lines. Leveraging these findings, we identify actionable cysteines in SOX10 and develop corresponding covalent ligands. We demonstrate the SOX10 ligand increases SOX10-SOX10 interactions and disrupts melanoma transcriptional signaling. Our findings illustrate the use of covalent probes to disrupt oncogenic transcription factor activity.

2:55 Sponsored Presentation *(Opportunity Available)*

3:25 Refreshment Break in the Exhibit Hall with Poster Viewing

EMERGING TRANSCRIPTIONAL MODULATORS

4:15 Innovative Strategies to Develop Pathway-Biased Small Molecule Transcriptional Modulators

Nava Krishnan, PhD, Associate Research Fellow, Primary Pharmacology Group, Pfizer Inc.

Transcriptional regulators are promising but challenging targets for drug discovery and development. Dynamic conformational changes, a high degree of intrinsic disorder in structure, and multiple binding partners pose challenges to identify functional binders. In addition, transcriptional modulators could regulate several downstream pathways by controlling gene expression. Here, I will discuss multiple strategies taken to identify pathway-specific biased modulators to impact a specific signaling pathway.

4:45 WDR5 WIN Site Inhibitors for Cancer Therapy

William Tansey, PhD, Ingram Professor of Cancer Research, Professor of Cell & Development Biology, Vanderbilt University

WDR5 is a co-factor for MYC oncoprotein transcription factors and an auspicious target for anti-cancer drug development. We have discovered small molecule inhibitors of the "WIN" site of WDR5 that are highly potent, orally bioavailable, and active against multiple cancer types in preclinical studies. I will discuss our recent efforts to define the optimal strategies for implementation of WIN site inhibitors for the future treatment of solid and hematologic malignancies.

5:15 Dinner Short Course Registration*

**Premium Pricing or separate registration required. See Short Courses page for details.*

5:15 Diversity Discussion *(Sponsorship Opportunity Available)*

IN-PERSON DISCUSSION: Fostering Diversity through Mentoring

Naytia Byrd, Manager, Human Resources, Ovid Therapeutics, Inc.
Saudat Fadeyi, PhD, MBA, Director, Business Development, Ovid Therapeutics, Inc.
Fred Manby, DPhil, Co-Founder & CTO, Iambic Therapeutics
Joel Omage, Research Scientist II, CVM Disease Area, Novartis Institutes for BioMedical Research, Inc.
Andrew Zhang, PhD, Director, Chemical Biology, AstraZeneca

Topics for discussion will include, but certainly not be limited to:

- How to increase awareness and address hidden barriers and biases in life sciences
- How to motivate early-career scientists to seek out mentors and resources

• How to convince senior leadership to take time for coaching the next generation of leaders and support DEI initiatives
• How to create simple and impactful opportunities for mentors and mentees to connect and collaborate

6:00 Dinner Short Courses*

**Premium Pricing or separate registration required. See Short Courses page for details.*

8:30 Close of Day

THURSDAY, OCTOBER 3

7:30 am Registration Open and Morning Coffee

INSIGHTS FROM VENTURE CAPITALISTS

8:00 PANEL DISCUSSION: Trends in Drug Discovery
Moderator: Daniel A. Erlanson, PhD, Chief Innovation Officer, Innovation and Discovery, Frontier Medicines Corporation
Panelists:
Jernej Godec, PhD, Principal, Atlas Venture
Jenna Hebert, PhD, Senior Associate, RA Capital Management
Jamie Kasuboski, PhD, Partner, Luma Group
Jasmina Marjanovic, PhD, Partner, Takeda Ventures
Swetha Murali, PhD, Vice President, OMX Ventures

CHEMOPROTEOMIC & COVALENT APPROACHES

8:45 Chairperson's Remarks
Alexander Federation, PhD, Co-Founder & CEO, Talus Bioscience

8:50 Discovery and Optimization of Transcription Factor Modulators Using Cell-Based, Functional Chemoproteomics
Alexander Federation, PhD, Co-Founder & CEO, Talus Bioscience
Previously "undruggable" transcription factors tend to fold and function properly only within native cellular environments. To address these targets, we developed TF-Scan, a live-cell assay that measures changes in TF DNA-binding activity after small molecule treatment. Using TF-Scan, we discovered covalent compounds capable of binding and inhibiting dozens of previously undruggable TFs. This was followed by rapid optimization of a lead brachyury inhibitor that blocks chordoma tumor growth *in vivo*.

9:20 In-Cell Ligand Discovery for Challenging Targets Using Alkyne-Bearing Electrophiles
Lynn McGregor, PhD, Senior Principal Scientist, Novartis BioMedical Research
For many difficult-to-drug targets, the milieu of the native cellular environment is critical to capturing the relevant biological state for ligand discovery. Alkyne-bearing electrophiles offer a flexible toolset for in-cell assay development, including both mass spectrometry (MS)-based and non-MS based approaches toward binder discovery for transcription factors and beyond.

9:50 ML-Guided Covalent Library Design Informed by Activity-Based Protein Profiling Accelerates Hit-ID in Lead-Like Space
Adam Schwaid, PhD, Director, Chemical Biology & Proteomics, Odyssey Therapeutics
Covalent molecules can target proteins once considered undruggable, sparking renewed interest in covalency. Odyssey has built a lead-like covalent library characterized by live-cell ABPP to determine binding and selectivity. These measurements inform ML models, guiding library expansion towards a goldilocks range of reactivity to identify selective hits. Screening our library has led to the identification of ligands for 40% of the proteome, including functional ligands for undrugged transcription factors.

10:20 In-Person Breakouts
In-Person Breakouts are informal, moderated discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator who keeps the discussion on track and the group engaged. To get the most out of this format, please come prepared to share examples from your work, be a part of a collective, problem-solving session, and participate in active idea sharing. Please visit the Breakouts page on the conference website for a complete listing of topics and descriptions.

IN-PERSON BREAKOUT: Leveraging Novel Strategies for Transcription Factors and Undruggable Targets
Kristy Stengel, PhD, Assistant Professor, Department of Cell Biology, Albert Einstein College of Medicine
Asad Taherbhoy, PhD, Director, Drug Discovery, Foghorn Therapeutics
William Tansey, PhD, Ingram Professor of Cancer Research, Professor of Cell & Development Biology, Vanderbilt University
Pamela Ting, PhD, Associate Director, Hematology, Novartis Institutes for BioMedical Research

11:05 Coffee Break in the Exhibit Hall with Poster Viewing and Best of Show Awards Announced

SCREENING APPROACHES

11:45 Screening DNA Binding Proteins with DNA Encoded Libraries
Christopher B. Phelps, PhD, Vice President and Head, Early Discovery, Nurix Therapeutics, Inc.
Transcription factors are historically a challenging target class to drug. Although DNA-encoded libraries (DEL) have become a staple for ligand discovery, transcription factors and other proteins that specifically bind DNA present distinct challenges for DEL technology. Nurix has developed a broadly applicable approach for applying affinity selection and informatic methods to transcription factors, and these methods have yielded tractable hits for the EWS-FLI1 fusion oncoprotein.

12:15 pm Small Molecule Inhibition of a TF-BAF Protein-Protein Interaction in Cancer
Asad Taherbhoy, PhD, Director, Drug Discovery, Foghorn Therapeutics
Transcription factors (TFs) make for compelling drug targets but have been historically hard to drug. In disease settings, TFs can hijack the BAF chromatin remodeling complex to open incorrect regions of the genome, promoting the diseased state. Here we highlight how Foghorn's transcription factor platform has been set up to understand TF-BAF interactions, develop various HTS assays, and find chemical matter for the disruption of protein-protein interactions.

12:45 Sponsored Presentation *(Opportunity Available)*

1:15 Transition to Lunch

1:20 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:50 Dessert Break in the Exhibit Hall with Last Chance for Poster Viewing

DEGRADING TRANSCRIPTION FACTORS

2:30 Chairperson's Remarks

Kristy Stengel, PhD, Assistant Professor, Department of Cell Biology, Albert Einstein College of Medicine

2:35 Targeted Transcription Factor Degradation Reveals Therapeutic Vulnerabilities and Mechanisms of Regulation

Kristy Stengel, PhD, Assistant Professor, Department of Cell Biology, Albert Einstein College of Medicine

Transcription factors (TFs) are among the most frequently mutated and/or translocated genes in cancer, suggesting that a detailed understanding of their mechanism-of-action could better define disease etiology and help identify novel nodes for therapeutic intervention. Recently, our lab has employed novel degron technologies to rapidly degrade TF proteins. This technology, when combined with nascent transcript sequencing and multiomic readouts, allows us to identify direct mechanisms of TF action.

3:05 Discovery of Highly Potent, Selective, and Efficacious STAT3 PROTAC Degraders Capable of Achieving Long-Lasting Tumor Regression

Haibin Zhou, PhD, Associate Research Scientist, Laboratory of Dr. Shaomeng Wang, Department of Hematology & Oncology, University of Michigan

STAT3 is a transcription factor and a promising therapeutic target for cancer and other human diseases. We have discovered a highly potent, selective, and efficacious STAT3 degrader UM-STAT3-1218. UM-STAT3-1218 is a highly promising STAT3 degrader for the treatment of human cancers and other human diseases in which STAT3 plays a key role.

3:35 Novel Heterobifunctional Modalities for Targeted Protein Degradation and Stabilization

H. Ümit Kaniskan, PhD, Associate Professor, Laboratory of Dr. Jian Jin, Department of Pharmacological Sciences, Icahn School of Medicine at Mt. Sinai

The Jian Jin Laboratory at Icahn School of Medicine at Mount Sinai is a leader in discovering novel degraders targeting oncogenic proteins and developing new technologies for advancing targeted protein degradation and stabilization. Our lab's recent progress will be presented featuring our latest studies such as Methyl-PROTAC, Z-PROTAC, and more.

4:05 Degradation of Nuclear Receptors for Oncology: AR Degrader HP518 and ER Degrader HP568

Wu Du, PhD, Senior Vice President, Department of Medicinal Chemistry, Hinova Pharmaceuticals, Inc.

Hinova discovered highly potent and orally available AR degrader HP518 and ER-targeting degrader HP568. HP518 demonstrated an excellent preclinical profile and is currently in Phase I/II clinical trial. Thus far, HP518 has showed a satisfactory safety profile and encouraging efficacy signals in heavily pretreated prostate cancer patients. HP568 showed oral PK and preclinical efficacy superior to current leading AR degraders. Both compounds are promising best-in-class AR and ER degraders.

4:35 Close of Conference

TUESDAY, OCTOBER 1

7:00 am Registration Open and Morning Coffee

AI FOR DRUG DESIGN & OPTIMIZATION

7:55 Welcome Remarks

8:00 Chairperson's Remarks

Fred Manby, DPhil, Co-Founder & CTO, Iambic Therapeutics

8:05 AI and Lab Automation to Move from Launch to IND in Two Years: Discovering IAM1363, a Pan-Mutant, Brain-Penetrant HER2 Inhibitor

Fred Manby, DPhil, Co-Founder & CTO, Iambic Therapeutics

I'll describe the main elements of our AI-driven experimental platform (including models like NeuralPLexer for structure prediction, and plate-based experimentation for closed-loop exploration and data generation). As an example of how these technologies have been effectively brought to bear in discovery projects at Iambic, I'll talk through our lead program, which went from launch to IND in 24 months, and is now being studied in a Phase 1 clinical trial.

8:35 Leveraging ML- and Physics-Based Methods for Design, Optimization, and Acceleration of the Development of Antibody Agonists

J.C. Hus, PhD, Senior Director, Informatics, Diagonal Therapeutics

The DIAGONAL platform, a cutting-edge integration of ML and physics-based methodologies overcomes technical limitations that hindered agonist antibody discovery in the past and allows for reproducible and reliable design of developable agonist antibodies against any multimeric receptor complex. We will illustrate the method by presenting the four case studies where the DIAGONAL platform helped us to design antibody agonists targeting four structurally distinct receptor complexes with a 100% success rate.

9:05 A Compendium of Kinase Anti-Targets Associated with Adverse Events Mined from Toxicity Data

Rayees Rahman, PhD, Co-Founder & CEO, Harmonic Discovery

Kinase inhibitors are a successful category of therapeutics used in treating a wide variety of disease. Despite their efficacy, these drugs often present clinically relevant adverse events that can limit their therapeutic utility. To improve modeling of kinase inhibitor toxicity in patients, we extensively mined both literature and publicly available toxicity data to develop the Kinase Anti-Targets Compendium, a database of kinases statistically associated with specific toxicities.

9:35 Networking Coffee Break

10:05 Foundation Models Require Significantly Less Bioactivity Data to Discover Potent and Selective Ligands for a New Target

Jason Rolfe, PhD, Co-Founder & CTO, Variational AI

Generative AI foundation models trained on enormous datasets achieve human-level performance in domains like natural language. A complementary approach to small-molecule drug discovery is hampered because the hundreds of millions of available bioactivity measurements are noisy and inconsistently collected. We overcome these difficulties and construct a small-molecule foundation model that yields high-accuracy predictions and discovers potent and selective ligands on targets with orders of magnitude less bioactivity data.

10:35 Has Generative AI Had an Impact on Small Molecule Design?

Alba Macias, PhD, Director, Drug Design, Exscientia Inc.

We present Exscientia's approach to drug discovery and the important role of generative small molecule design in the process. The discovery of a novel LSD1 inhibitor and a successful proof-of-concept study leading to the discovery of novel, bispecific anti-malaria agents are presented as applications of generative design.

11:05 Has AI/ML Significantly Impacted Drug Design & Optimization: Discussion With Session Speakers

11:35 Predicting Bioactivity Before the Clinic

Henry Valle, Customer Support Specialist, CAS

The latest offering from CAS, the makers of CAS SciFinder, combines our high-quality, comprehensive substance and chemistry data with the biological data needed to advance medicinal chemistry and drug discovery processes. In this session, you'll get a chance to preview the CAS BioFinder Discovery Platform, including integrated predictive models, and learn about the future of the CAS life sciences initiative.

12:05 pm Transition to Lunch

12:10 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

12:40 Session Break

AI FOR RNA DRUG DISCOVERY

1:15 Chairperson's Remarks

1:20 Combining NMR Transverse Relaxation Times (T2) and Computational Chemistry to Target RNA

Barak Akabayov, PhD, Professor, Department of Chemistry, Ben Gurion University of the Negev

Using a unique combination of NMR and computational chemistry, we have developed novel antibacterial small molecules by targeting an RNA hairpin within the ribosomal PTC. The optimization models used a dataset of small molecules, and their docking scores were crucial in establishing design principles for new small molecules with improved bioactivity. We synthesized molecules, tested their ability to inhibit the ribosome, and demonstrated the binding mechanism to the RNA hairpin.

1:50 LightON mRNA: Anima's mRNA Lightning Brings AI to mRNA Biology

Generoso Ianniciello, Chief Business Officer, Anima Biotech

Using high-content, high-throughput imaging, we have generated over 2 billion visualizations to train our mRNA image neural network to identify disease signatures. Our massively parallel automated mRNA lab tests thousands of molecules, identifying active ones that visually restore diseased cells to their healthy state. MOAi technology utilizes the mRNA knowledge graph, our LLM, and the Lightning co-pilot, rapidly pinpointing mechanisms of action and molecular targets, through a unified, scalable interface.

2:20 Presentation to be Announced

2:50 In-Person Breakouts

In-Person Breakouts are informal, moderated discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator who keeps the discussion on track and the group engaged. To get the most out of this format, please come prepared to share examples from your work, be a part of a collective, problem-solving session, and participate in active idea sharing. Please visit the Breakouts page on the conference website for a complete listing of topics and descriptions.

IN-PERSON BREAKOUT: How to Quantify Biology to Inform AI/ML-Driven Decisions in Drug Discovery
Arvind Rao, PhD, Associate Professor, Department of Computational Medicine and Bioinformatics, University of Michigan
Yuan Wang, PhD, Head of Research Analytics, UCB Pharma

3:35 Grand Opening Refreshment Break in the Exhibit Hall with Poster Viewing and Best of Show Voting Begins

AI MODELS HELPING TRANSLATIONAL RESEARCH

4:30 Chairperson's Remarks
Yuan Wang, PhD, Head of Research Analytics, UCB Pharma

4:35 Computational Evaluation of Human-Relevant *in vitro* Disease Models Enables Phenotype Differentiation
Yuan Wang, PhD, Head of Research Analytics, UCB Pharma
Early translational studies using human-relevant *in vitro* models can help our understanding of disease pathobiology by simulating hallmark phenotypes in patients. To study these phenotypes, we have developed both 2D and 3D *in vitro* human models using iPSC-derived cardiomyocytes. We have analyzed the behavior of these models using computational methods like signal processing and computer vision. We will present promising results from this analysis as well as potential caveats.

5:05 Generative AI for Toxicology and Drug Safety
Weida Tong, PhD, Director, Division of Bioinformatics & Biostatistics, National Center for Toxicological Research, US FDA
This presentation will showcase examples from FDA projects in Generative AI, focusing on its application using Generative Adversarial Networks (GANs) in predictive toxicology, translational toxicology, and drug safety assessment. Specifically, these projects apply GANs to: (1) Learn from existing animal study data to generate animal study results without conducting actual experiments; (2) Generate toxicogenomics data based solely on experimental design; and (3) Translate findings from one organ to another.

5:35 AI Methods to Integrate Multi-modal Omics, Spatial and Single Cell Profiling to Identify Gene Regulatory Programs
Arvind Rao, PhD, Associate Professor, Department of Computational Medicine and Bioinformatics, University of Michigan
Spatial profiling technologies coupled with non-spatial profiling like scRNAseq have the potential to enable a multi-factorial, multi-modal characterization of the tissue microenvironment. Advances in statistics and ML can aid interpretation and integration with companion data like bulk and singlecell genomics. I will discuss analysis paradigms from machine learning that can be used to integrate and then prioritize gene regulatory programs underlying oncogenesis (as well as therapeutic candidates) using case studies.

6:05 Welcome Reception in the Exhibit Hall with Poster Viewing

7:05 Close of Day

WEDNESDAY, OCTOBER 2

7:30 am Registration Open and Morning Coffee

7:55 Chairperson's Remarks
Woody Sherman, PhD, CIO, Psivant Therapeutics

8:00 FEATURED PRESENTATION: Grand Challenges for Computers in Drug Discovery
Woody Sherman, PhD, CIO, Psivant Therapeutics
We present a set of grand challenges for computational tools in small molecule drug discovery. This unifying framework will enable the community to more readily evaluate the effectiveness of computational methods that have the potential to aid in the discovery of novel therapeutics. Insights presented here stem from experts that span drug hunters, method developers, and thought leaders in addition to lessons learned from our internal drug discovery efforts.

9:00 Computationally Augmented Total Synthesis
Timothy Newhouse, PhD, Associate Professor, Department of Chemistry, Yale University
Efficient syntheses of complex small molecules often involve speculative experimental approaches. The challenge of such plans is that experimental evaluation of high-risk strategies is resource intensive, as it entails iterative attempts at unsuccessful strategies. This presentation describes a complementary strategy that combines creative human-generated synthetic plans with robust computational prediction of synthetic feasibility. This work defines how machine learning models can drive complex molecule synthesis.

9:30 Sponsored Presentation *(Opportunity Available)*

10:00 Coffee Break in the Exhibit Hall with Poster Viewing

PLENARY KEYNOTE PROGRAM

10:50 Plenary Keynote Chairperson's Remarks
An-Dinh Nguyen, Team Lead, Discovery on Target, Cambridge Healthtech Institute

10:55 PLENARY KEYNOTE: Discovery of Transformative Rx to Treat Obesity and Related Diseases
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12:25 pm Close of AI/ML-Enabled Drug Discovery – Part 1 Conference

WEDNESDAY, OCTOBER 2

PLENARY KEYNOTE PROGRAM

10:50 am Plenary Keynote Chairperson's Remarks
An-Dinh Nguyen, Team Lead, Discovery on Target, Cambridge Healthtech Institute

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12:25 pm Enjoy Lunch on Your Own

AI/ML FOR PROPERTY PREDICTIONS

1:45 Welcome Remarks

1:50 Chairperson's Remarks
Sean Ekins, PhD, Founder & CEO, Collaborations Pharmaceuticals, Inc.

1:55 Predicting Proteolysis-Targeting Chimeras' (PROTACs) ADME/Tox Properties
Sean Ekins, PhD, Founder & CEO, Collaborations Pharmaceuticals, Inc.
We have tested a small set of PROTACs against several human drug transporters *in vitro* as well as in zebrafish for their effects on embryo and larval mortality, morphology, embryo photomotor response, and larval photomotor response. We will report the preliminary outcomes of these combined assessments and discuss the implications for PROTACs development as well as how this data could be used for machine learning model generation and evaluation.

2:25 Structure Prediction of Cyclic Peptides via Molecular Dynamics and Machine Learning
Yu-Shan Lin, PhD, Associate Professor, Chemistry, Tufts University
A major obstacle to cyclic peptide development is that little structural information is available, as most cyclic peptides adopt multiple conformations in solution. By combining molecular dynamics simulation and machine learning, we can now provide simulation-quality cyclic peptide structure predictions in seconds to enable structure-based design of cyclic peptides and an understanding of their sequence–activity relationships.

2:55 Maximizing your return on computational drug discovery with AI-powered serverless HPC FOVUS
Fengbo Ren, Founder & CEO, Fovus Corp
Fovus is a groundbreaking serverless HPC platform designed to simplify and optimize cloud HPC for enterprises. Utilizing AI-powered cloud HPC strategy optimization and logistics orchestration, Fovus eliminates cloud complexities. It ensures and sustains time-cost optimality, making HPC easily accessible and manageable for the digital R&D teams in Fortune 500 and high-tech startups/unicorns alike. Fovus recently empowered a biotech startup to get drug discovery insights >100x faster while slashing the cloud cost by 7x. Join this talk to learn how you get back lost productivity and speed up drug discovery at reduced costs by leveraging Fovus.

3:25 Refreshment Break in the Exhibit Hall with Poster Viewing

4:15 Data-Driven Optimization in Medicinal Chemistry
Barak Akabayov, PhD, Professor, Department of Chemistry, Ben Gurion University of the Negev
Data-driven drug design relies on computational optimization and chemoinformatics to identify molecular features and predict bioactivity. This involves collecting and preprocessing chemical datasets, identifying influential features, and using selected features to optimize molecular structures and improve bioactivity. By incorporating these steps in our process, we have generated new molecules with improved bioactivity for various targets, outperforming traditional methods in terms of speed and precision.

4:45 DNA-Encoded Libraries for Machine Learning: Deep Data at Scale
Patrick McEnaney, PhD, Senior Scientist, High Throughput Chemistry, insitro
To build better models of small molecule binders to target proteins, high-quality training sets are essential. Leveraging DNA-encoded libraries (DELs) with billions of molecules, we utilize our selection technology to generate data with true negatives and accurately rank ordered true positive binders. We are working to utilize these large-scale data sets to enhance the predictive power of our small molecule protein binding models.

5:15 Dinner Short Course Registration*
**Premium Pricing or separate registration required. See Short Courses page for details.*

5:15 Diversity Discussion *(Sponsorship Opportunity Available)*

IN-PERSON DISCUSSION: Fostering Diversity through Mentoring
Naytia Byrd, Manager, Human Resources, Ovid Therapeutics, Inc.
Saudat Fadeyi, PhD, MBA, Director, Business Development, Ovid Therapeutics, Inc.
Fred Manby, DPhil, Co-Founder & CTO, Iambic Therapeutics
Joel Omage, Research Scientist II, CVM Disease Area, Novartis Institutes for BioMedical Research, Inc.
Andrew Zhang, PhD, Director, Chemical Biology, AstraZeneca
Topics for discussion will include, but certainly not be limited to:
• How to increase awareness and address hidden barriers and biases in life sciences
• How to motivate early-career scientists to seek out mentors and resources

• How to convince senior leadership to take time for coaching the next generation of leaders and support DEI initiatives
• How to create simple and impactful opportunities for mentors and mentees to connect and collaborate

6:00 **Dinner Short Courses***

**Premium Pricing or separate registration required. See Short Courses page for details.*

8:30 **Close of Day**

THURSDAY, OCTOBER 3

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

INSIGHTS FROM VENTURE CAPITALISTS

8:00 **PANEL DISCUSSION: Trends in Drug Discovery**
Moderator: Daniel A. Erlanson, PhD, Chief Innovation Officer, Innovation and Discovery, Frontier Medicines Corporation
Panelists:
Jernej Godec, PhD, Principal, Atlas Venture
Jenna Hebert, PhD, Senior Associate, RA Capital Management
Jamie Kasuboski, PhD, Partner, Luma Group
Jasmina Marjanovic, PhD, Partner, Takeda Ventures
Swetha Murali, PhD, Vice President, OMX Ventures

AI-ENABLED DECISION-MAKING

8:45 **Chairperson's Remarks**
Shruthi Bharadwaj, PhD, Global Lead, Digital & Analytics, R&D Global Operations, Sanofi

8:50 **A Specialized Platform for Innovative Research Exploration (ASPIRE): Lowering the Barrier to Drug Development by Applying Automation, Data Analytics, and AI/Machine Learning to Chemistry and Biology**
Sean Gardner, MS, Scientific Program Manager, Office of Special Initiatives, NCATS, National Institutes of Health
The gap between drug discovery and information science continues to close, hence there has never been a better time to leverage the power of AI/ML techniques to advance our understanding of the relationships between chemical and biological space. NCATS and the greater scientific community have identified focus areas that need to be addressed and supported in order to transform the design-synthesize-test cycle to transition to be more data-driven.

9:20 **AI-Driven Hit Finding: A Perspective from the CACHE Challenges**
Matthieu Schapira, PhD, Principal Investigator, Structural Genomics Consortium, Professor, Pharmacology & Toxicology, University of Toronto
CACHE is a series of prospective computational hit-finding challenges. Results from the first challenges confirm that the field is in an exploratory mode, where a variety of ways to implement deep learning methodologies are tested with mixed success. Fragment-based and *de novo* generative design strategies are repeatedly among the best performing computational workflows in the first challenge. Lessons from the second challenge will also be presented.

9:50 **FEATURED PRESENTATION: A Primer on Machine Learning for Experimental Molecular Researchers – Principles, Practicalities, and Pitfalls**
Adrian Whitty, PhD, Associate Professor, Department of Chemistry, Boston University
Lowering the barrier to entry to Machine Learning (ML), for scientists without strong backgrounds in computer science and statistics, is important for broadening access to these powerful methods. I will describe a set of methods we, as experimentalists, have found useful as entry points to ML, with examples. The focus is on conceptualizing the underlying principles, and on appreciating the key scientific decisions and controls that lead to meaningful outcomes.

10:20 **In-Person Breakouts**
In-Person Breakouts are informal, moderated discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator who keeps the discussion on track and the group engaged. To get the most out of this format, please come prepared to share examples from your work, be a part of a collective, problem-solving session, and participate in active idea sharing. Please visit the Breakouts page on the conference website for a complete listing of topics and descriptions.

IN-PERSON BREAKOUT: How Successful Are AI/ML Approaches in Drug Development Today?
Shruthi Bharadwaj, PhD, Global Lead, Digital & Analytics, R&D Global Operations, Sanofi
Sean Gardner, MS, Scientific Program Manager, Office of Special Initiatives, NCATS, National Institutes of Health
Dmitri Kireev, PhD, Professor, Department of Chemistry, University of Missouri

IN-PERSON BREAKOUT: Using AI/ML for Lead and Target Discovery
Barak Akabayov, PhD, Professor, Department of Chemistry, Ben Gurion University of the Negev
Diane M. Joseph-McCarthy, PhD, Professor of the Practice, Biomedical Engineering, Boston University
Petrina Kamya, PhD, Global Head of AI Platforms, Vice President Insilico Medicine; President, Insilico Medicine Canada, Insilico
Harpreet Saini, PhD, Senior Director, Informatics, Astex Pharmaceuticals Ltd.

11:05 **Coffee Break in the Exhibit Hall with Poster Viewing and Best of Show Awards Announced**

ACCELERATING DISCOVERY USING AI/ML STRATEGIES

11:45 **AI at the Frontier: Pioneering Rare Disease Research and Patient Outcomes**
Linxin Gu, MS, CEO, TechConnect
In the fight against rare diseases, AI technologies offer unprecedented opportunities to accelerate discovery and enhance patient care. We utilize AI to bridge significant gaps in rare disease research, focusing on improving diagnostic accuracy, speeding up discovery, and tailoring treatments to individual patient needs. Our approach leverages deep learning and genetic algorithms to identify novel drug targets and predict therapeutic outcomes, thus reducing time and cost bringing treatments to market.

12:15 pm **Closed-Loop Discovery: Integrating AI, Data Science, and Human Expertise**
Jessen Yu, Senior Director, Data Science, Valo Health

Our talk explores how data scientists, ML modelers, medicinal chemists, and others have collaborated to accelerate small molecule drug discovery through our closed-loop discovery process. At its core, closed-loop discovery is an integrated, streamlined pipeline that rapidly propagates information through the design-make-test-analyze cycle. We'll illustrate how each expert contributes to the overarching goal and how we've tackled the challenge of enabling effective collaboration among these diverse personas.

12:45 DEL-ML: BIG Data Leap in Early Stage Drug Discovery

Mohamed Abouzleikha, VP & Head, X-Chem

DNA-encoded libraries (DELs) have transformed the landscape of early-stage drug discovery, facilitating the identification of novel modulators targeting a wide array of therapeutic protein targets. The vast amount of data generated by DELs presents an exceptional opportunity for harnessing machine learning techniques in hit identification within drug discovery. However, this leap into big data landscape is accompanied by challenges such as data quality, imbalanced datasets, and model evaluation. In this presentation, we explore the current state of machine learning applications in DELs, shedding light on challenges and proposing strategies to address them. Additionally, we introduce ArtemisAI DEL implementation, a pipeline tailored specifically for processing DEL data, showcasing its efficacy across a comprehensive array of targets. Within this overview, we aim to navigate the integration of machine learning in the field of DELs, guiding the way for groundbreaking advancements in early-stage drug discovery.

1:15 Transition to Lunch

1:20 LUNCHEON PRESENTATION: Talk Title to be Announced

Michael Bellucci, Sr Dir of R&D, XtalPi Inc

1:50 Dessert Break in the Exhibit Hall with Last Chance for Poster Viewing

AI-DRIVEN TARGET DISCOVERY

2:30 Chairperson's Remarks

Harpreet Saini, PhD, Senior Director, Informatics, Astex Pharmaceuticals Ltd.

2:35 Integrative Computational Genetics Approach for Target Discovery of ALS

Harpreet Saini, PhD, Senior Director, Informatics, Astex Pharmaceuticals Ltd.

We have developed a computational, genetics-based approach which integrates functional data from GWAS, ontologies, and biological networks to predict potential drug targets with evidence for disease association. We obtained a list of target genes associated with ALS and prioritized potential target genes by integrating structural information and cell-type transcriptomics data.

3:05 FEATURED PRESENTATION: Target Discovery Using AI—The Story behind Insilico Medicine's Discovery and Validation of MYT1 as a Target Implicated in Breast Cancer

Petrina Kamya, PhD, Global Head of AI Platforms, Vice President Insilico Medicine; President, Insilico Medicine Canada, Insilico

Using PandaOmics, we identified MYT1 as a promising new therapeutic target for breast and gynecological cancer. PandaOmics is Insilico Medicine's AI-driven target discovery platform that leverages multi-modal data to discover targets implicated in a disease. To further validate the selection of MYT1, we leveraged Chemistry42 to design and optimize a lead compound that exhibits remarkable selectivity over WEE1 and has promising *in vivo* antitumor efficacy.

3:35 Interaction-Based Hit Discovery Platform to Orphan Targets

Dmitri Kireev, PhD, Professor, Department of Chemistry, University of Missouri

Interaction-based screening and design are promising novel strategies for hit finding and lead optimization. The key information unit in the interaction realm is a thin interface between the interacting ligand and protein. When fed to deep neural networks, interaction signatures may infer SAR for unliganded proteins by exploiting structural data across ligands and proteins. We give an overview of the approach and describe its successful applications to several challenging targets.

4:05 Assessment of Target Druggability Enabled by Machine Learning

Diane M. Joseph-McCarthy, PhD, Professor of the Practice, Biomedical Engineering, Boston University

Identification of hot spots on the surface of macromolecules is key to evaluating the druggability of novel targets and the likelihood of finding new chemical entities. Computational hot-spot mapping was performed across a set of drug targets, and a machine learning approach was employed to select the top druggable sites. Within this context, the utility of AI-generated protein models obtained using AlphaFold, including ensembles of structural models, was assessed.

4:35 Close of Conference

TUESDAY, OCTOBER 1

7:00 am Registration Open and Morning Coffee

UNDERSTANDING TRANSLATIONAL CHALLENGES

7:55 Welcome Remarks

8:00 Chairperson's Remarks
Madhu Lal Nag, PhD, CSO, InSphero

8:05 Perspectives and Opportunities Analysis of Translational *in vitro* Models from the 3Rs Collaborative
Sally Thompson-Iritani, DVM, PhD, Assistant Vice Provost, Animal Care & Outreach & 3Rs, University of Washington
This presentation will include a comprehensive analysis of translational *in vitro* models from the perspective of the 3Rs Collaborative. We will explore current methodologies, challenges, and opportunities in developing and utilizing these models to enhance biomedical research while minimizing animal use. It delves into the potential impact of these models for future advancements and collaboration in the pursuit of humane and effective research practices.

8:35 Evidentiary Considerations to Build Confidence Including Complex *in vitro* Models in a Weight-of-Evidence Approach to Support Advancing New Therapies to Clinical Trials
Nicholas King, MS, Executive Director, Critical Path Institute
There is a significant opportunity for a paradigm shift in drug development and discovery by integrating complex *in vitro* models (CIVM). Stakeholders need to identify unmet needs and establish criteria for qualification and implementation of CIVM. CIVMs may play an important role in a weight-of-evidence approach when utilizing human CIVMs to address questions when animal models cannot.

9:35 Networking Coffee Break

10:05 FEATURED PRESENTATION: Advancing Alternative Methods for Regulatory Use
Rodney L. Rouse, DVM, MBA, PhD, Deputy Director, Division of Applied Regulatory Science, Center for Drug Evaluation and Research, United States Food and Drug Administration
This talk will attempt to convey FDA perspective on and interest in developing and adopting alternative methods including review of FDA involvement in efforts to advance alternative methods for regulatory use.

10:35 PANEL DISCUSSION: Navigating the Non-Animal Models Ecosystem in Therapeutic Development
Moderator: Madhu Lal Nag, PhD, CSO, InSphero
Panelists:
Marc Ferrer, PhD, Director, 3D Tissue Bioprinting Laboratory, Division of Preclinical Innovation, National Center for Advancing Translational Sciences, National Institutes of Health (NIH)
Nicholas King, MS, Executive Director, Critical Path Institute
Rodney L. Rouse, DVM, MBA, PhD, Deputy Director, Division of Applied Regulatory Science, Center for Drug Evaluation and Research, United States Food and Drug Administration
Sally Thompson-Iritani, DVM, PhD, Assistant Vice Provost, Animal Care & Outreach & 3Rs, University of Washington
Lindsay Tomlinson, PhD, Global Pathologist Resource Lead, Pfizer Inc.

11:35 Presentation to be Announced

12:05 pm Transition to Lunch

12:10 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

12:40 Session Break

EFFECTIVENESS OF IN VITRO MODELS

1:15 Chairperson's Remarks
Marc Ferrer, PhD, Director, 3D Tissue Bioprinting Laboratory, Division of Preclinical Innovation, National Center for Advancing Translational Sciences, National Institutes of Health (NIH)

1:20 Characterization of a Human Colonic Microtissue as a Novel *in vitro* Tool to Investigate Colonic Drug Disposition
Stephanie Kourula, PhD, Principal Scientist, Johnson & Johnson Innovative Medicine
Human drug absorption is one of the critical parameters to define the bioavailability of drug candidates. Traditional *in vitro* models focus on the small intestine where most drugs are absorbed. However, accurately predicting colonic absorption has become increasingly relevant for drugs targeting the colon to treat colonic diseases. Therefore, we have characterized an organotypic 3D colon microtissue (*EpiColon*) as a novel *in vitro* platform to model colonic drug disposition.

1:50 FEATURED PRESENTATION: Microphysiological Models of Chronic Inflammatory Diseases
Linda Griffith, PhD, Professor, Biological Engineering & Teaching Innovation, Massachusetts Institute of Technology
Can Microphysiological Systems (MPS) become true replacements for animals in research and drug development? The answer depends on the development of (relatively) low-cost, turnkey technologies and bridging the gap between modern systems biology and the MPS community. It requires conceptualizing human pathophysiology through the lens of systems biology to design MPS that capture chronic inflammatory diseases: immune components, organ-organ crosstalk, and sex dimorphism.

2:20 Human-on-a-Chip Systems for Therapeutic Evaluation and Regulation Submission for Neurological Diseases
James Hickman, PhD, Professor, NanoScience Technology Center, University of Central Florida
Human-on-a-chip systems for safety and efficacy—with up to 5 organs—have demonstrated up to a 28-day evaluation of compounds. Embodiments are a functional NMJ system for ALS, MG, CMT, and an LTP model for AD. Sanofi has used efficacy data from our conduction velocity model for an IND for CIDP that enabled a clinical trial (#NCT04658472), now in Phase III. Other INDs for phenotypic models have also been filed.

2:50 In-Person Breakouts
In-Person Breakouts are informal, moderated discussions, allowing participants to exchange ideas and experiences and develop future collaborations around a focused topic. Each discussion will be led by a facilitator who keeps the discussion on track and the group engaged. To get the most out of this format, please come prepared to share examples from your work, be a part of a collective, problem-solving session, and participate in active idea sharing. Please visit the Breakouts page on the conference website for a complete listing of topics and descriptions.

IN-PERSON BREAKOUT: Standardization of Complex *in vitro* Models (CIVMs) in Drug Development
Linda Griffith, PhD, Professor, Biological Engineering & Teaching Innovation, Massachusetts Institute of Technology
James Hickman, PhD, Professor, NanoScience Technology Center, University of Central Florida
Stephanie Kourula, PhD, Principal Scientist, Johnson & Johnson Innovative Medicine
Lindsay Tomlinson, PhD, Global Pathologist Resource Lead, Pfizer Inc.

3:35 Grand Opening Refreshment Break in the Exhibit Hall with Poster Viewing and Best of Show Voting Begins

AI MODELS HELPING TRANSLATIONAL RESEARCH

4:30 Chairperson's Remarks
Yuan Wang, PhD, Head of Research Analytics, UCB Pharma

4:35 Computational Evaluation of Human-Relevant *in vitro* Disease Models Enables Phenotype Differentiation
Yuan Wang, PhD, Head of Research Analytics, UCB Pharma
Early translational studies using human-relevant *in vitro* models can help our understanding of disease pathobiology by simulating hallmark phenotypes in patients. To study these phenotypes, we have developed both 2D and 3D *in vitro* human models using iPSC-derived cardiomyocytes. We have analyzed the behavior of these models using computational methods like signal processing and computer vision. We will present promising results from this analysis as well as potential caveats.

5:05 Generative AI for Toxicology and Drug Safety
Weida Tong, PhD, Director, Division of Bioinformatics & Biostatistics, National Center for Toxicological Research, US FDA
This presentation will showcase examples from FDA projects in Generative AI, focusing on its application using Generative Adversarial Networks (GANs) in predictive toxicology, translational toxicology, and drug safety assessment. Specifically, these projects apply GANs to: (1) Learn from existing animal study data to generate animal study results without conducting actual experiments; (2) Generate toxicogenomics data based solely on experimental design; and (3) Translate findings from one organ to another.

5:35 AI Methods to Integrate Multi-modal Omics, Spatial and Single Cell Profiling to Identify Gene Regulatory Programs
Arvind Rao, PhD, Associate Professor, Department of Computational Medicine and Bioinformatics, University of Michigan
Spatial profiling technologies coupled with non-spatial profiling like scRNAseq have the potential to enable a multi-factorial, multi-modal characterization of the tissue microenvironment. Advances in statistics and ML can aid interpretation and integration with companion data like bulk and singlecell genomics. I will discuss analysis paradigms from machine learning that can be used to integrate and then prioritize gene regulatory programs underlying oncogenesis (as well as therapeutic candidates) using case studies.

6:05 Welcome Reception in the Exhibit Hall with Poster Viewing

7:05 Close of Day

WEDNESDAY, OCTOBER 2

7:30 am Registration Open and Morning Coffee

DEVELOPING COMPLEX DISEASE MODELS

7:55 Chairperson's Remarks
Claus Jorgensen, PhD, Team Leader, Systems Oncology, Institute of Cancer Research

8:00 Modeling Complex Interactions between Tumor and Host Using Organoids
Claus Jorgensen, PhD, Team Leader, Systems Oncology, Institute of Cancer Research
Tumors are complex ecosystems where cancer cells are embedded within a complex microenvironment comprising multiple infiltrating cell types and a pathologically remodeled extracellular matrix. While much progress has been made in establishing and interrogating epithelial and stem cell-like models, incorporation of cells from the microenvironment and biophysical changes is challenging. Here, I will describe our efforts to develop and interrogate models of tumor cells and the conscripted microenvironment.

8:30 Functional Brain Region-Specific Neural 3D Cellular Models for Drug Screening
Marc Ferrer, PhD, Director, 3D Tissue Bioprinting Laboratory, Division of Preclinical Innovation, National Center for Advancing Translational Sciences, National Institutes of Health (NIH)
There is a need for neural models that incorporate the physiological complexity of the brain and are compatible with high throughput screening platforms. We have used iPSC-derived neural cells to make functional brain region-specific neural 3D cellular models in multi well plate format for drug screening. We will show data demonstrating neural spheroids with spontaneous and synchronized calcium oscillations and spatially defined neural circuit models produced using bioprinting techniques.

9:00 Monolayers, Organoids, and Multi-Cell Type Spheroids: Patient-Derived Tumor Models for the Preclinical Assessment of Experimental Therapeutics
Nathan P. Coussens, PhD, Scientific Director, Molecular Pharmacology Laboratory, Frederick National Laboratory for Cancer Research
Translation throughout the discovery/development pipeline into the clinic requires assays and model systems with physiological and pharmacological relevance. The ability to incorporate patient-derived tumor cells into assays with sufficient complexity to predict patient tumor responses could accelerate the development of new therapies. This presentation will describe the use of various patient-derived tumor models from the National Cancer Institute's Patient-Derived Models Repository for the evaluation of approved and investigational anticancer agents.

9:30 Sponsored Presentation *(Opportunity Available)*

10:00 Coffee Break in the Exhibit Hall with Poster Viewing

PLENARY KEYNOTE PROGRAM

10:50 Plenary Keynote Chairperson's Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target, Cambridge Healthtech Institute

10:55 PLENARY KEYNOTE: Discovery of Transformative Rx to Treat Obesity and Related Diseases

Richard DiMarchi, PhD, Distinguished Professor of Chemistry and Chair, Biomolecular Sciences, Indiana University; former Executive, Lilly and Novo Research Labs

To address obesity, a medicinal challenge that warrants broad molecular diversity, we pioneered the pharmacological strategy of recruiting endogenous hormones to optimize physiological mechanisms. Our discovery of single-molecule, multi-mechanism incretins enabled breakthrough efficacy in lowering body weight. The integrated pharmacology of these endocrine proteins and nuclear hormones is providing a library of drug candidates that promises great clinical outcomes for obesity and associated diseases that have historically been intractable.

11:40 PLENARY KEYNOTE: Fragment-Based Drug Discovery for Elusive Cancer Targets

Stephen W. Fesik, PhD, Professor of Biochemistry, Pharmacology & Chemistry; Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University

The most highly validated cancer targets (KRAS, MYC, and WNT) affecting the majority of cancers are thought to be impossible to drug. Using fragment-based methods that I pioneered over 25 years ago, we have discovered mutant selective and pan KRAS inhibitors, potent inhibitors of the MYC cofactor WDR5, and degraders of b-catenin in the WNT pathway. These novel inhibitors/degraders should have a tremendous impact on cancer treatment in the future.

12:25 pm Close of Physiologically Relevant Translational Models Conference

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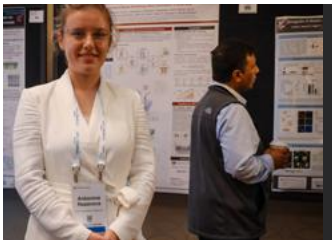

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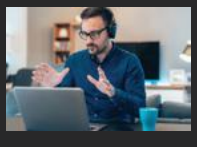

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