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

FINAL AGENDA

20th Annual Discovery on TARGET

OCTOBER 17-20, 2022
BOSTON, MA
Sheraton Boston & Virtual [EDT]

Plenary Keynote Program

Pirating Biology to Detect and Degrade Extracellular Proteins

James A. Wells, PhD
Professor, Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco

Therapeutic Modalities for Neuroscience Diseases

Anabella Villalobos, PhD
Senior Vice President, Biotherapeutics & Medicinal Sciences, Biogen

Conference Programs

October 17

Emerging Immune Modulation Strategies NEW

October 18-19

- PROTACs and Molecular Glues – Part 1
- Target Identification and Validation – Part 1
- Targeting RNA
- Small Molecule Immuno-Oncology Targets
- GPCR-Based Drug Discovery
- Antibodies Against Membrane Protein Targets – Part 1
- Targeting KRAS and Other Small G Proteins
- Artificial Intelligence in Drug Discovery – Part 1 NEW

October 19-20

- PROTACs and Molecular Glues – Part 2
- Target Identification and Validation – Part 2
- New Antivirals NEW
- NASH and Fibrosis
- Neurodegeneration Targets NEW
- Antibodies Against Membrane Protein Targets – Part 2
- Drug Lead Generation Strategies
- Artificial Intelligence in Drug Discovery – Part 2 NEW

Final Days to Register!

#BostonDOT22 | DiscoveryOnTARGET.com

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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 for informative presentations, lively dialogue, and meaningful connections with peers. Customize your experience further through focused short courses, interactive discussions, and networking options that help you engage with experts and solutions providers.

Our 20th Annual event brings back popular topics like PROTACs and RNA plus **new programming** on immunomodulation, antivirals, neurodegeneration targets, KRAS, and AI.

EVENT FEATURES

- 16 Conference Programs
- NEW Pre-Conference Symposium: Emerging Immune Modulation Strategies
- Dinner Short Courses (IN-PERSON ONLY)
- Interactive Discussions (IN-PERSON ONLY)
- And Much More

EVENT AT-A-GLANCE

#BostonDOT22

MONDAY October 17

Pre-Conference Dinner Short Courses* — IN-PERSON ONLY

- SC1: Protein Degraders: A Focus on PROTACs from a Beyond Rule of Five Space Perspective
- SC2: Chemical Biology for Phenotypic Screening and Target Deconvolution
- SC3: Best Practices for Targeting GPCRs, Ion Channels, and Transporters with Monoclonal Antibodies

Pre-Conference Symposium*

- Emerging Immune Modulation Strategies — NEW

TUESDAY October 18

- PROTACs and Molecular Glues – Part 1
- Target Identification and Validation – Part 1
- Targeting RNA
- Small Molecule Immuno-Oncology Targets
- GPCR-Based Drug Discovery
- Antibodies Against Membrane Protein Targets – Part 1
- Targeting KRAS and Other Small G Proteins
- Artificial Intelligence in Drug Discovery – Part 1 — NEW

WEDNESDAY October 19

- PROTACs and Molecular Glues – Part 1
- Target Identification and Validation – Part 1
- Targeting RNA
- Small Molecule Immuno-Oncology Targets
- GPCR-Based Drug Discovery
- Antibodies Against Membrane Protein Targets – Part 1
- Targeting KRAS and Other Small G Proteins
- Artificial Intelligence in Drug Discovery – Part 1 — NEW

Plenary Keynote Program

- PROTACs and Molecular Glues – Part 2
- Target Identification and Validation – Part 2
- New Antivirals — NEW
- NASH and Fibrosis
- Neurodegeneration Targets — NEW
- Antibodies Against Membrane Protein Targets – Part 2
- Drug Lead Generation Strategies
- Artificial Intelligence in Drug Discovery – Part 2 — NEW

Dinner Short Courses* — IN-PERSON ONLY

- SC4: Protein Degraders: A Focus on PROTACs from an ADME-Tox Perspective
- SC5: Biophysical Tools for Membrane Proteins: Drug Discovery Applications
- SC6: DNA-Encoded Libraries

THURSDAY October 20

- PROTACs and Molecular Glues – Part 2
- Target Identification and Validation – Part 2
- New Antivirals — NEW
- NASH and Fibrosis
- Neurodegeneration Targets — NEW
- Antibodies Against Membrane Protein Targets – Part 2
- Drug Lead Generation Strategies
- Artificial Intelligence in Drug Discovery – Part 2 — NEW

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

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 19 | 11:00 AM - 12:35 PM

11:00 am Plenary Chairperson's Remarks
An-Dinh Nguyen, Team Lead, Discovery on Target, Cambridge Healthtech Institute

11:05 Pirating Biology to Detect and Degrade Extracellular Proteins
James A. Wells, PhD, Professor, Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco

In contrast to intracellular PROTACs, approaches to degrade extracellular proteins are just emerging. I'll describe our recent progress to harness natural mechanisms such as transmembrane E3 ligases to degrade extracellular proteins using fully genetically encoded bi-specific antibodies we call AbTACs. We have also engineered a peptide ligase which can be tethered to cells to detect proteolysis events and target them with recombinant antibodies for greater selectivity for the tumor microenvironment.

11:50 Therapeutic Modalities for Neuroscience Diseases
Anabella Villalobos, PhD, Senior Vice President, Biotherapeutics & Medicinal Sciences, Biogen

Many effective medicines exist to treat neurological diseases, but medical need remains high. We have a unique multi-modality approach to discover novel therapies and our goal is to find the best modality regardless of biological target. With a multi-modality approach, we aim to expand target space, leverage synergies across modalities, and offer options to patients. Opportunities and challenges associated with small molecules, biologics, oligonucleotides, and gene therapy will be discussed.

12:35 pm Enjoy Lunch on Your Own

1:25 Refreshment Break in the Exhibit Hall with Poster Viewing

PLENARY KEYNOTE BIOGRAPHIES

James A. Wells, PhD, Professor, Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco

Wells's group pioneered the engineering of proteins, antibodies, and small molecules that target catalytic, allosteric, and protein-protein interaction sites; technologies including protein phage display, alanine-scanning, engineered proteases for improved hydrolysis, bioconjugations, N-terminomics, disulfide "tethering" (a novel site-directed fragment-based approach for drug discovery); and more recently an industrialized recombinant antibody production pipeline for the proteome. These led to important new insights into protease mechanisms, growth factor signaling, hot-spots in protein-protein interfaces, role of caspases in biology, and more recently to determining how cell surfaces change in health and disease. His team was integral to several protein products, including Somavert for acromegaly, Avastin for cancer, Lifitegrast for dry eye disease, and engineered proteases sold by Pfizer, Genentech, Shire and Genencor, respectively. He is an elected member of the US National Academy of Science, American Association of Arts and Science, and the National Academy of Inventors.

Anabella Villalobos, PhD, Senior Vice President, Biotherapeutics & Medicinal Sciences, Biogen

Prior to joining Biogen, Anabella was at Pfizer for 28 years where she was Vice President of Medicinal Synthesis Technologies and Neuroscience Medicinal Chemistry. As the leader of several medicinal chemistry groups throughout her career at Pfizer, Anabella's teams delivered >30 candidates which showed increased survival to the clinic. Anabella also championed new scientific directions that have changed design practices in medicinal chemistry, such as the Central Nervous System Multi-Parameter Optimization (CNS MPO) design tool and a novel PET ligand design and discovery approach. Anabella obtained her BS in Chemistry at the University of Panama and her PhD in Medicinal Chemistry at the University of Kansas where she was a Fulbright-Hays Fellow. She was a National Institutes of Health Postdoctoral Fellow at Yale University in synthetic organic chemistry for two years.

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VIEW EXHIBIT SCHEDULE

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Download Prospectus

For more information regarding exhibit and sponsorship, please contact:

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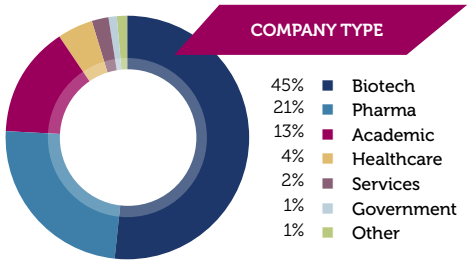
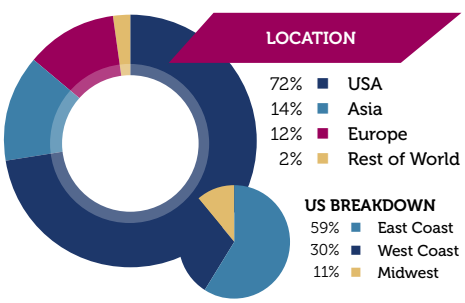
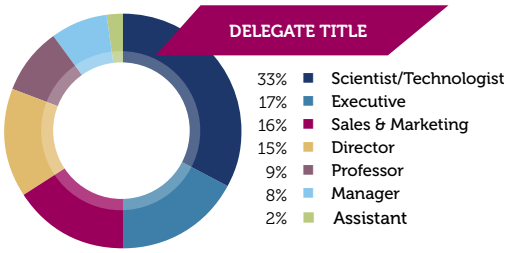
2021 ATTENDEE DEMOGRAPHICS







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PharmaBlock

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Promega

ProteoGenix

proteome sciences

Sai

Sino Biological

SpiroChem

TandemAI

TargetMol

Dinner Short Courses*

*Premium Pricing or separate registration required

SHORT COURSES WILL BE OFFERED IN-PERSON ONLY.

MONDAY, OCTOBER 17 5:00-7:30 PM

SC1: Protein Degraders: A Focus on PROTACs from a Beyond Rule of Five Space Perspective

Instructor:

John Erve, PhD, Senior Principal Scientist, Jerve Scientific Consulting

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 first 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 some aspects of transporters and how drug-PROTAC interactions may arise.

ROOM LOCATION: Back Bay A

SC2: Chemical Biology for 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

Andrew Zhang, PhD, Team Leader, Chemical Biology, AstraZeneca

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.

ROOM LOCATION: Back Bay C

SC3: 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 are important therapeutic targets and together 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 to discover therapeutic antibodies against them. This course will examine emerging technologies and strategies for enabling the isolation of specific and functional antibodies against GPCRs, ion channels, and transporters, and highlight progress via case studies.

ROOM LOCATION: Back Bay B

WEDNESDAY, OCTOBER 19 6:30-9:00 PM

SC4: Protein Degraders: A Focus on PROTACs from an ADME-Tox Perspective

Instructors:

Matthew Hoffmann, PhD, Senior Director, Drug Metabolism & Pharmacokinetics, Bristol Myers Squibb Co.

John Erve, PhD, Senior Principal Scientist, Jerve Scientific Consulting

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 second part of the course will include an examination of the assays used to determine ADME properties and the challenges that PROTACs pose. We will also look at the metabolism of PROTACs including how the linker affects stability and pharmacokinetics. The unique mechanism of action of PROTACs give 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.

ROOM LOCATION: Back Bay C

SC5: Biophysical Tools for Membrane Proteins: Drug Discovery Applications

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.

Back Bay A

SC6: DNA-Encoded Libraries

Instructors:

Svetlana Belyanskaya, PhD, Vice President, Biology, Anagenex

Ghotas Evindar, PhD, Vice President, Head of Drug Discovery, Exo Therapeutics

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.

Back Bay B

Interactive Discussions

OFFERED IN-PERSON ONLY.

Interactive Discussions 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 Interactive Discussions page for a complete listing of topics and descriptions.

Pre-Conference Symposium*

NEW

Cambridge Healthtech Institute's Inaugural

Emerging Immune Modulation Strategies

Assays and Techniques for Identifying, Monitoring and Predicting Immune Responses | OCTOBER 17, 2022

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

MONDAY, OCTOBER 17

9:00 am Pre-Conference Symposium Registration Open & Morning Coffee (Grand Ballroom Foyer)

IMMUNE PROFILING OF TUMOR MICROENVIRONMENT

9:50 Welcome Remarks

9:55 Chairperson's Remarks

Daniel Schramek, PhD, Associate Professor, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto

10:00 *In vivo* CRISPR Screens Reveal Adam2 as Regulators of Immune Therapy in Lung Cancer

Daniel Schramek, PhD, Associate Professor, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto

How the genetic landscape of a tumor governs the tumor's response to immunotherapy remains largely elusive. Here, we established a direct *in vivo* CRISPR/Cas9 gene editing methodology to assess the immune-modulatory capabilities of 573 putative cancer genes associated with altered cytotoxic activity in human cancers. Using KrasG12D- and BrafV600E-driven mouse lung cancer models, we identify Adam2 as our top immune enhancing genes.

10:30 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 like hyper-plex immunostaining in tissue, spatial transcriptomics have the potential to enable a multi-factorial, multi-modal characterization of the tissue microenvironment. Objective scoring methods can serve to aid the interpretation of these datasets, as well as their integration with other companion data. Here we will discuss elements of spatial profiling from multiple studies, as well as tools from statistics and machine learning in the context of these problems.

11:00 Machine Learning Approaches to Identify Targets for Immunotherapy in Glioblastoma

Todd Bartkowiak, PhD, Research Fellow, Department of Cell and Developmental Biology, Vanderbilt University

Immunotherapies have shown limited efficacy in treating glioblastoma. While radiographic tumor contact with the lateral ventricle correlates with worse outcomes; the extent to which ventricle proximity impacts immunobiology in the tumor microenvironment remains unknown. Using CyTOF profiling and machine learning approaches, we identify the suppressive impact of ventricle contact on anti-tumor immunity in the brain and reveal potential clinically actionable immune targets and patient stratification methods for glioblastoma.

11:30 Enjoy Lunch on Your Own

IMMUNE MODULATORS & PROTEIN DEGRADERS

12:55 pm Chairperson's Remarks

Jin Wang, PhD, Professor, Pharmacology & Chemical Biology, Baylor College of Medicine

1:00 A First-in-Class RIPK1 Degrader Sensitizes Immune Checkpoint Blockades

Jin Wang, PhD, Professor, Pharmacology & Chemical Biology, Baylor College of Medicine

Receptor-interacting protein kinase 1 (RIPK1) is a master regulator of cell fate and controls proinflammatory signaling downstream of multiple innate immune pathways. Leveraging the Proteolysis targeting chimera (PROTAC) technology, we developed a first-in-class RIPK1 degrader, which sensitizes ICBs by not only overcoming the intrinsic resistance in cancer cells but also activating a B cell subpopulation to contribute to antitumor immunity.

1:30 Chemical Proteomic Approaches to Study Inflammation

Katya Vinogradova, PhD, Assistant Professor & Head, Laboratory of Chemical Immunology and Proteomics, Rockefeller University

Genomic and functional genomic approaches have revolutionized our understanding of the role the immune system plays in human health and disease; however, our knowledge of the post-translational drivers of immune dysregulation in diverse pathologies is still incomplete. This talk will describe an integrated chemical proteomic and phenotypic screening approach that enables interrogation of structural and functional changes in the proteomes of immune cells and identification of small-molecule covalent protein degraders.

2:00 Modulation of T Helper Cells by IMiDs

Pratik Vikhe, PhD, Scientist, Immunology, Center for Protein Degradation, Dana-Farber Cancer Institute

Immunomodulatory drugs (IMiDs) are molecular glues that can modulate the immune system by targeting certain proteins for degradation by remodeling the surface of cereblon, a component of an E3 ubiquitin ligase. We demonstrate that five IMiDs currently used in the clinic, or are currently in clinical trials, can stimulate T helper cell polarization towards different phenotypes. We also address the cereblon-independent effects of the IMiDs on T helper cells.

2:30 Networking Refreshment Break

3:00 The Immunosuppressive Role of Cell-Surface Sialoglycans

Li Peng, PhD, CSO, Palleon Pharmaceuticals

A critical immune pathway being brought to light by research at Palleon is sialoglycan-mediated immune modulation. Sialoglycans are novel therapeutic targets that are upregulated in many cancers and play an immune-suppressing role. Palleon has designed therapeutic candidates able to degrade sialoglycans, as well as tools to measure a patient's specific tumor sialoglycan signature. Palleon is now testing its enzymatic sialoglycan degrader in a Phase 1/2 study.

3:30 3D Lung Models to Profile Innate Immune Response to Respiratory Viral Infections

Emily Lee, PhD, Staff Scientist I & Functional Group Lead, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health

Pre-Conference Symposium*

NEW

Cambridge Healthtech Institute's Inaugural

Emerging Immune Modulation Strategies

Assays and Techniques for Identifying, Monitoring and Predicting Immune Responses | OCTOBER 17, 2022

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

High impact respiratory viruses such as pathogenic beta-coronaviruses and influenza viruses, pose an ongoing global health threat There is a critical need for physiologically relevant, robust, and ready-to-use *in vitro* cellular assays to rapidly model the infectivity of emerging respiratory viruses. We are using a panel of 3D platforms of varying complexity, paired with scRNAseq and cytokine profiling, to characterize high impact respiratory viral infections in physiologically relevant lung models.

4:00 Close of Symposium

4:00 Dinner Short Course Registration*

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

TUESDAY, OCTOBER 18

7:00 am Registration and Morning Coffee (Grand Ballroom Foyer)

NEXT-GENERATION PROTEIN DEGRADERS

ROOM LOCATION: Constitution A

7:55 Welcome Remarks

8:00 Chairperson's Remarks

Scott Eron, PhD, Senior Research Scientist II, Biochemistry Biophysics and Crystallography Group, C4 Therapeutics, Inc.

8:05 Where Next in the Search for Next-Generation Protein Degraders?

Andrea Testa, PhD, Head, Chemistry, Amphista Therapeutics Ltd.

Rapid progress has been made advancing novel TPD therapies in recent years, highlighting their huge clinical potential but also identifying opportunities where further enhancements can increase their impact further. This presentation will reflect on where there is the biggest opportunity for next-generation TPD approaches to achieve clinical impact and Amphista's own progress in identifying new degrading mechanisms and warheads which are directly expanding the potential of the TPD field.

8:35 Novel Monovalent Protein Degraders and Molecular Glues in Cancer Drug Discovery

Simon Bailey, PhD, MBA, Executive Vice President & Head of Drug Discovery, Plexium, Inc.

Degradation of pathogenic protein represents an important new modality in drug discovery. Here we describe the discovery of novel monovalent protein degraders and molecular glues using Plexium's approach. These monovalent degraders extend the options for targeted protein degradation beyond bivalent degraders and cereblon IMIDs.

9:05 The Arvinas PROTAC Discovery Engine: Insights from Discovering and Developing Molecules that Induce Targeted Protein Degradation

Miklos Bekes, PhD, Associate Director, Degrader Mechanisms Group, Platform Biology, Arvinas, Inc.

Targeted protein degradation (TPD) is an emerging therapeutic modality that has spawned a mini-biotech industry based on molecules that induce 'proximity' to impact target biology. Arvinas is a pioneer in the field and continues pushing the boundaries of TPD. This presentation will highlight recent developments in the Arvinas PROTAC Discovery Engine, focusing on the mechanistic and structural basis of small molecule degrader discovery highlighting recruitment of new ubiquitin ligases.

9:35 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

10:25 Monofunctional Degradation Activating Compounds: From Platform Development to the Clinic

Scott Eron, PhD, Senior Research Scientist II, Biochemistry Biophysics and Crystallography Group, C4 Therapeutics, Inc.

This presentation highlights C4T's platform build enabling rational and efficient discovery of Monofunctional Degradation Activating Compounds (MonoDACs) through design and evolution of a diverse chemical library combined with various screening approaches. Leveraging this platform, we'll discuss a snapshot of the key SAR advancements leading to the discovery of IKZF1/3 degrader, CFT7455, currently in clinical development, as well as the identification of the first MonoDAC hit to a novel therapeutic target.

10:55 PANEL DISCUSSION: Translational Challenges Developing PROTACs and Molecular Glues

Moderator: Scott Eron, PhD, Senior Research Scientist II, Biochemistry Biophysics and Crystallography Group, C4 Therapeutics, Inc.
Panelists:
Simon Bailey, PhD, MBA, Executive Vice President & Head of Drug Discovery, Plexium, Inc.
Miklos Bekes, PhD, Associate Director, Degrader Mechanisms Group, Platform Biology, Arvinas, Inc.
Andrea Testa, PhD, Head, Chemistry, Amphista Therapeutics Ltd.
Chris De Savi, PhD, Senior Vice President & Head, Drug Discovery, Kymera Therapeutics
Jim Henderson, PhD, Vice President, Chemistry, C4 Therapeutics, Inc.

12:25 pm Transition to Lunch

12:35 : Accelerate the Discovery of PROTACs and Molecular Glues from Lead Identification to Protein Degradation Validation

charles river

Zachary Gurard-Levin, PhD, Chief Scientific Officer, SAMDI Tech
Katherine Jones, PhD, Senior Research Leader, Charles River

This presentation will describe innovative tools to initiate and advance drug discovery efforts focused on PROTACs and Molecular Glues. Through a series of case studies, we will describe a novel affinity selection mass spectrometry technique with distinct advantages over traditional approaches to accelerate hit finding efforts. We will then describe medicinal chemistry efforts to advance leads towards functional modalities and highlight assays to validate target degradation in multiple models.

1:05 Session Break

DEGRADATION STRATEGIES FOR ONCOLOGY

1:25 Chairperson's Remarks

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

1:30 Strategies for Dynamic Protein Control to Advance Oncology Drug Discovery

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

Targeted protein degradation technologies including the degradation tag (dTAG) system have emerged as powerful approaches to control protein abundance using small molecule degraders. This talk will describe the development and recent advances of the dTAG technology platform and will highlight case studies demonstrating utility for preclinical target discovery and validation in refractory cancers.

2:00 A First-in-Class RIPK1 Degrader Sensitizes Immune Checkpoint Blockades

Jin Wang, PhD, Professor, Pharmacology & Chemical Biology, Baylor College of Medicine

Receptor-interacting protein kinase 1 (RIPK1) is a master regulator of cell fate and controls proinflammatory signaling downstream of multiple innate immune pathways. Leveraging the Proteolysis targeting chimera (PROTAC) technology, we developed a first-in-class RIPK1 degrader, which sensitizes ICBs by not only overcoming the intrinsic resistance in cancer cells but also activating a B cell subpopulation to contribute to antitumor immunity.

2:30 Building a Comprehensive Platform for Discovery and Optimization of Bifunctional Molecules

WuXi AppTec

Dave Madge, PhD, Vice President, WuXi AppTec

Therapeutic strategies that are based on using a multi-functional molecule to induce the proximity of two proteins, or indeed an oligonucleotide and a protein, have become increasingly well validated. In this presentation we will discuss some of the chemical and biological tools that have been developed to enable the discovery, characterization and optimization of such bifunctional, proximity-inducing, molecules and show how these tools can dramatically accelerate drug discovery in this area.

2:45 Overcome common roadblocks during the characterization of your PROTAC candidates with Spectral Shift technology

Amit Gupta, PhD, MBA, Senior Product Manager, Product, NanoTemper

To develop effective PROTAC candidates, you need a method that tackles common challenges while screening small compound molecules and characterizing ternary complex, cooperativity, and hook effect. With Dianthus — a plate-based affinity screening platform — you succeed at binary and ternary complex characterizations with in-solution, mass-independent measurements that result in high-quality data for reliable affinity constants, cooperativity values, and hook effect characterization.

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

ROOM LOCATION: Constitution A

TARGETED DEGRADATION FOR INTRACELLULAR CANCER TARGETS

3:40 FEATURED PRESENTATION: Development of a STAT3 Targeted Protein Degrader

Chris De Savi, PhD, Senior Vice President & Head, Drug Discovery, Kymera Therapeutics

Signal Transducer and Activator of Transcription 3 (STAT3) plays important roles in the transduction of signals from growth factors and cytokines in both normal and malignant cells. Aberrant activation of STAT3 has been observed in many cancers including lymphoma and leukemias. Here we introduce a first-in-class, potent, and selective STAT3 heterobifunctional degrader KT-333 that is being developed for the treatment of hematologic malignancies and solid tumors.

4:10 Discovery and Optimization of CBL-B Inhibitors for Immune-Cell Mediated Tumor Rejection

Frederick Cohen, PhD, Vice President, Medicinal Chemistry, Nurix Therapeutics, Inc.

Casitas B-lineage lymphoma b (CBL-B) is an E3 ligase that functions as a negative regulator of T, NK, and myeloid cells. Mice deficient in cbl-b reject tumors in syngeneic models, suggesting pharmacological inhibition of CBL-B as a novel therapeutic strategy. We present discovery of compounds, including NX-1607, that glue CBL-B into an inactive conformation and result in antitumor effects in tumor models upon daily oral dosing.

4:40 Characterization of the Molecular Glue-Induced Interactions of IO Target IKZF2 with Cereblon

Charles A. Wartchow, PhD, Associate Director, Global Discovery Chemistry, Novartis Institutes for BioMedical Research

Formation of ternary complexes between a ligase, a molecular glue, and a disease-modulating protein is the first step in a sequence of events leading to protein degradation. In this presentation, we discuss the SPR and X-ray crystallographic characterization of ternary complexes involving a molecular glue that binds to the ligase Cereblon and induces the binding of the zinc finger-containing transcription factor IKZF2.

5:10 Interactive Discussions

Interactive Discussions 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 conference website's Interactive Discussions page for a complete listing of topics and descriptions.

IN-PERSON INTERACTIVE DISCUSSION: Degrader Strategies for Cancer and Beyond

Miklos Bekes, PhD, Associate Director, Degrader Mechanisms Group, Platform Biology, Arvinas, Inc.

Chris De Savi, PhD, Senior Vice President & Head, Drug Discovery, Kymera Therapeutics

- Why is oncology especially well-suited for targeted protein degradation (TPD) strategies?
- What are the TPD approaches most likely to succeed in cancer?
- What areas and which approaches show the most promise for non-cancer indications?

5:55 Welcome Reception in the Exhibit Hall with Poster Viewing (Grand Ballroom)

6:55 Close of Day

WEDNESDAY, OCTOBER 19

7:30 am Registration and Morning Coffee (Grand Ballroom Foyer)

EMERGING DEGRADER MODALITIES

ROOM LOCATION: Constitution A

7:55 Chairperson's Remarks

Jessica Friedman, PhD, Director, Molecular & Cellular Pharmacology, EMD Serono

8:00 Targeted Degradation of Extracellular Proteins with ATACs (ASGPR-Targeting Chimeras)

Kevin Lumb, DPhil, Vice President, Biology, Avilar Therapeutics

Targeted protein degradation is a promising new therapeutic modality. Established protein degradation technologies using PROTACs or molecular glues utilize the ubiquitin proteasome system to degrade intracellular proteins. A novel approach has emerged for extracellular protein degradation that utilizes the asialoglycoprotein receptor (ASGPR) to recruit pathogenic proteins for endolysosomal degradation. We describe the discovery of novel bifunctional compounds called ATACs (ASGPR-Targeting Chimeras) containing Avilar's proprietary, high affinity, small-molecule ASGPR-binding ligands.

8:30 Quantitative Analysis of Binding Affinities for Small Molecules Targeting STAT Transcription Factors

Jean Bernatchez, PhD, Senior Scientist and San Diego R&D Group Leader, Research & Development, Eurofins Discovery

Transcription factors, such as the STAT proteins, are critical for the regulation of gene expression in the cell; deregulation of the biochemical functions of these proteins can be important hallmarks of cancer and inflammation. Eurofins Discovery presents its new line of STAT binding assays, showing

selective binding for published small molecules targeting the SH2 domains of the STAT proteins. This platform is ideal for accelerated screening and SAR analysis.

8:45 Rationally Design PROTACs and Molecular Glues

Karteek Kadimisetty, Ph.D., Director, R&D, LifeSensors, Inc.

PROTACs have emerged as new class of drugs that can target the "undruggable" proteome by hijacking the ubiquitin proteasome system. Traditional methods are prone to artifacts. New methods that can monitor PROTAC function on endogenous targets at physiological expression levels are essential to accelerate the PROTAC discovery process. Current study highlights use of TUBE technology to rationally design molecular glue and PROTAC mediated ubiquitination and degradation of targets.

9:00 Nanobodies for Targeted Degradation of the RNA Binding Protein HNRNPA2B1

Yongku Cho, PhD, Associate Professor, Chemical & Biomolecular Engineering, University of Connecticut

Development and validation of high-specificity nanobodies for intracellular targeting remain a bottleneck. Here we describe a yeast surface display based nanobody screening approach that led to high-specificity nanobodies against several intracellular targets in parallel. We also present a comprehensive comparison of nanobody-ubiquitin ligase F-box fusions for targeted degradation of intracellular proteins. Using these approaches, we demonstrate robust degradation of the RNA-binding protein HNRNPA2B1, implicated in multiple cancers and neurodegenerative diseases.

9:30 TPD² – Dual Precision Target Protein Degradation: Antibody-Enabled GSPT1 Degraders for Breast Cancer and AML

Peter Park, PhD, CSO, Orum Therapeutics

TPD² approach merges the power of targeted protein degraders with the precision of antibodies to deliver molecular glues or PROTACs intracellularly with cell-specificity and increases the therapeutic index of degraders. Using the TPD² approach, Antibody neoDegrader Conjugate (AnDC) platform has been developed using highly specific GSPT1 degraders that show promising efficacy against tumors. Two AnDCs in clinical/late preclinical testing, ORM-5029 for breast cancer and ORM-6151 for AML will be discussed.

10:00 Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

PLENARY KEYNOTE PROGRAM

ROOM LOCATION: Constitution A + B

11:00 Plenary Chairperson's Remarks

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

11:05 PLENARY: Pirating Biology to Detect and Degrade Extracellular Proteins

James A. Wells, PhD, Professor, Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco

In contrast to intracellular PROTACs, approaches to degrade extracellular proteins are just emerging. I'll describe our recent progress to harness natural mechanisms such as transmembrane E3 ligases to degrade extracellular proteins using fully genetically encoded bispecific antibodies we call AbTACs. We have also engineered a peptide ligase which can be tethered to cells to detect proteolysis events and target them with recombinant antibodies for greater selectivity for the tumor microenvironment.

11:50 PLENARY: Therapeutic Modalities for Neuroscience Diseases

Anabella Villalobos, PhD, Senior Vice President, Biotherapeutics & Medicinal Sciences, Biogen

Many effective medicines exist to treat neurological diseases, but medical need remains high. We have a unique multi-modality approach to discover novel therapies and our goal is to find the best modality regardless of biological target. With a multi-modality approach, we aim to expand target space, leverage synergies across modalities, and offer options to patients. Opportunities and challenges associated with small molecules, biologics, oligonucleotides, and gene therapy will be discussed.

12:35 pm Enjoy Lunch on Your Own

1:25 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom Foyer)

2:05 Close of PROTACs and Molecular Glues – Part 1 Conference

WEDNESDAY, OCTOBER 19

PLENARY KEYNOTE PROGRAM

ROOM LOCATION: Constitution A + B

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12:35 pm Enjoy Lunch on Your Own

1:25 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom Foyer)

ROOM LOCATION: Constitution A

AI/ML FOR PROTEIN DEGRADATION

2:35 Welcome Remarks

2:40 Chairperson's Remarks

Woody Sherman, PhD, CEO, Psivant Therapeutics

2:45 Accelerating Rational Degrader Design via Computational Prediction of Ternary Structure Ensembles

Woody Sherman, PhD, CEO, Psivant Therapeutics

TPD involves the formation of an induced proximity complex. Here, we address three critical aspects of the TPD process using biophysics, atomistic simulations, and AI: 1) Structural prediction of the ternary complex induced by degrader molecules. 2) Conformational heterogeneity of the ternary complex. 3) Prediction of degradation efficiency via the CRL assembly. We combine HDX-MS, MD, and AI to predict induced proximity ensembles, guide design, and improve degradation efficiency.

3:15 How Artificial Intelligence Enhances Drug Discovery

Sang Eun Jee, PhD, Application Scientist, Xtalpi

AI can cut down the development timeline and cost for drug discovery by answering two significant questions: What molecules should be made next and how are the lead molecules modified? AI technology in drug discovery will be introduced with case studies of how we solved challenging problems with AI. The key to success in AI-driven drug discovery in the future will also be discussed with the lessons learned from history.

3:45 Dessert Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

4:25 Estimating Target Degradability from Protein-Intrinsic Features

Shourya Roy Burman, PhD, Research Fellow, Cancer Biology, Dana-Farber Cancer Institute

Chemo-proteomics profiling of PROTACs designed from pan-class inhibitors revealed a large difference in the degradation frequencies of the target proteins engaged by these molecules. Using protein-intrinsic features, we developed a machine learning classifier that discriminates target proteins based on their observed degradation patterns and highlights properties that dictate their degradability. Using computational structural modeling, we provide mechanistic insight into the predicted features and obtain actionable information for rational PROTAC design.

4:55 Closing the Gap: Heterogeneous Molecular Modeling & Machine Learning for Accurate Modeling

Victor Guallar, PhD, Professor, Barcelona Supercomputing Center and Nostrum Biodiscovery

Combining the state-of-the-art molecular modeling, in heterogeneous data sources and in machine learning techniques, we are dramatically increasing the accuracy in our computational predictions. We will showcase recent successful case studies including virtual screening enrichment, ligase screening for TPD, and ternary complex formation in PROTACs. Overall, the enrichment of machine learning techniques with data augmentation from molecular modeling seems to provide the necessary boost that prediction models might need.

5:25 PANEL DISCUSSION: Challenges with Using AI Predictions for Designing Protein Degraders

Moderator: Woody Sherman, PhD, CEO, Psivant Therapeutics
Panelists:
Shourya Roy Burman, PhD, Research Fellow, Cancer Biology, Dana-Farber Cancer Institute
Victor Guallar, PhD, Professor, Barcelona Supercomputing Center and Nostrum Biodiscovery

5:55 Dinner Short Course Registration*

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

9:00 Close of Day

THURSDAY, OCTOBER 20

7:30 am Registration and Morning Coffee (Grand Ballroom Foyer)

NEW LIGASES & DEGRADATION STRATEGIES

ROOM LOCATION: Constitution A

7:55 Chairperson's Remarks

Daniel A. Erlanson, PhD, Senior Vice President, Innovation and Discovery, Frontier Medicines Corporation

8:00 Molecular Glues for Protein Degradation and Beyond

Eric Fischer, PhD, Associate Professor, Biological Chemistry and Molecular Pharmacology, Harvard Medical School; Director Center for Protein Degradation, Dana-Farber Cancer Institute

Small molecules that induce protein degradation through ligase-mediated ubiquitination, are showing considerable promise as a new pharmacological modality. Significant progress has been made towards chemically induced targeted protein degradation using heterobifunctional small molecule ligands and exciting opportunities arise from better understanding molecular glues. We will present recent work towards a better understanding of the molecular principles that govern neo-substrate recruitment by small molecule degraders.

8:30 Discovery of Novel E3 Ligands for Targeted Protein Degradation

Yue Xiong, PhD, Co-Founder & CSO, Cullgen

Three distinct characteristics of targeted protein degradation empower drug discovery; the catalytic nature that can achieve high efficacy, the ability to target previously undruggable proteins and to deliver the drug activity to selective tissues. E3 ligands hold the key to realize the full potential of TPD, but are very limited at present. Cullgen has discovered multiple novel E3 ligands for the targeted protein degradation.

9:00 FEATURED PRESENTATION: An E3 Ligase Guide to the Galaxy of Small Molecule-Induced Protein Degradation

Michael Rape, PhD, Professor, Department of Cell & Developmental Biology, University of California, Berkeley; Investigator, Howard Hughes Medical Institute

Human cells express ~600 E3 ligases that could be harnessed by small molecules to alter the stability or activity of pathological proteins. How to select an E3 ligase for therapeutic application is still unclear. We have used biology to guide ligase selection: by discovering new pathways for ubiquitin-dependent protein quality control and unlocked new enzymes for targeted protein degradation. I will discuss this mechanism-inspired approach to E3 ligase selection.

9:30 Interactive Discussions

Interactive Discussions 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 conference website's Interactive Discussions page for a complete listing of topics and descriptions.

IN-PERSON INTERACTIVE DISCUSSION: Targeted Protein Degradation – Where Are We Headed?

Daniel A. Erlanson, PhD, Senior Vice President, Innovation and Discovery, Frontier Medicines Corporation
Nikki R. Kong, PhD, Senior Scientist; Biology Group Leader, Center for Protein Degradation, Dana-Farber Cancer Institute
Yue Xiong, PhD, Co-Founder & CSO, Cullgen

- Exploring novel E3 ligases and ligands for targeted protein degradation
- Rational design strategies for molecular glue degraders
- New assays and screening approaches for mechanistic studies of degraders and glues

10:15 Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

11:00 Target Protein Localization and Its Impact on PROTAC-Mediated Degradation

Gopal Sapkota, PhD, Programme Leader, MRC Protein Phosphorylation & Ubiquitylation Unit, Sir James Black Centre, School of Life Sciences, University of Dundee

To interrogate whether subcellular context of POI influences PROTAC-mediated degradation, we expressed either Halo or FKBP12F36V (dTAG) constructs consisting of varying localisation signals and tested the efficacy of their degradation by von Hippel-Lindau (VHL)- or cereblon (CRBN)-recruiting PROTACs targeting either Halo or dTAG. POIs were localised to the nucleus, cytoplasm, outer mitochondrial membrane, endoplasmic reticulum, Golgi, peroxisome, or lysosome. Differentially localised Halo or FKBP12F36V proteins displayed varying levels of degradation.

11:30 Employing Phenotypic Assays to Dissect Mechanisms of Molecular Glue Degraders

Nikki R. Kong, PhD, Senior Scientist; Biology Group Leader, Center for Protein Degradation, Dana-Farber Cancer Institute

Despite identification of IMiD-induced neo-substrates of E3 ligase CRL4-Cereblon in hematopoietic malignancies, the cell-type specific mechanisms of these molecules have not been extensively explored, especially in the immune context. As a result, there are a number of unknowns regarding the efficacy and safety of TPD therapeutics derived from these molecules. Here, we employed complex phenotypic assays to better understand the on-target mechanisms of this class of drugs.

12:00 pm Surveying the Landscape of Drug Resistance Mutations within Neosubstrates to Molecular Glue Degraders Using CRISPR Scanning

Brian Liau, PhD, Associate Professor, Department of Chemistry and Chemical Biology, Harvard University

CRISPR scanning was used to broadly survey the landscape of drug resistance mutations to molecular glue degraders in neosubstrates. Integrative analysis of resistance sites revealed varying levels of sequence conservation and mutational constraint that control the emergence of different resistance mechanisms, highlighting that many regions co-opted in targeted protein degradation are inessential. Altogether, we outline a rapid and general approach to survey neosubstrate requirements necessary for effective degradation.

12:30 Targeted Protein Degrader Discovery Using SPRINTer Cell-Based Assay

Chao Tsung Yang, PhD, Principal Scientist Group Leader, R&D Department, Eurofins DiscoverX

Rapidly screen small molecule therapeutics, evaluate target engagement, and measure changes in endogenous protein levels using SPRINTer functional, cell-based assays for multiple targets.
In this talk, we will discuss:
- SPRINTer assay principle and characterization of bi-functional degraders and molecular glues for multiple targets
- Assay applicability to evaluate protein stabilization using the SPRINTer CDKN1A (p21) assay to monitor TP53 modulation by MDM2 inhibitors
- Evaluation of compound-target engagement using select SPRINTer cell lines

1:00 Enjoy Lunch on Your Own

1:40 Refreshment Break in the Hall with Poster Viewing (Grand Ballroom)

DEGRADATION APPROACHES FOR ONCOLOGY

2:10 Chairperson's Remarks

Jun Yang, PhD, Professor and Vice Chair, Department of Pharmacy and Pharmaceutical Sciences, St. Jude Children's Research Hospital

2:15 Therapeutic Evaluation of Multi-Targeted SRC Kinase PROTAC in Cancer

Jun Yang, PhD, Professor and Vice Chair, Department of Pharmacy and Pharmaceutical Sciences, St. Jude Children's Research Hospital

Clinically used as an ABL inhibitor, dasatinib promiscuously targets other tyrosine kinases, especially those in the SRC family. We developed a series of dasatinib-based PROTAC molecules, using phenyl-glutarimide as the cereblon binder. These SRC-directed PROTACs exhibited remarkable activity in LCK-activated T cell leukemia, *in vitro,* and *in vivo*. Because SRC family kinases are important therapeutic targets in cancer, we are evaluating these PROTACs systematically in ~1,000 tumors across histologic types.

2:45 New Opportunities for Studying the Function of the Nucleosome Remodeling Factor, NURF through Inhibition and Degradation

William Pomerantz, PhD, Associate Professor, Department of Medicinal Chemistry, University of Minnesota, Twin Cities

BPTF is an essential member of the nucleosome remodeling factor, NURF, and has become increasingly identified as a pro-tumorigenic factor, prompting investigations into the mechanisms associated with BPTF function. Our lab has developed novel screening approaches to develop the first inhibitor of the BPTF bromodomain. Building on these results I will present our efforts at developing the first BPTF degraders to study the role of this protein in pediatric cancers.

3:15 Positive Selection Screens for Oncoprotein Degraders

Vidyasagar Koduri, MD, PhD, Instructor in Medicine, Harvard Medical School; Department of Hematology, Brigham and Women's Hospital

Matthew Oser, MD, PhD, Assistant Professor, Department of Medicine, Dana-Farber Cancer Institute, Harvard Medical School

Current loss of signal ("down") assays for identifying degraders often exhibit poor signal-to-noise ratios and false positives from compounds that nonspecifically suppress transcription or translation. Here we describe a gain of signal ("up") assay for degraders that can be used in both chemical and genetic screens. This should facilitate the identification of drugs that directly or indirectly degrade undruggable proteins.

3:45 Close of Conference

LIVE IN-PERSON OR VIRTUAL REAL-TIME

Present a Poster and Save $50*

Cambridge Healthtech Institute encourages attendees to gain further exposure by presenting their work in the poster sessions. To secure an onsite poster board and/or ensure your virtual poster presentation is scheduled and included in the conference materials, your full submission must be received, and your registration paid in full by September 23, 2022.

Deadline: September 23, 2022

Reasons you should present your research poster at this conference:

- Your research will be seen by our international delegation, representing leaders from top pharmaceutical, biotech, academic and government institutions
- Discuss your research and collaborate with other attendees
- Your poster content will be published in our conference materials
- Receive $50 off your registration*

**This discount does not apply to product or service providers*

TUESDAY, OCTOBER 18

7:00 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Republic Ballroom B

CHEMOPROTEOMICS & INDUCED PROXIMITY

7:55 Welcome Remarks

8:00 Chairperson's Remarks

Gizem Akcay, PhD, Head of Chemical Biology, Bayer Research and Innovation Center Cambridge

8:05 Taking a Functional Multiomic Approach to Uncover Novel Cancer Targets

Gizem Akcay, PhD, Head of Chemical Biology, Bayer Research and Innovation Center Cambridge

We coupled multiplexed cell line viability technology to functional genomics and chemical proteomics for identifying novel cancer targets. Here, a specific case study from the initial screen to target deconvolution and follow-up functional validation will be presented.

8:35 Mapping Cellular Interactions via Photocatalytic-Based Proximity Labeling

Tamara Reyes Robles, PhD, Associate Principal Scientist, Experimental and Chemical Biology, Merck Exploratory Science Center

Cell-cell interaction environments are attractive therapeutic regions of interest, yet while many key interactions take place across these environments, our ability to unbiasedly characterize the proteins and cell types involved with high resolution remains challenging. Here we provide updates on a recently disclosed visible light-based photocatalytic platform for the targeted labeling of cell surface proteins and its successful pairing with downstream workflows to uncover protein microenvironments and cell-cell interactions.

9:05 Architecture of the Outbred Brown Fat Proteome Defines Regulators of Metabolic Physiology

Haopeng Xiao, PhD, Postdoctoral Research Fellow, Department of Cell Biology, Harvard Medical School; Department of Cancer Biology, Dana Farber Cancer Institute

Brown adipose tissue (BAT) regulates metabolic physiology and disease. However, nearly all studies of BAT occurred in one mouse strain, C57BL/6, limiting the translational potential. Here we measure BAT proteomes across 163 Diversity Outbred mice, defining the Outbred Proteome Architecture of BAT (OPABAT) to annotate the functions of thousands of proteins in thermogenesis and metabolic disease. OPABAT is a resource for understanding conserved mechanisms of BAT regulation over metabolic physiology.

9:35 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

10:25 Chemical Biology and Chemoproteomics Methods to Advance Covalent Ligand Drug Discovery

Heather Murrey, PhD, Principal Scientist, 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.

10:55 Chemical Proteomic Approaches to Study Inflammation

Katya Vinogradova, PhD, Assistant Professor & Head, Laboratory of Chemical Immunology and Proteomics, Rockefeller University

Genomic and functional genomic approaches have revolutionized our understanding of the role the immune system plays in human health and disease, however our knowledge of the post-translational drivers of immune dysregulation in diverse pathologies is still incomplete. This talk will describe an integrated chemical proteomic and phenotypic screening approach that enables interrogation of structural and functional changes in the proteomes of immune cells and identification of small-molecule covalent protein degraders.

11:25 Discovery of Selective Inhibitors Targeting a SARM1 Allosteric Cysteine through Chemical Proteomics

Hannah Feldman, PhD, Postdoctoral Fellow, Department of Chemistry, Laboratory of Dr. Benjamin Cravatt, Scripps Research Institute

The enzyme SARM1 is a key regulator of axon degeneration. We provide evidence for an alternative allosteric mode of controlling SARM1 function through the chemical proteomic discovery of a druggable cysteine in the autoregulatory ARM1 domain of the enzyme. We describe a series of electrophilic small molecules that site-specifically and stereoselectively react with this cysteine residue to suppress SARM1 activity and protect axons from chemical toxin-induced axonal degeneration.

11:55 Session Break

NEW CHEMICAL PROBES & ASSAYS

1:25 pm Chairperson's Remarks

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

1:30 Tetrazines in Chemical Biology

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

The bioorthogonal reaction between tetrazines and trans-cyclooctenes (TCOs) has shown immense utility in chemical biology. This presentation will focus on the development of new methods to prepare tetrazine-containing probe molecules and their utility in a variety of chemical biology applications. Moreover, a new approach, utilizing unreactive, stable, and cell permeable dihydrotetrazines, which under photochemical conditions are transformed into highly reactive tetrazines in cells, will also be described.

2:00 Application of Clickable Fumarate Probes for Target Identification and Engagement Studies

Luna Zhang, PhD, Scientist I, Chemical Biology & Proteomics, Biogen

Dimethyl fumarate has been an established oral therapy for multiple sclerosis worldwide. To better understand the mechanism of action of DMF and its active metabolite, monomethyl fumarate (MMF), we designed and utilized clickable probes to visualize and enrich probe-modified proteins. We further perform quantitative chemoproteomics analysis for proteome-wide target identification and validate several unique and shared targets of DMF/MMF, which provide insight into their reactivity, selectivity, and target engagement.

2:30 A Versatile Assay Suite for The Discovery of New KRAS Pathway Inhibitors

REACTION BIOLOGY

Ekaterina Kuznetsova, PhD, Senior Director of Product Development, Reaction Biology

KRAS, is a known oncogene and a desirable drug target due to prevalence of mutations with poor disease prognosis. To facilitate drug discovery activities targeting KRAS/MAPK pathway, we have produced the full spectrum of pathway proteins including kinases, wild type and mutated KRAS, and the

upstream guanine nucleotide exchange factor protein SOS1. This presentation will summarize our most recent assay development efforts for biochemical and biophysical assays for these targets

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

3:40 Proteomics of Protein Trafficking by *in vivo* Tissue-Specific Labeling

Justin Bosch, PhD, Post-doctoral Fellow, Department of Genetics, Harvard Medical School

We established a platform to identify secreted protein trafficking between organs using an engineered biotin ligase. Applying this approach in *Drosophila* and mice indicate that the communication network of secreted proteins is vast. This approach has broad potential across different model systems to identify cell-specific secretomes and mediators of interorgan communication in health or disease.

4:10 An Affinity-Directed Phosphatase (AdPhosphatase) System for Targeted Protein Dephosphorylation

Gopal Sapkota, PhD, Programme Leader, MRC Protein Phosphorylation & Ubiquitylation Unit, Sir James Black Centre, School of Life Sciences, University of Dundee

Reversible protein phosphorylation is a fundamental process that controls protein function and intracellular signalling and failure of phospho-control accounts for many human diseases. We have developed the affinity-directed phosphatase (AdPhosphatase) system for targeted dephosphorylation of specific phospho-proteins in cells. By deploying the PP1/2A catalytic subunits conjugated to an antigen-stabilised anti-GFP nanobody, we can promote the dephosphorylation of two independent phospho-proteins, FAM83D or ULK1, knocked in with GFP-tags, with exquisite specificity.

4:40 FEATURED PRESENTATION: A Proteome-Wide Atlas of Drug Mechanism of Action

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

Defining the cellular response to pharmacological agents is critical for understanding the mechanism of action of small molecule perturbagens. We developed a 96-well-plate-based high-throughput screening infrastructure for quantitative proteomics and profiled 875 compounds in a human cancer cell line with near-comprehensive proteome coverage. We used protein-protein and compound-compound correlation networks to uncover mechanisms of action for several compounds and highlight polypharmacology.

5:10 Interactive Discussions

Interactive Discussions 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 conference website's Interactive Discussions page for a complete listing of topics and descriptions.

IN-PERSON INTERACTIVE DISCUSSION: Innovative Chemoproteomics-Based Strategies for Target Identification

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

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

- Challenges with finding and validating good targets
- How can proteomics best be used in the drug discovery pipeline?
- Which improvements are most needed in sample handling and data quality? Application of photoaffinity probes in target identification, advantages, and disadvantages
- Novel technologies for activation of photoaffinity probes to covalently label their protein target

5:55 Welcome Reception in the Exhibit Hall with Poster Viewing (Grand Ballroom)

6:55 Close of Day

WEDNESDAY, OCTOBER 19

7:30 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Republic Ballroom B

CHEMICAL BIOLOGY FOR TARGET DECONVOLUTION

7:55 Chairperson's Remarks

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

8:00 Chemical Biology Tools to Understand the *in vivo* Target Occupancy of Covalent XPO1 Inhibitors

Jeffrey Martin, PhD, Scientist II, Drug Discovery, Biogen

XPO1 is a therapeutic target in both oncology and amyotrophic lateral sclerosis (ALS). The development and application of clickable probes and a mass spectrometry-based chemoproteomic workflow to measure *in vivo* XPO1 target occupancy will be presented. Additionally, we will discuss the use of these tools in different biological matrices and *in vivo* models.

8:30 Leveraging Multi-Platform High-throughput Cell-Based Screening Paradigms for Target Identification

horizon a PerkinElmer company

James Goldmeyer, PhD, Associate Director of Product Management, Screening Services, Horizon a PerkinElmer Company

Information about cellular backgrounds and gene targets is essential to collect during the therapeutic development process. The combination of running cell panel screening and functional genomics screens helps ensure clear identification of gene targets and accessible indications for a potential therapeutic agent. We will present information around how leveraging these platforms in tandem can help deliver high confidence in determining cell and gene targets.

9:00 A Chemical Biology Toolkit for Epigenetic Targets

Antony Burton, PhD, Senior Scientist, Chemical Biology & Proteomics, Discovery Sciences, AstraZeneca Pharmaceuticals

Mapping target selectivity of epigenetic proteins, for understanding safety and efficacy, is important yet challenging as they span a wide range of enzyme families and often exist as subunits within large and dynamic complexes. Here, we will describe recent work at AstraZeneca to evaluate target engagement and selectivity using full-length epigenetic proteins in endogenous complexes using a combination of affinity matrices, cellular thermal shift assays, and proximity labeling technologies.

9:30 Discovery of First-in-Class Covalent Chemistry and Ligands

Ken Hsu, PhD, Associate Professor, Department of Chemistry, University of Virginia

Several groundbreaking medicines in cancer produce a therapeutic response through a covalent mechanism of action. Our group developed sulfonyl-triazoles as a covalent binder of tyrosines, and lysines to a lesser extent, to enable ligand discovery of catalytic and non-catalytic sites on proteins through sulfur-triazole exchange (SuTEx) chemistry. In my talk, I will describe our efforts to advance the capabilities of SuTEx for covalent probes and therapeutic discovery.

10:00 Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

PLENARY KEYNOTE PROGRAM

ROOM LOCATION: Constitution A + B

11:00 Plenary Chairperson's Remarks

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

11:05 PLENARY: Pirating Biology to Detect and Degrade Extracellular Proteins

James A. Wells, PhD, Professor, Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco

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11:50 PLENARY: Therapeutic Modalities for Neuroscience Diseases

Anabella Villalobos, PhD, Senior Vice President, Biotherapeutics & Medicinal Sciences, Biogen

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12:35 pm Enjoy Lunch on Your Own

1:25 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom Foyer)

2:05 Close of Target Identification and Validation – Part 1 Conference

WEDNESDAY, OCTOBER 19

PLENARY KEYNOTE PROGRAM

ROOM LOCATION: Constitution A + B

11:00 am Plenary Chairperson's Remarks

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

11:05 PLENARY: Pirating Biology to Detect and Degrade Extracellular Proteins

James A. Wells, PhD, Professor, Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco

In contrast to intracellular PROTACs, approaches to degrade extracellular proteins are just emerging. I'll describe our recent progress to harness natural mechanisms such as transmembrane E3 ligases to degrade extracellular proteins using fully genetically encoded bispecific antibodies we call AbTACs. We have also engineered a peptide ligase which can be tethered to cells to detect proteolysis events and target them with recombinant antibodies for greater selectivity for the tumor microenvironment.

11:50 PLENARY: Therapeutic Modalities for Neuroscience Diseases

Anabella Villalobos, PhD, Senior Vice President, Biotherapeutics & Medicinal Sciences, Biogen

Many effective medicines exist to treat neurological diseases, but medical need remains high. We have a unique multi-modality approach to discover novel therapies and our goal is to find the best modality regardless of biological target. With a multi-modality approach, we aim to expand target space, leverage synergies across modalities, and offer options to patients. Opportunities and challenges associated with small molecules, biologics, oligonucleotides, and gene therapy will be discussed.

12:35 pm Enjoy Lunch on Your Own

1:25 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom Foyer)

ROOM LOCATION: Constitution B

CRISPR SCREENING FOR TARGET DISCOVERY

2:05 Welcome Remarks

2:10 Chairperson's Remarks

Jason Sheltzer, PhD, Assistant Professor, Department of Surgery, Oncology, Yale University School of Medicine

2:15 Genomics Approaches to Identify the True Targets of Mischaracterized Small Molecules

Jason Sheltzer, PhD, Assistant Professor, Department of Surgery, Oncology, Yale University School of Medicine

Up to 97% of drug-indication pairs that are tested in clinical trials in oncology never advance to receive FDA approval. Mischaracterization of the mechanisms-of-action of these therapies likely contributes to this extremely high failure rate. We have developed a set of genomic techniques to help identify the true target(s) of small-molecule cancer drugs, to shed light on the likely reasons why certain drugs fail and to identify suitable patient populations.

2:45 Integrating Phenotypic and Functional Assays to Inform Target Identification

Steven Corsello, MD, Assistant Professor, Department of Medicine, Oncology, Stanford University

The systematic profiling of small molecules across information-rich cellular assays has revealed unexpected drug activities. My talk will describe how perturbational gene expression and cell viability profiling can be coupled with genome-scale CRISPR/Cas9 genetic modifier screens to discover novel anti-cancer drug mechanisms. I will also provide an overview of the Drug Repurposing Hub compound library and information resource.

3:15 Drug Discovery with Patient-Derived Intestinal Organoids

STEMCELL™ TECHNOLOGIES

Martin Stahl

3:45 Dessert Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

4:25 Unbiased Exploration of Drug-Protein Interactions Using CRISPR Base Editor Screens

Benjamin Lampson, PhD, Instructor in Medicine, Medical Oncology, Dana-Farber Cancer Institute

The identification of drug-resistant mutants in an enzyme of interest is a key step to understanding the functional relationship between the enzyme and a small molecule inhibitor. However, discovering such mutants is often challenging, particularly when no crystal structure of the protein bound to the molecule exists. This talk will explore the use of CRISPR base editor technology as a novel tool to functionally identify drug-resistant enzyme mutants.

4:55 Beyond On-Target Engagement: Illuminating Drug-Target Mechanism Using CRISPR Scanning

Brian Liau, PhD, Associate Professor, Department of Chemistry and Chemical Biology, Harvard University

CRISPR-suppressor scanning combines genome editing with chemical inhibitor profiling to systematically identify drug resistance alleles across drug targets. Beyond rapidly confirming on-target engagement, these drug resistance alleles can be used as powerful discovery tools to uncover new aspects of target biology. These capabilities and discoveries are showcased through two vignettes exploring (1) lysine-specific histone demethylase-1A and (2) the Polycomb Repressive Complex 2, to reveal mechanism of action and new cancer vulnerabilities.

5:25 PANEL DISCUSSION: Challenges with Correctly Identifying Targets and Cellular Interactions

Moderator: Jason Sheltzer, PhD, Assistant Professor, Department of Surgery, Oncology, Yale University School of Medicine

Panelists:

Steven Corsello, MD, Assistant Professor, Department of Medicine, Oncology, Stanford University

Benjamin Lampson, PhD, Instructor in Medicine, Medical Oncology, Dana-Farber Cancer Institute

Brian Liau, PhD, Associate Professor, Department of Chemistry and Chemical Biology, Harvard University

5:55 Dinner Short Course Registration*

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

9:00 Close of Day

THURSDAY, OCTOBER 20

7:30 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Constitution B

FUNCTIONAL GENOMICS-DRIVEN DRUG DISCOVERY

7:55 Chairperson's Remarks

Daniel Schramek, PhD, Associate Professor, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto

8:00 Target Discovery through Functional Genomics

Leire Escudero-Ibarz, PhD, Associate Director, Functional Genomics, AstraZeneca

Target identification and validation is a key aspect of the drug discovery paradigm. With the advent of various genome editing and artificial intelligence tools, we live in a world where the discovery of novel validated targets for treatment of human disease can be greatly augmented. I will review the key challenges and the unprecedented opportunities we face in target discovery. I will exemplify this with a few real-life project examples.

8:30 *In vivo* CRISPR/Cas9 Screening Identifies USP15 and SCAF1 as Tumor Suppressor Axis in Pancreatic Cancer

Daniel Schramek, PhD, Associate Professor, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto

Functionally characterizing the genetic alterations that drive pancreatic cancer progression is a prerequisite for Precision Medicine. Here, we developed a somatic CRISPR/Cas9 mutagenesis screen to assess the transforming potential of 125 recurrently mutated 'long-tail' pancreatic cancer genes, which revealed USP15 and SCAF1 as novel and potent PDAC tumor suppressors. Interestingly, we found that USP15 functioning in a haploinsufficient manner and that the SCAF1-USP15 axis regulates sensitivity to PARPi and gemcitabine.

9:00 Identifying Determinants of the Tumor Microenvironment by Spatial CRISPR Genomics

Brian Brown, PhD, Director, Icahn Genomics Institute and Professor, Department of Genetics & Genomic Sciences, Icahn School of Medicine at Mount Sinai

While CRISPR screens are helping uncover genes regulating many cell-intrinsic processes, existing approaches are suboptimal for identifying gene functions operating extracellularly or within a tissue context. To address this, we recently developed an approach for spatial functional genomics called Perturb-map, which enables resolution of CRISPR screens by multiplex tissue imaging and spatial transcriptomics. We are now applying Perturb-map to identify genetic determinants of ovarian tumor growth, metastasis, and immune composition.

9:30 Interactive Discussions

Interactive Discussions 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 conference website's Interactive Discussions page for a complete listing of topics and descriptions.

IN-PERSON INTERACTIVE DISCUSSION: Novel Functional Genomics Approaches for Target Discovery

Brian Brown, PhD, Director, Icahn Genomics Institute and Professor, Department of Genetics & Genomic Sciences, Icahn School of Medicine at Mount Sinai

Daniel Schramek, PhD, Associate Professor, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto

- Use of CRISPR screening, spatial genomics, imaging for target discovery
- *In vivo* profiling of drug targets

10:15 Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

11:00 Functional Screening and Other Approaches for the Discovery of Drug Targets, Resistance Mechanisms, and Biomarkers

CELLECTA

Paul Diehl, PhD, Chief Operating Officer, Cellecta, Inc.

We will discuss CRISPR screening and other approaches that can be used to discover the genetic drivers responsible for phenotypic variabilities, such as drug sensitivities, disease variation, and degrees of differentiation within cell populations, across tissue microenvironments, and between single cells. In addition, we will present an overview of novel Cellecta technologies.

11:30 Quantitative Nanopore Profiling of Pseudouridine Modification in the Human Transcriptome

Tao Pan, PhD, Professor, Department of Biochemistry & Molecular Biology, University of Chicago

Pseudouridine (Ψ) is an abundant mRNA modification in mammalian transcriptome, but its functions have remained elusive due to the difficulty of transcriptome-wide mapping. We developed a nanopore native RNA sequencing method for quantitative Ψ prediction (NanoPsu). Biologically we find interferon inducible Ψ modifications in interferon stimulated gene transcripts which is consistent with a role of Ψ in enabling efficacy of mRNA vaccines.

12:00 pm Systematic Phenotyping of Rare Pathogenic Disease Variants

Jessica Lacoste, Graduate Student, Department of Molecular Genetics, University of Toronto

Despite our knowledge of the genetic mutations that cause rare diseases, little is known of the cellular consequences of these genetic mutations. To bridge the gap between genetic and functional information, I systematically phenotyped a collection of rare pathogenic genetic variants for protein localization, protein interactions, protein degradation in the ER, and upregulation of the unfolded protein response. This resource will provide a platform for future efforts in drug discovery.

12:30 Understanding Lineage to Identify Vulnerabilities in Metastatic Carcinoma

Christopher Lengner, PhD, Associate Professor of Biomedical Sciences and Director, Center for Animal Transgenesis, School of Veterinary Medicine, University of Pennsylvania

The oncogenic transformation of normal tissue and its ultimate metastatic dissemination are believed to be driven by clonal competition resulting in the success of some lineages and loss of others. Understanding the molecular mechanisms governing clonal dominance is critical for the identification of points for therapeutic intervention. We discuss the development and application of novel genome editing tools to map and interrogate lineage in models of colon and pancreatic adenocarcinomas.

1:00 Transition to Lunch

1:10 : Panning for Gold: Identifying Novel Receptors and Deconvoluting Biotherapeutic Targets at Early Preclinical Stages

charles river

Nick Brown, Group Leader – Client Services, Charles River

Identifying primary targets and MOA for biotherapeutics (such as antibodies and related molecules) can be challenging, with traditional techniques such as mass spectrometry typically yielding low success rates. Cell microarray screening via the Retrogenix platform has been used by sponsors for over a

decade to accelerate biotherapeutics programs, profiling against the most comprehensive and high-quality library of human plasma membrane and secreted proteins available in the context of the human cell.

1:40 **Refreshment Break in the Hall with Poster Viewing (Grand Ballroom)**

AI PREDICTIONS FOR UNRAVELING DISEASE BIOLOGY

2:10 **Chairperson's Remarks**

Nicolas Stransky, PhD, Vice President & Head, Data Sciences, Celsius Therapeutics

2:15 **A Single-Cell RNAseq and Machine Learning Platform to Enable Target ID at Scale**

Nicolas Stransky, PhD, Vice President & Head, Data Sciences, Celsius Therapeutics

New genomic technologies hold great promise for the identification of actionable drug targets and associated biomarkers for several complex diseases. However, the discovery of novel targets is often complicated by multigenic effects and the involvement of multiple cell types in disease progression. Our approach uses single-cell RNAseq and machine learning to elucidate the precise cell types involved in the progression of complex diseases and to identify novel therapeutic targets.

2:45 **The Application of Artificial Intelligence to Drug Target Identification**

Olivier Elemento, PhD, Professor, Physiology, Biophysics & Systems Biology; Director, Englander Institute for Precision Medicine, Weill Cornell Medicine

In this talk, I will describe our continued efforts to use genomics and AI to identify the targets of compounds that may not have entirely known mechanisms of action. I will describe how these approaches can be used to screen libraries of compounds *in silico* to uncover repositioning opportunities. I will then describe the successful application to an anticancer compound, followed by precise clinical positioning in pediatric brain cancers.

3:15 **Mapping and Navigating Biology at Scale to Model Complex Disease and Accelerate Discovery**

Michael Cuccarese, PhD, Director, Translational Oncology, Recursion Pharmaceuticals, Inc.

Recursion is a clinical-stage pharmatech company, mapping human biology at scale to bring better medicines to patients. Enabled by 14 petabytes of imaging and other omics data, we use deep learning to build biological representations across multiple cell types, a whole-genome CRISPR library, and nearly 1 million compounds. Here, we demonstrate the capability of this platform to model complex disease and identify and optimize compounds as potential cancer therapies.

3:45 **Close of Conference**

TUESDAY, OCTOBER 18

7:00 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Back Bay A

TARGETING RNA BINDING PROTEINS

7:55 Welcome Remarks

8:00 Chairperson's Remarks
Bryce Allen, PhD, Co-Founder & CEO, Differentiated Therapeutics

8:05 Discovery of Novel Degraders of RNA-Binding Proteins by Integrating Molecular Dynamics with Fragment Screening
Bryce Allen, PhD, Co-Founder & CEO, Differentiated Therapeutics
RNA-binding proteins (RBPs) are paramount effectors of gene expression, and their malfunction underlies the origin of many diseases. However, therapeutically targeting RBPs with small molecules has proven challenging due to highly polar orthosteric ribonucleic interactions and a lack of lipophilic cavities indicative of druggability. We present an integrated screening campaign integrating fragment-based differentiable design with molecular dynamics to discover a cryptic site enabling targeted protein degradation of an RBP.

8:35 Nanobodies Targeting RNA-binding Proteins
Yongku Cho, PhD, Associate Professor, Chemical & Biomolecular Engineering, University of Connecticut
We describe a yeast surface display-based nanobody screening approach that led to high-specificity nanobodies against RNA-binding proteins (RBPs) hnRNPA2B1 and TIA1. We demonstrate that nanobodies enable fluorescence imaging of RBPs in live cells. We also show that nanobody-E3 ligase adapter domain fusions can target RBPs for proteasomal degradation. We anticipate these reagents will greatly aid the study of endogenous RBP dynamics and provide a novel means of interrogating RBP function.

9:05 RNA-Binding Proteins (RBPs) as Therapeutic Targets
Eugene Yeo, PhD, Professor, Cellular Molecular Medicine, University of California, San Diego
I will speak about our efforts in clarifying and identifying RNA-binding proteins as targets in oncology and neurodegeneration. We use focused pooled CRISPR inhibition and knock-out approaches to identify RBPs as vulnerabilities in different diseases, initially in oncology. We then use cutting-edge genomic methods to study the molecular pathways by which RBPs affect gene expression. Small molecule discovery approaches are then applied to modulate these in cancer, like avatars.

9:35 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

TARGETING mRNA

10:25 Discovery of Small Molecule mRNA Drugs and Their Mechanisms of Action Using Phenotypic Screening with AI-Driven MOA Elucidation
Kevin Pong, PhD, Chief Business Officer, Anima Biotech, Inc.
Anima's mRNA Lightning platform has generated many novel compounds that modulate mRNA translation, contributing to the RNA-targeting small molecule field. Anima's approach using phenotypic screening combined with AI-driven MOA elucidation identifies and validates the impact of small molecules on mRNA translation, providing an opportunity for tissue-selective and target-specific modulation. Anima's lead preclinical programs in fibrosis and oncology have demonstrated efficacy in animal and patient-derived models.

10:55 Modifying mRNA to Produce Functional CAR T Cells *in vivo* for the Treatment of Heart Disease
Haig Aghajanian, PhD, Co-Founder and Vice President of Research, Capstan Therapeutics
Using targeted lipid nanoparticles (tLNP), we were able to transiently reprogram T cells *in vivo* by delivering modified mRNA encoding a CAR against fibroblast activation protein (FAP). This treatment resulted in the reduction of cardiac fibrosis and the restoration of cardiac function. The ability to produce transient, functional CAR T cells *in vivo* with mRNA addresses some of the biggest hurdles in cell therapy including manufacturing, scalability, and safety concerns.

11:55 Discovery of RNA Targeting Small Molecule Using DNA-Encoded Library Technology
Zhifeng Yu, PhD, Director, WuXi AppTec
By utilizing newly-developed DNA-encoded small molecule library technology (DEL), researchers are able to over come scalability challenges often seen in RNA-target drug discovery. This presentation will review the "DNA-Zipper" strategy proposed by WuXi AppTec. It has been shown to significantly reduce the interference between DNA tags from DEL molecules and RNA targets, and effectively decreases the false positive readouts.

12:25 pm Session Break

MODULATING RNA CONFORMATION & FUNCTION

1:25 Chairperson's Remarks
Amanda Hargrove, PhD, Associate Professor, Department of Chemistry, Duke University

1:30 Discovery of RNA-Targeted Small Molecule Therapeutics
Kathleen McGinness, PhD, Head of Platform Biology, Arrakis Therapeutics
RNA offers a broad array of folded, three-dimensional structures that mediate their functional roles. Our drug discovery platform at Arrakis Therapeutics is directed at the intervention of those functions to therapeutic benefit using drug-like small molecules that bind folded RNA structures. This presentation will touch on some of the unique challenges in building a broad and robust RNA-targeted small molecule platform and provide early data on specific RNA targets.

2:00 Exploring the Undiscovered Country of RNA as a Drug Target--Finding Bioactive Ligands against XIST RNA with Affinity-Selection MS Screening
Elliott Nickbarg, PhD, Principal Scientist, Quantitative Biosciences, Merck Research Laboratories
Most of the human genome is non-coding but may still be relevant to disease. We adapted Affinity-selection MS screening to identify small molecule ligands binding to non-coding RNAs. We found bioactive ligands acting upon the non-coding RNA Xist and showed that these compounds can affect the ncRNA structure and biological activities. This shows that ncRNA can be targeted in a structure-agnostic fashion to find drug-like tool compounds.

2:30 Expanding the DNA-Encoded Library Toolbox: Identifying Small Molecules Targeting RNA
You Li, Director of NGS and Bioinformatics, Lead Generation Unit, HitGen Inc.

DNA-encoded library (DEL) technology is a powerful hit/lead identification method in drug discovery, yet the reported DEL selection strategies were not generally applicable for RNA due to the overwhelmed interactions between DNA tags and RNA targets. To overcome this limitation, we developed strategies that efficiently reduce the level of DNA:RNA interaction. This optimized protocol enables the use of DEL for RNA targets and can theoretically be applied in any given RNA types.

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

3:40 Patterns and Predictions in Small Molecule RNA Interactions

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

We have analyzed patterns in both RNA-biased small molecule chemical space and RNA topological space privileged for differentiation. In a recent example, quantitative structure-activity relationships (QSAR) models have allowed prediction of small molecule binding and/or modulation of specific RNA structures. We have applied these and other principles to functionally modulate conformations of the 3′-triple helix of the long noncoding RNA MALAT1, as well as several viral RNA structures.

4:10 Pharmacokinetics, Pharmacodynamics, Pharmaceutical Properties, and Efficacy of Small Molecule Splicing Modifiers

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

Utilizing small molecules to modulate splicing has emerged as a successful therapeutic approach to regulating protein expression. Here, three diseases where small molecule splicing modulators can be utilized are described: spinal muscular atrophy, familial dysautonomia, and Huntington's disease. For each of these indications, I will discuss the correlation between pharmaceutical properties and pharmacokinetics, pharmacokinetics and pharmacodynamics, and the correlation between pharmacodynamics and efficacy.

4:40 FEATURED PRESENTATION: Design of Bioactive Ligands Targeting RNA

Matthew Disney, PhD, Professor, Department of Chemistry, Scripps Research Institute

One of the challenges in RNA targeted small molecule is the design of bioactive ligands. Our function-first approach has been broadly deployed across the human transcriptome and has helped develop multiple bioactive ligands from cells to pre-clinical animal models of disease. In this talk, we will describe the design RNAs whose function can be affected by binders but also by using targeted degradation.

5:10 Interactive Discussions

Interactive Discussions 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 conference website's Interactive Discussions page for a complete listing of topics and descriptions.

IN-PERSON INTERACTIVE DISCUSSION: Challenges and Opportunities Pursuing RNA as a Drug Target

Matthew Disney, PhD, Professor, Department of Chemistry, Scripps Research Institute
Amanda Hargrove, PhD, Associate Professor, Department of Chemistry, Duke University
Marla Weetall, PhD, Vice President, Pharmacology and Biomarkers, PTC Therapeutics

- Emerging techniques for probing and modulating RNA
- Corelating RNA binding with function and physiological response
- New drug modalities for targeting RNA

5:55 Welcome Reception in the Exhibit Hall with Poster Viewing (Grand Ballroom)

6:55 Close of Day

WEDNESDAY, OCTOBER 19

7:30 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Back Bay A

TOOLS FOR TARGETING RNA

7:55 Chairperson's Remarks

Jay Schneekloth Jr., PhD, Principal Investigator, Chemical Biology Laboratory, NIH NCI

8:00 Multiplex tRNA Sequencing and Application to Cells and Microbiomes

Tao Pan, PhD, Professor, Department of Biochemistry & Molecular Biology, University of Chicago

Small RNAs include tRNA, snRNA, micro-RNA that constitute >90% of RNA copy numbers in a human cell and perform essential functions. We developed a multiplex small RNA-seq library preparation method (MSR-seq) to investigate various samples. We applied MSR-seq to study stress response in human cells, infections in nasal cavity, and microbiomes that reveal the importance of simultaneous investigation of small RNAs and their modifications in response to varying biological conditions.

8:30 Targeting RNA with Small Molecules: Tools and Technologies for Medicinal Chemistry

Jay Schneekloth Jr., PhD, Principal Investigator, Chemical Biology Laboratory, NIH NCI

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

9:00 PANEL DISCUSSION: Challenges with Developing RNA-Targeting Small Molecule Drugs?

Moderator: Thomas Hermann, PhD, Professor, Department of Chemistry & Biochemistry, University of California, San Diego
Panelists:
Haig Aghajanian, PhD, Co-Founder and Vice President of Research, Capstan Therapeutics
Karthik Iyer, PhD, Associate Director, Chemical Sciences, Arrakis Therapeutics
Elliott Nickbarg, PhD, Principal Scientist, Quantitative Biosciences, Merck Research Laboratories
Marla Weetall, PhD, Vice President, Pharmacology and Biomarkers, PTC Therapeutics

10:00 Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

PLENARY KEYNOTE PROGRAM

ROOM LOCATION: Constitution A + B

11:00 Plenary Chairperson's Remarks
An-Dinh Nguyen, Team Lead, Discovery on Target, Cambridge Healthtech Institute

11:05 PLENARY: Pirating Biology to Detect and Degrade Extracellular Proteins
James A. Wells, PhD, Professor, Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco
In contrast to intracellular PROTACs, approaches to degrade extracellular proteins are just emerging. I'll describe our recent progress to harness natural mechanisms such as transmembrane E3 ligases to degrade extracellular proteins using fully genetically encoded bispecific antibodies we call AbTACs. We have also engineered a peptide ligase which can be tethered to cells to detect proteolysis events and target them with recombinant antibodies for greater selectivity for the tumor microenvironment.

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12:35 pm Enjoy Lunch on Your Own

1:25 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom Foyer)

2:05 Close of Targeting RNA Conference

Cambridge Healthtech Institute's Inaugural

New Antivirals

NEW

Oral-Based Approaches, to Combat HBV, SARS-CoV-2 and Other and Emerging Viruses | OCTOBER 19-20, 2022

WEDNESDAY, OCTOBER 19

PLENARY KEYNOTE PROGRAM

ROOM LOCATION: Constitution A + B

11:00 am Plenary Chairperson's Remarks

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

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James A. Wells, PhD, Professor, Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco

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Anabella Villalobos, PhD, Senior Vice President, Biotherapeutics & Medicinal Sciences, Biogen

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12:35 pm Enjoy Lunch on Your Own

1:25 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom Foyer)

ROOM LOCATION: Back Bay A

DIRECT-ACTING ANTIVIRALS IN THE PIPELINE (HBV AND RSV)

2:05 Welcome Remarks

2:10 Chairperson's Remarks

Angela M. Lam, PhD, Vice President, Biology, Arbutus Biopharma Corp.

2:15 HBV Core Inhibitors for the Treatment of Chronic Viral Infection

Michael A. Walker, PhD, Executive Director Chemistry, Chemistry, Assembly Biosciences, Inc.

The HBV core-protein forms the viral nucleocapsid and is an attractive target for the treatment of viral infection. Capsid inhibitors (CIs) bind at the core-protein dimer of dimer interface, and this leads to aberrant assembly of the nucleocapsid thereby blocking the production of a new virus. Additionally, certain CIs exploit the same dimer-dimer binding site on the mature rcDNA-filled capsid to destabilize it and block the establishment of infection.

2:45 AB-161 as an Oral HBV RNA Destabilizer to Suppress HBV RNA and HBsAg

Angela M. Lam, PhD, Vice President, Biology, Arbutus Biopharma Corp.

HBV surface antigen (HBsAg) is believed to play a major role in maintaining persistent infection in chronic hepatitis B patients. HBV RNA destabilizers inhibit enzymatic activities of noncanonical poly(A) polymerases PAPD5 and PAPD7, destabilize HBV RNA, and suppress viral protein productions, including HBsAg. AB-161 is our next-generation liver-centric HBV RNA destabilizer targeting PAPD5/7 to reduce HBV RNA and HBsAg in multiple HBV cell-based models and in AAV-HBV infected mice.

3:15 Targeted Protein Degradation for Antivirals

Priscilla L. Yang, PhD, Professor, Department of Microbiology and Immunology, Stanford University

Conventional direct-acting antivirals have occupancy-driven pharmacology and generally require high affinity-binding for antiviral efficacy. Small molecules that instead induce degradation of their target ("antiviral degraders") can potentially exert significant antiviral activities without high affinity and residence times due to their event-driven pharmacology. I will describe my group's proof-of-concept work developing antiviral degraders and comparing the ability of these compounds to address viral genetic diversity when compared to functional inhibitors.

3:45 Dessert Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

4:25 EDP-323, a Small Molecule L-Protein Inhibitor in Development Against Respiratory Syncytial Virus

Michael Rhodin, PhD, Principal Scientist, ENANTA Pharmaceuticals, Inc.

EDP-323 is a novel small molecule, non-nucleoside RSV L-protein inhibitor developed as a potential treatment for RSV infection with sub-nanomolar potency against multiple RSV strains. EDP-323 inhibits L-polymerase activity, blocking both transcription and replication. *In vivo*, EDP-323 protected BALB/c mice from viral-induced changes in body and lung weights, lung histopathology, inflammatory cytokine production, and significantly reduced viral replication. Together, these data support further evaluation of EDP-323 for treatment of RSV infection.

4:55 Discovery and Development of PBI-0451: A novel Oral Protease Inhibitor for the Potential Treatment of SARS-CoV-2

Ann D. Kwong, PhD, Executive Vice President, Research, Pardes Biosciences, Inc.

There is a need for safe, effective, and simple-to-use oral SARS-CoV-2 antivirals for use by people who take common medications for comorbid conditions. PBI-0451 has demonstrated potent pan-coronaviral antiviral activity *in vitro*, favorable nonclinical and clinical safety and tolerability to date, and a clinical PK profile anticipated to provide potent antiviral activity against SARS-CoV-2. PBI-0451 as a stand-alone agent is currently in Phase 2 studies in patients with COVID-19.

5:25 Discovery and Development of Novel Direct-Acting Antivirals (HBV CpAM and RSV Fusion Inhibitor)

Wei Zhu, PhD, Head of Medicinal Chemistry, Roche Innovation Center, Shanghai

In this talk, we will present the two stories on the discovery and development of novel RSV fusion inhibitor (currently Ph3) and HBV core protein assembly modulator (currently Ph2). In particular, we will highlight how the modern drug discovery technologies, such as virtual screening, structural biology, and sophisticated medicinal chemistry know-how, are successfully applied in hit identification, molecular mechanism understanding, and fine-tuning drug-like properties (potency, DMPK, PD, and safety).

5:55 Dinner Short Course Registration*

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

9:00 Close of Day

THURSDAY, OCTOBER 20

7:30 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Back Bay A

SMALL MOLECULES FOR COVID

7:55 Chairperson's Remarks

Alpha Lee, PhD, Chief Scientific Officer, PostEra

8:00 Oral 3Cl-Protease Inhibitors for Treating Coronaviral Infections

Koen Vandyck, PhD, Senior Director, Medicinal Chemistry, Aligos Therapeutics, Inc.

The emergence of the COVID-19 pandemic resulted in a large R&D effort to discover direct-acting antiviral therapeutics against SARS-CoV-2. Rapid evolution of new SARS-CoV-2 variants and the presence of multiple other coronaviruses indicates the need for broadly acting antivirals across all coronaviruses. The SARS-CoV-2 3CL protease (3CLpro) is a clinically validated target and is conserved across coronaviruses. Here we will describe our discovery efforts toward oral pan-coronaviral 3CLpro inhibitors.

8:30 Opaganib – An Oral, Host Cell Targeted Anti-Viral and Anti-Inflammatory Drug in Development for the Treatment of COVID-19 Pneumonia

Mark L. Levitt, PhD, Medical Director, Oncology, RedHill Biopharma Ltd.

In a randomized, double-blind Phase 2/3 clinical trial in severe COVID-19 pneumonia, opaganib (a sphingosine kinase-2 inhibitor) was superior to placebo for time to room air (primary) and secondary endpoints including mortality and time to discharge in patients requiring an FiO2 </=60%. Additional superiority was demonstrated in time to viral clearance, to WHO 1 status, and concomitant administration of remdesivir and corticosteroids in the entire cohort, regardless of FiO2 status.

9:00 EDP-235: A Potent, Once-Daily Oral Antiviral Treatment for COVID-19

Lijuan Jiang, PhD, Vice President, Drug Metabolism, Pharmacokinetics & Bioanalysis, ENANTA Pharmaceuticals, Inc.

COVID-19 has led to a global health crisis. Herein, we present EDP-235, a novel and potent SARS-CoV-2 3C-like protease inhibitor being developed as a once-daily oral antiviral therapy for COVID-19. EDP-235 has demonstrated nanomolar potency preclinically against currently circulating COVID-19 variants and other coronaviruses. Moreover, EDP-235 has optimized pharmacokinetic properties with excellent target tissue penetration. The favorable EDP-235 profile suggests the potential as a best-in-class antiviral treatment for SARS-CoV-2 infection.

9:30 Interactive Discussions

Interactive Discussions 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 conference website's Interactive Discussions page for a complete listing of topics and descriptions.

ROOM LOCATION: Back Bay A

IN-PERSON INTERACTIVE DISCUSSION: Antiviral Drug Development Challenges

Christian Lerner, PhD, Senior Principal Scientist, Medicinal Chemistry, Roche Innovation Center Basel

Xiao Tong, PhD, Executive Director, Virology, Pardes Biosciences Inc

- Pan-antivirals: For which viruses? When?
- HBV combo potentials
- TPD approaches: A good strategy for antivirals?
- Has COVID impacted antiviral drug discovery?

10:15 Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

TARGETING THE HOST

11:30 SLR14, a Novel RIG-I Agonist under Development as a Broad-Spectrum Antiviral Agent

Radhakrishnan Iyer, PhD, CSO, RIGImmunce, Inc.

SLR14 is a novel RNA oligonucleotide with potent antiviral activity against a broad panel of RNA viruses. SLR14 is a highly selective and potent RIG-I agonist that activates the IFN-signaling cascade for prophylactic and therapeutic antiviral defense. SLR14 has demonstrated potent activity in multiple mouse models of SARS-CoV-2, influenza, and *bunya viridae*, representing a family of viruses with different compositions and biological mechanisms.

12:00 pm Targeting Host Lipid Biosynthesis Pathways for Hepatitis B Virus Cure

Anastasia Hyrina, PhD, Research Scientist, Discovery Virology, Gilead Sciences

Sustained loss of lipoprotein-like hepatitis B surface antigen (HBsAg) particles is correlated with improved liver outcomes and is a key goal of functional cure. Statin use in chronic hepatitis B (CHB) patients is also associated with improved liver outcomes suggesting a potential role in the perturbation of the lipid composition of HBsAg. In this talk, we will present our data focused on targeting host lipid biosynthesis for treatment of HBV.

12:30 Enjoy Lunch on Your Own

1:40 Refreshment Break in the Hall with Poster Viewing (Grand Ballroom)

ORAL-BASED ANTIVIRALS ON THE HORIZON

2:10 Chairperson's Remarks

Christian Lerner, PhD, Senior Principal Scientist, Medicinal Chemistry, Roche Innovation Center Basel

2:15 Targeting Influenza Endonuclease

Christian Lerner, PhD, Senior Principal Scientist, Medicinal Chemistry, Roche Innovation Center Basel

The Influenza Endonuclease is an attractive target for stand-alone therapy or in combination offering a fast onset of action and a high genetic barrier to resistance. The talk will illustrate the structure-based optimization of early leads to an advanced candidate with *in vivo* activity. We demonstrate how the identification and prioritization of a high-throughput cellular assay over a biochemical assay has played a crucial role to accelerate project progression.

2:45 Open Science Discovery of Preclinical Candidates Against SARS-CoV-2 Main Protease with Machine Learning

Alpha Lee, PhD, Chief Scientific Officer, PostEra

COVID Moonshot is an international open science consortium aiming to discover oral antiviral against SARS-CoV-2, targeting Mpro. In less than 18 months, we went from fragment hits to development candidates now under preclinical evaluation. In my talk, I will discuss Moonshot's journey, specifically how machine learning has accelerated our design-make-test cycle. I will also discuss our vision for pandemic preparedness and the newly established NIH-funded ASAP antiviral discovery platform.

3:15 Close of Conference

TUESDAY, OCTOBER 18

7:00 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Back Bay D

MODULATING IMMUNO-METABOLISM AND IMMUNE-SUPPRESSION WITH SMALL MOLECULES

7:55 Welcome Remarks

8:00 Chairperson's Remarks

Thomas Sundberg, PhD, Principal Scientist, Immunology Discovery, Janssen Pharmaceuticals

8:05 FEATURED PRESENTATION: Selectively Inhibiting Kinase HPK1 for IO

William N. Pappano, PhD, Senior Principal Research Scientist, AbbVie, Inc.

HPK1 has long been of interest as a potential pharmacological target for immune therapy because of its central role in negatively regulating T cell function. The development of a small molecule HPK1 inhibitor remains challenging because of the need for high specificity relative to other kinases that are required for efficient immune cell activation. We will present our efforts at generating selective HPK1 inhibitors to enhance the anti-tumor immune response.

8:35 Identification of a Potent and Highly Selective HPK1 Inhibitor

David Ciccone, PhD, Senior Director, Immunology & Immuno-Oncology, Nimbus Therapeutics

Neelu Kaila, PhD, Executive Director, Medicinal Chemistry, Nimbus Therapeutics

HPK1 is a hematopoietic cell-restricted member of the MAP4K family that acts as a negative regulator of T-cell function. Genetic studies show HPK1 removal or functional inactivation result in increased T-cell proliferation and cytokine production. We disclose a structure-based drug design approach to identify NTX-810, a potent and selective HPK1 inhibitor that enhanced immune cell activation and induced robust tumor growth inhibition in multiple murine syngeneic tumor models.

9:05 Cancer-Associated Fibrosis: Tumor Biology and Associated Macrophages

Alexander M.S. Barron, PhD, Senior Scientist, Leukocyte Tissue Interface Group, Pfizer Inc.

Macrophages and desmoplastic reactions are associated with resistance to current immuno-oncology therapies. We identified a subset of macrophages that expanded in both oncologic and non-oncologic fibrosis across tissues and species. Leveraging human cells and murine models we uncovered cytokines that drive phenotypic and functional aspects of these scar-associated macrophages. These macrophages appear to be associated with poor survival outcomes for subsets of cancer patients.

9:35 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

10:25 Targeting the TGF-ß Pathway for Checkpoint Resistance

Natalia J. Reszka-Blanco, PhD, Principal Scientist, Morphic Therapeutic

Innate and therapy-induced resistance to checkpoint inhibitors limit the response rate in many cancers. An increased TGF-ß signature is linked to poor clinical outcomes and checkpoint resistance. avß8 controls localized and cell-type-specific activation of TGF-ß 1 and 3 to negatively regulate immunity and promotes tolerance. Selective avß8 inhibition is a safe and efficient approach to reverse TGF-ß-driven immunosuppression, improving anti-tumor adaptive immune responses and immune infiltration into the TME.

10:55 Leveraging the *RAPID* Chemoproteomics Platform to Unlock Targets in the STING Pathway

Justin Rettenmaier, PhD, Senior Director, Head of Early Discovery, Jnana Therapeutics

RAPID is a next-generation chemoproteomics technology for discovering small molecules that bind to any target of interest inside of a living cell. Using RAPID, we have discovered the first described ligands for the transcription factor IRF3, which drives the interferon response downstream of STING. We will also describe the discovery of an orphan transporter that is required for the uptake of paracrine 2',3'-cGAMP into primary macrophages.

11:25 Cellular Transporters as IO Targets

Vincent Sandanayaka, PhD, President & CSO, Nirogy Therapeutics

Tumors consume large amount of glucose releasing lactate to the tumor microenvironment (TME) via membrane-bound transporters, MCT1 and MCT4. Lactate is an immunosuppressive metabolite in the TME. Here we describe small molecule dual inhibitors of MCT1/4 which enable intrinsic cell killing and activation of local anti-tumor immunity, leading to tumor growth reduction in multiple mouse tumor models. This novel therapeutic modality could address deficiencies of current treatments, including I/O inhibitors.

11:55 Cellular and Translational Models Supporting Immuno-Oncology Drug Discovery.

Syngene
Putting Science to Work

Atul Tiwari, PhD, Director Biology & Head-Discovery Service Solutions, Syngene International Ltd.

Syngene International is an established and recognized partner in the discovery and development of small and large molecules for different therapeutic areas. With Immuno-oncology at the mainstay of drug discovery research, we offer customized solutions and platforms for cellular and translational science. An overview of our approaches and platforms as it pertains to different endpoints and biomarkers related to immuno-oncology along with related case studies will be presented.

12:25 pm Transition to Lunch

12:35 LUNCHEON PRESENTATION: p38 as off-Target for Kinase Inhibitors

Creoptix

Thomas Schubert, PhD, CEO, 2bind

The superfamily of kinases with its >500 members contains several prominent Immuno-Oncology targets such as p38. Selectivity of kinase inhibitors is critical due to the high conservation between kinases. Missing selectivity can result in severe off target effects. In this study, we use biophysical binding assays to characterize the interaction of >80 described kinase inhibitors to p38, thereby demonstrating that p38 is an off target for several kinase inhibitors.

1:05 Session Break

NEW APPROACHES FOR IO TARGETS

1:25 Chairperson's Remarks

Christina Baumgartner, PhD, Principal Research Scientist I, Oncology, AbbVie, Inc.

1:30 Discovery of Subasumstat (TAK-981) a First-in-Class Inhibitor of SUMO Activating Enzyme

Steven P. Langston, PhD, Senior Scientist, Oncology Discovery Chemistry, Millennium The Takeda Oncology Co.

SUMOylation is a post-translational modification that regulates protein function and requires activation of SUMO protein by SUMO Activating Enzyme (SAE). Here we describe the identification of subasumstat (TAK-981), a mechanism-based inhibitor of SAE, which forms a SUMO-TAK-981 adduct. Treatment with TAK-981 in murine models was shown to activate multiple immune cells through induction of a type I interferon response to promote anti-tumor immunity. Subasumstat is currently under clinical evaluation.

2:00 ABBV-CLS-484: A First-in-Class Orally Active PTPN2/N1 Inhibitor for Immunotherapy

Jennifer Frost, PhD, Research Fellow, Centralized Medicinal Chemistry, AbbVie, Inc.

PTPN2/N1, negative regulators of immune activation pathways, emerged as hits in an *in vivo* CRISPR screen to identify tumor-intrinsic targets that enhance sensitivity and overcome resistance to anti-PD-1 treatment. Here we report the discovery of a first-in-class PTPN2/N1 inhibitor, a promising novel immunotherapy that both increases tumor sensitivity to immune-mediated killing and enhances the function of multiple immune cell subsets. ABBV-CLS-484 is currently being evaluated in Phase I clinical trials.

2:30 Using GCI to Support Challenging Drug Discovery Programmes

Trevor Askwith, PhD, Group Leader, Assay Biology, Domainex

Biophysical assays are a critical component of many screening cascades, enabling the measurement of detailed pharmacology including binding kinetics. New modalities are pushing drug discovery pipelines towards target classes that have been classically deemed undruggable, which increases the technical demands for biophysical platforms. This presentation will describe how Domainex has incorporated the Creoptix WAVE into their biophysical suite and has used the platform to prosecute challenging targets.

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

ROOM LOCATION: Constitution A

TARGETED DEGRADATION FOR INTRACELLULAR CANCER TARGETS

3:40 FEATURED PRESENTATION: Development of a STAT3 Targeted Protein Degrader

Chris De Savi, PhD, Senior Vice President & Head, Drug Discovery, Kymera Therapeutics

Signal Transducer and Activator of Transcription 3 (STAT3) plays important roles in the transduction of signals from growth factors and cytokines in both normal and malignant cells. Aberrant activation of STAT3 has been observed in many cancers including lymphoma and leukemias. Here we introduce a first-in-class, potent, and selective STAT3 heterobifunctional degrader KT-333 that is being developed for the treatment of hematologic malignancies and solid tumors.

4:10 Discovery and Optimization of CBL-B Inhibitors for Immune-Cell Mediated Tumor Rejection

Frederick Cohen, PhD, Vice President, Medicinal Chemistry, Nurix Therapeutics, Inc.

Casitas B-lineage lymphoma b (CBL-B) is an E3 ligase that functions as a negative regulator of T, NK, and myeloid cells. Mice deficient in cbl-b reject tumors in syngeneic models, suggesting pharmacological inhibition of CBL-B as a novel therapeutic strategy. We present discovery of compounds, including NX-1607, that glue CBL-B into an inactive conformation and result in antitumor effects in tumor models upon daily oral dosing.

4:40 Characterization of the Molecular Glue-Induced Interactions of IO Target IKZF2 with Cereblon

Charles A. Wartchow, PhD, Associate Director, Global Discovery Chemistry, Novartis Institutes for BioMedical Research

Formation of ternary complexes between a ligase, a molecular glue, and a disease-modulating protein is the first step in a sequence of events leading to protein degradation. In this presentation, we discuss the SPR and X-ray crystallographic characterization of ternary complexes involving a molecular glue that binds to the ligase Cereblon and induces the binding of the zinc finger-containing transcription factor IKZF2.

5:10 Interactive Discussions

Interactive Discussions 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 conference website's Interactive Discussions page for a complete listing of topics and descriptions.

IN-PERSON INTERACTIVE DISCUSSION: Degrader Strategies for Cancer and Beyond

Miklos Bekes, PhD, Associate Director, Degrader Mechanisms Group, Platform Biology, Arvinas, Inc.

Chris De Savi, PhD, Senior Vice President & Head, Drug Discovery, Kymera Therapeutics

- Why is oncology especially well-suited for targeted protein degradation (TPD) strategies?
- What are the TPD approaches most likely to succeed in cancer?
- What areas and which approaches show the most promise for non-cancer indications?

5:55 Welcome Reception in the Exhibit Hall with Poster Viewing (Grand Ballroom)

6:55 Close of Day

WEDNESDAY, OCTOBER 19

7:30 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Constitution B

TARGETING GPCRs IN THE TUMOR MICRO-ENVIRONMENT

7:55 Chairperson's Remarks

Nicolas Villanueva, MBA, PhD, Director, Bioscience Strategy, Dassault Systèmes BIOVIA

8:00 Discovery of Etrumandenant: A Potent Dual Adenosine Receptor Antagonist for Cancer Immunotherapy

Brandon Rosen, PhD, Senior Scientist, Medicinal Chemistry, Arcus Biosciences

The presence of extracellular adenosine is frequently responsible for the creation of an immunosuppressed tumor microenvironment through activation of the A2a and A2b receptors expressed on intratumoral immune cells. AB928 is a small molecule dual A2aR/A2bR antagonist designed to block the immunosuppressive effects of adenosine in the tumor microenvironment. This presentation discusses the design, characterization, and SAR of a series of A2aR/A2bR antagonists culminating in the discovery of etrumadenant.

8:30 Data Organization Using CDD Vault to Streamline the Discovery Process

Kelly Bachovchin, PhD, Customer Engagement Scientist, Technical Support, Collaborative Drug Discovery

Collaborative Drug Discovery (CDD) provides a whole solution for today's biological and chemical data needs, differentiated by ease-of-use and superior collaborative capabilities. CDD Vault® software includes Activity & Registration, Visualization, Inventory, and ELN capabilities. Researchers can archive, mine, and securely collaborate within CDD Vault. Collaborative hypothesis generation and evaluation allow multiple perspectives for multi-parameter optimization for all types of entities.

8:45 Kinetic Characterization of Ligand and Antibody Binding to Cell Surface Expressed CCRL2 Using Surface Plasmon Resonance Microscopy (SPRM)

Jonathan Brooks, Inflammation & Remodeling Department, Pfizer Inc.

C-C motif chemokine receptor-like 2 (CCRL2), is a non-signaling 7TM receptor, referred to as an atypical chemokine receptor (ACKR). Unlike conventional GPCR chemoattractants which initiate intracellular signaling to direct leukocyte migration, ACKRs are unable to activate G-protein-dependent signaling and the cellular responses required to direct cell migration. We utilized a new biophysical technique, SPR Microscopy, in addition to other biophysical techniques, to characterize ligand and antibody binding to CCRL2.

9:00 Targeting the Chemokine Receptor CCR2 in Immuno-Oncology: Opportunities and Challenges

Irina Kufareva, PhD, Associate Adjunct Professor, University of California, San Diego

CCR2 is pursued as a target in autoimmunity and immuno-oncology due to its immune-cell trafficking role. This pursuit, however, has not yet yielded any clinical candidates. Failures have been attributed to complexities of CCR2 biology and suboptimal properties of the therapeutic candidates. I will present an overview of CCR2-targeting modalities, discuss the structural principles of their affinity and selectivity, and share recent findings about unexpected side-effects of CCR2 inhibition.

9:30 FLX475: A Potent and Selective CCR4 Antagonist to Target Treg Selectively in the TME

David J. Wustrow, PhD, Senior Vice President Discovery & Preclinical Development, Discovery & Preclinical Development, RAPT Therapeutics

High levels of Treg infiltration in the tumor microenvironment (TME) lead to a poor prognosis in patients. The chemokine receptor CCR4 is highly expressed on Treg where it functions to attract them into the TME where they inhibit immune response. To reduce the prevalence of Treg in the TME we have discovered and developed FLX475 a potent, selective, and orally available CCR4 antagonist.

10:00 Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

PLENARY KEYNOTE PROGRAM

ROOM LOCATION: Constitution A + B

11:00 Plenary Chairperson's Remarks

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

11:05 PLENARY: Pirating Biology to Detect and Degrade Extracellular Proteins

James A. Wells, PhD, Professor, Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco

In contrast to intracellular PROTACs, approaches to degrade extracellular proteins are just emerging. I'll describe our recent progress to harness natural mechanisms such as transmembrane E3 ligases to degrade extracellular proteins using fully genetically encoded bispecific antibodies we call AbTACs. We have also engineered a peptide ligase which can be tethered to cells to detect proteolysis events and target them with recombinant antibodies for greater selectivity for the tumor microenvironment.

11:50 PLENARY: Therapeutic Modalities for Neuroscience Diseases

Anabella Villalobos, PhD, Senior Vice President, Biotherapeutics & Medicinal Sciences, Biogen

Many effective medicines exist to treat neurological diseases, but medical need remains high. We have a unique multi-modality approach to discover novel therapies and our goal is to find the best modality regardless of biological target. With a multi-modality approach, we aim to expand target space, leverage synergies across modalities, and offer options to patients. Opportunities and challenges associated with small molecules, biologics, oligonucleotides, and gene therapy will be discussed.

12:35 pm Enjoy Lunch on Your Own

1:25 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom Foyer)

2:05 Close of Small Molecule Immuno-Oncology Targets Conference

WEDNESDAY, OCTOBER 19

PLENARY KEYNOTE PROGRAM

ROOM LOCATION: Constitution A + B

11:00 am Plenary Chairperson's Remarks

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

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12:35 pm Enjoy Lunch on Your Own

1:25 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom Foyer)

ROOM LOCATION: Back Bay D

FIBROSIS CONNECTIONS

2:05 Welcome Remarks

2:10 Chairperson's Remarks

Bernard B. Allan, PhD, Senior Director & Head, Liver Research & GI Drug Discovery, Takeda Pharmaceuticals, Inc.

2:15 The ExtraCellular Matrix (ECM) and Inflammatory Dermatological Disease: the ECM beyond Cutaneous Fibrosis

Vanessa M. Morales-Tirado, PhD, Principal Research Scientist I, Discovery Dermatology, Abbvie Bioresearch Center

The extracellular matrix is considered a common link in chronic diseases. Its physical and biochemical regulation are essential in normal tissue homeostasis and could also be the driving force in several diseases, including fibrosis and cancer. Herein, we explore and present recent findings in the ECM-immune system crosstalk in inflammatory skin diseases, such as Psoriasis and Hidradenitis suppurativa.

2:45 The Intestinal Fibrosis Drug Discovery Landscape

Bryan C. Fuchs, PhD, Senior Director & Research Therapeutic Area Head, GI & Liver Disease, Ferring Research Institute

Intestinal fibrosis is defined as an excessive accumulation of scar tissue in the intestinal wall and is a common complication of inflammatory bowel diseases. I will review the biological pathways leading to intestinal fibrosis, including the different fibroblast subtypes in the intestine. I will also discuss points of intersection with other fibroproliferative diseases including potential targets, and touch upon the drug development landscape for intestinal fibrosis.

3:15 A Lung-Regenerative, Caveolin-Targeted Peptide for IPF

Cory M. Hogaboam, PhD, Professor, Medicine, Cedars-Sinai Medical Center

Lung Therapeutics LTI-03 is an inhaled 7mer peptide which restores the key components of caveolin-1 scaffolding domain activity in several target IPF immune and non-immune lung cells. To date, this therapeutic approach has shown outstanding efficacy in several preclinical and translational IPF models. Most notably, LTI-03 promotes AEC2 and AEC1 survival and proliferation based upon key AEC2 (SPC) and AEC1 (soluble RAGE) biomarkers in a precision cut lung slice system.

3:45 Dessert Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

4:25 FEATURED PRESENTATION: Scar-Associated Macrophages in NASH and Chronic Liver Disease

Kevin Hart, PhD, Associate Research Fellow, Inflammation and Immunology Research Unit, Pfizer Inc.

Macrophages serve as central regulators of hepatic homeostasis as well as orchestrators of the response to injury in liver disease. We utilized human and murine liver single-cell RNA sequencing datasets to identify a unique subset of macrophages associated with fibrotic liver disease that localize to the fibrotic margins. *In vitro* and *in vivo* studies revealed regulatory cytokines that drive phenotypic and functional aspects of these scar-associated macrophages.

4:55 Lanifibranor Therapy Improves Markers of Cardiometabolic Health in Patients with NASH and Fibrosis

Michael P. Cooreman, MD, CMO, Inventiva Pharma

Liver cirrhosis and cardiovascular disease are major causes of mortality in patients with NASH. The pan-PPAR agonist lanifibranor has shown efficacy on NASH resolution and fibrosis improvement (NATIVE study). Lanifibranor also improved a broad panel of markers of cardiometabolic health, incl. insulin resistance, lipid and glucose metabolism, systemic inflammation, blood pressure and hepatic steatosis. Lanifibranor therapy addresses hepatic injury and fibrosis as well as the metabolic-immune disease biology of NASH.

5:55 Dinner Short Course Registration*

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

9:00 Close of Day

THURSDAY, OCTOBER 20

7:30 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Back Bay D

CROSS-FIBROTIC TARGETS

7:55 Chairperson's Remarks

Cory M. Hogaboam, PhD, Professor, Medicine, Cedars-Sinai Medical Center

8:00 Selective Targeting of Matrix-Associated TGFb1 is an Attractive Approach for Anti-Fibrotic Therapy

Rohan Manohar, PhD, Associate Director, Fibrosis, Scholar Rock

TGFß inhibition remains a promising anti-fibrotic approach. However, inhibition of all 3 TGFß isoforms is associated with safety liabilities. Scholar Rock has identified a selective antibody that inhibits matrix-associated TGFß1 complexed with LTBP1 and 3, spares TGFß1 presented by immune cells, and reduces TGFß signaling and fibrosis in preclinical models of kidney disease. This LTBP-TGFß1 antibody may offer a safety profile that is better suited to treating chronic fibrotic indications.

8:30 Targeting Transforming Growth Factor beta (TGFß) Pathway Safely for Fibrosis Diseases

Min Lu, PhD, Director & Head, Fibrosis, Morphic Therapeutic

TGFß isoforms, 1, 2, and 3, are master profibrogenic cytokines in many tissues. However, they are pleiotropic factors that are involved in development, immune homeostasis, and cell cycle regulation, which poses safety challenges to develop successful therapies for fibrosis indications. Recently, inhibition of TGFß via isoform-specific antibodies or local inhibition of TGFß activation have demonstrated the therapeutic potential of the selective targeting of TGFß family members.

9:00 Targeting Galectin-3 Inhibition in IPF via Inhaled GB0139

Rob Slack, PhD, Director of Pharmacology, Galecto, Inc.

Galectin-3 is a ß-galactoside-binding lectin highly expressed in fibrotic tissue of diverse etiologies and has been shown to play a key role in lung and liver fibrosis. Galecto, Inc. has developed several high affinities and selective galectin-3 inhibitors including the inhaled small molecule GB0139 that is currently undergoing clinical investigation in IPF. This talk will focus on the translational pharmacology of GB0139 and its potential as an anti-fibrotic therapy.

9:30 Interactive Discussions

Interactive Discussions 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 conference website's Interactive Discussions page for a complete listing of topics and descriptions.

ROOM LOCATION: Back Bay D

IN-PERSON INTERACTIVE DISCUSSION: Quantifying Fibrosis

Michael P. Cooreman, MD, CMO, Inventiva Pharma
Bryan C. Fuchs, PhD, Senior Director & Research Therapeutic Area Head, GI & Liver Disease, Ferring Research Institute
Vanessa M. Morales-Tirado, PhD, Principal Research Scientist I, Discovery Dermatology, Abbvie Bioresearch Center

- Markers for initial diagnosis
- Measuring treatment response
- Which is best for what?: AI, imaging, lab tests, histology scoring, more?

10:15 Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

LIVER & LUNG FIBROSIS

11:00 Phase III Development of Resmetirom, a Thyroid Hormone Receptor Beta Agonist, for the Treatment of NASH with Significant Fibrosis

Rebecca A. Taub, MD, CMO and President of R&D, Madrigal Pharmaceuticals

I will discuss Madrigal's lead candidate, resmetirom, a once daily, oral, thyroid hormone receptor (THR)-β selective agonist designed to target key underlying causes of NASH in the liver. Resmetirom is currently being evaluated in two Phase 3 clinical studies (MAESTRO-NASH and MAESTRO-NAFLD-1) designed to demonstrate multiple benefits in patients with NASH. MAESTRO-NAFLD-1 has completed with positive results.

11:30 Innovating in NASH Cirrhosis: Belapectin, a Galectin-3 Inhibitor for Preventing Esophageal Varices in Patients with NASH Cirrhosis

Pol F. Boudes, CMO, Galectin Therapeutics

Belapectin is a polycarbohydrate drug candidate in Phase 2/3 for liver cirrhosis due to NASH and, in combination with a PD-1 inhibitor, in Phase 2 for advanced/metastatic head and neck cancers. Belapectin is a galectin-3 inhibitor and disrupts the galectin-3 fibrosome that plays a major role in these diseases. Belapectin targets and acts primarily on activated macrophages that invade the liver in cirrhosis and the tumor microenvironment in advanced cancers.

12:00 pm Discovery and Preclinical Validation of Therapeutic Leads with Novel MOAs for NASH and IPF

Anjali Pandey, PhD, Senior Vice President, Nonclinical R&D, Chemistry, Aria Pharmaceuticals

We identified ten novel MOAs with predicted efficacy in NASH and twenty novel MOAs for IPF. This process took 15 weeks and 12 weeks, respectively, from program start to *in vivo* results, identifying lead molecule TXR-612 for NASH and TXR-1002 and TXR-1007 for IPF. Preclinical results have demonstrated significant safety and efficacy in NASH and IPF.

12:30 Enjoy Lunch on Your Own

1:40 Refreshment Break in the Hall with Poster Viewing (Grand Ballroom)

TARGETING ADVANCED FIBROSIS AND REGENERATION

2:10 Chairperson's Remarks

Vanessa M. Morales-Tirado, PhD, Principal Research Scientist I, Discovery Dermatology, Abbvie Bioresearch Center

2:15 Targeting Claudin-1 for the Treatment of Fibrotic Diseases

Thomas F. Baumert, Founder, Alentis Therapeutics AG

Tissue fibrosis is a major cause of end-stage organ failure and cancer. Using highly specific monoclonal antibodies and patient-derived models, we uncovered Claudin-1 as a safe and efficient target for treatment of liver fibrosis. Antifibrotic effects in lung and kidney fibrosis models confirm a role of Claudin-1 as a therapeutic target for fibrosis across organs. Our preclinical data enabled the clinical development of Claudin-1-targeting therapies for fibrotic diseases in patients.

2:45 Close of Conference

TUESDAY, OCTOBER 18

7:00 am Registration and Morning Coffee (Grand Ballroom Foyer)

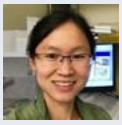
ROOM LOCATION: Constitution B

GPCRs IN DISEASE

7:55 Welcome Remarks

8:00 Chairperson's Remarks

Bethany L. Kormos, PhD, Associate Research Fellow, Medicine Design, Pfizer Inc.



8:05 FEATURED PRESENTATION: Case Study: A (Soon-to-be-Disclosed) GPCR Structure-Based Drug Design Project

Huixian Wu, PhD, Structural Biology Lab Head, Discovery Sciences, Medicine Design, Pfizer Worldwide Research & Development

Containing more than 800 members, the GPCR superfamily comprises nearly 150 validated drug targets which account for 1/3 of the FDA-approved drugs to date. Drug discovery targeting GPCRs continues to be an important focus in pharmaceutical industry and SBDD has been proven to be an enabling approach to accelerating early discovery programs to lead development and candidate selection. A recent example in Pfizer discovery will be shared in this talk.

8:35 CryoEM and Design of Novel mu Opioid Modulators

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

Sodium acts as a negative allosteric modulator at numerous GPCRs. We used a structure-based approach on the fentanyl template to rationally target the sodium site in the mu opioid receptor. We solved cryoEM structures of lead bitopics highlighting key interactions in the Na+-binding pocket. Lead bitopic showed a unique Gi/o/z signaling fingerprint compared to other opioids and was found to be analgesic devoid of some classical MOR adverse effects.

9:05 Impact of Oligomerization on Apelin Receptor Structure and Signaling

Michael Hanson, PhD, Co-Founder and Scientific Advisor, Structure Therapeutics

The apelin receptor is an important target for pulmonary fibrosis and heart failure. Agonists for APJR are at various stages of clinical investigation. Here we capture a snapshot of the GPCR monomer-dimer in equilibrium. We show how to manipulate this dynamic process through mutagenesis and link the oligomeric state to downstream efficacy properties. This analysis will open new opportunities for understanding how the oligomeric state of GPCRs influences pharmacology

9:35 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

NEWER APPROACHES FOR TARGETING GPCRs

10:25 Structure-Based Screening of Chemical Spaces for GPCR Hit Discovery

Anastasiia Sadybekov, PhD, Research Scientist, Laboratory of Seva Katritch, The Bridge Institute, University of Southern California

Drug discovery has recently been revolutionized by the abundance of target 3D structures and the development of ultra-large libraries of drug-like compounds. Inspired by the fragment screening concept, we have developed V-SYNTHES, a new iterative synthon-based approach for fast structure-based virtual screening of billions of readily available (REAL) compounds (Sadybekov et al. Nature 2022). I discuss the latest developments and applications of V-SYNTHES fragment-based lead discovery, especially for GPCRs.

10:55 NMR Applications for GPCR-Based Drug Discovery

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

We present biophysical data investigating the role of endogenous phospholipids as allosteric modulators of GPCR signaling. We find that lipids influence the function-related conformational dynamics of GPCRs to the same, or greater, extent as orthosteric drugs. We will discuss experimental NMR data of a protypical class A human GPCR that provide a mechanism for the influence of phospholipids on signaling complex formation.

11:25 GPCR Biased Agonists from DNA-Encoded Libraries

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

We present novel approaches for the direct selection of molecules from DNA-encoded libraries that activate GPCRs via either the G-protein or arrestin signaling pathways. We present results of discovery of biased agonists from DELs with live cell selections against the opioid receptor family.

11:55 Identification of Novel Peptide Leads against GPCRs Using the Orbit Discovery Display Platform

ORBIT DISCOVERY

Simon Bushell, PhD, Head of Structural Biology, Orbit Discovery

The Orbit Platform utilises a bead-based DNA-encoded display system to screen peptide libraries against difficult protein targets, including GPCRs. The platform is universal and can be used for FACS-based affinity screening against recombinant target protein, as well as functional screening against single target-overexpressing reporter cells via our unique microfluidics-based approach. Here, we demonstrate the capabilities of the Orbit platform by identifying novel peptide leads which bind and activate the Melanocortin-4 Receptor

12:25 pm Enjoy Lunch on Your Own

GPCR COMPLEXES AND COMPLEXITIES

1:25 Chairperson's Remarks

Pedro Serrano Navarro, PhD, Principal Scientist, Structural Biology & Biophysics, Takeda San Diego

1:30 Molecular Mechanism of the Wake-Promoting Agent TAK-925

Aaron McGrath, PhD, Senior Scientist, Structural Biology, Takeda, San Diego

Agonism of OX2R is a potentially powerful approach for narcolepsy type 1. Using cryo-EM, we determine how the first clinically tested OX2R agonist TAK-925 activates OX2R in a highly selective manner. TAK-925-bound OX2R with either a Gq mimetic or Gi reveal that TAK-925 binds at the same site occupied by antagonists yet interacts with the helices to trigger activating micro switches. The mechanisms of TAK-925's activation and selectivity will be discussed.

2:00 Exploring Structure-Kinetic Relationships for Drugs Binding GPCRs

David A. Sykes, PhD, Senior Experimental Officer, Center of Membrane Proteins & Receptors, Nottingham University Hospitals National Health Service Trust

The physicochemical properties of drugs influence their measured binding kinetics. Drug association-rate enhancing effects can occur through hydrophobic and polar interactions with membrane-like structures. Crucial interactions at the extracellular surfaces of receptors occur via contact with specific amino acids in vestibular regions. Rapid water loss likely contributes to a fast on-rate, while complimentary structural features dictate the strength of the interaction in the orthosteric pocket and influence dissociation rates.

2:30 Multispan, Your Partner for Drug Discovery Research

Lisa Minor, PhD, Business Development, Multispan, Inc.

Multispan brings collaborative approach, dedication to research, commitment to quality, and deep expertise to help you succeed in drug discovery research for GPCRs and beyond. Empowered by 500+ functionally validated MULTISCREEN™ stable cell lines, new chemotypes can now be profiled in our 32-GPCR safety/liability panel for central nervous, cardiac, pulmonary and GI toxicity, while new targets and MOAs can be discovered in the our custom and 231-GPCR panels. With tools such as β-Arrestin-expressing BacMam viral particles and parental stable cell line clones, oGPCRs can be tested transiently, quickly, and "tagless" for proof-of-concept. To take advantage of CRISPR's unlimited potential to accelerate drug discovery from target ID, through HTS, LO to pre-clinical studies, Multispan aims to bring your CRISPR initiatives to fruition by leveraging its two-decade long practical experience in cell line engineering, assays and HTS.

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

3:40 Single-Molecule Flourescence for GPCRs

Rajan Lamichhane, PhD, Assistant Professor, Biochemistry & Cellular and Molecular Biology, University of Tennessee at Knoxville

The dynamic nature of GPCRs enables to recognize a wide range of extracellular molecules. While the structures of some GPCR conformers have been characterized, the dynamics of these conformations are mostly unknown. The lack of such knowledge limits our ability to develop drugs with precise therapeutic effects. Single-molecule fluorescence helps to visualize the dynamic behavior of GPCRs, which reveals hidden structural characteristics and provides new insights into GPCR functions.

4:10 Proximity-Labeling Proteomics: Defining Receptor Interactions beyond What is Currently Known

Thomas Shroka, PhD Candidate, Laboratory of Tracy Handel, Biomedical Sciences, University of California, San Diego

Following GPCR activation, there is a dogmatic view on the subsequent interactions and pathways which result in the ultimate fate of a receptor. Although the key players cannot be ignored (i.e. G proteins, GRKS, β-arrestin, etc.) it is increasingly clear that the interactome of GPCRs is far more complex. Here I present ongoing work highlighting the need for and efforts towards better understanding these non-canonical interactions and pathways.

4:40 The Discovery of Agonistic Therapeutic Antibodies against GPCRs

Christel Menet, PhD, CSO, Confo Therapeutics

ConfoBodies, single-domain antibody fragments from camelids (VHH) stabilize a desired conformational state of a GPCR and enable conformation-directed drug screening. We will show the unique potential of ConfoBody-stabilized GPCR conformations to facilitate *de novo* discovery of therapeutic antibodies exhibiting full agonist pharmacology to human GPCRs.

5:10 Interactive Discussions

Interactive Discussions 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 conference website's Interactive Discussions page for a complete listing of topics and descriptions.

IN-PERSON INTERACTIVE DISCUSSION: Facilitating GPCR-Targeted Discovery

Elisa Barile, PhD, Principal Scientist, Structural Biology & Biophysics, Takeda, San Diego

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

- NMR and other biophysical approaches for GPCRs
- Implications of CryoEM advances to GPCR-targeted drug discovery
- Other innovations for GPCR translational work

5:55 Welcome Reception in the Exhibit Hall with Poster Viewing (Grand Ballroom)

6:55 Close of Day

WEDNESDAY, OCTOBER 19

7:30 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Constitution B

TARGETING GPCRs IN THE TUMOR MICRO-ENVIRONMENT

7:55 Chairperson's Remarks

Nicolas Villanueva, MBA, PhD, Director, Bioscience Strategy, Dassault Systèmes BIOVIA

8:00 Discovery of Etrumandenant: A Potent Dual Adenosine Receptor Antagonist for Cancer Immunotherapy

Brandon Rosen, PhD, Senior Scientist, Medicinal Chemistry, Arcus Biosciences

The presence of extracellular adenosine is frequently responsible for the creation of an immunosuppressed tumor microenvironment through activation of the A2a and A2b receptors expressed on intratumoral immune cells. AB928 is a small molecule dual A2aR/A2bR antagonist designed to block the immunosuppressive effects of adenosine in the tumor microenvironment. This presentation discusses the design, characterization, and SAR of a series of A2aR/A2bR antagonists culminating in the discovery of etrumadenant.

8:30 Data Organization Using CDD Vault to Streamline the Discovery Process

Kelly Bachovchin, PhD, Customer Engagement Scientist, Technical Support, Collaborative Drug Discovery

Collaborative Drug Discovery (CDD) provides a whole solution for today's biological and chemical data needs, differentiated by ease-of-use and superior collaborative capabilities. CDD Vault® software includes Activity & Registration, Visualization, Inventory, and ELN capabilities. Researchers can archive, mine, and securely collaborate within CDD Vault. Collaborative hypothesis generation and evaluation allow multiple perspectives for multi-parameter optimization for all types of entities.

8:45 Kinetic Characterization of Ligand and Antibody Binding to Cell Surface Expressed CCRL2 Using Surface Plasmon Resonance Microscopy (SPRM)

Jonathan Brooks, Inflammation & Remodeling Department, Pfizer Inc.

C-C motif chemokine receptor-like 2 (CCRL2), is a non-signaling 7TM receptor, referred to as an atypical chemokine receptor (ACKR). Unlike conventional GPCR chemoattractants which initiate intracellular signaling to direct leukocyte migration, ACKRs are unable to activate G-protein-dependent signaling and the cellular responses required to direct cell migration. We utilized a new biophysical technique, SPR Microscopy, in addition to other biophysical techniques, to characterize ligand and antibody binding to CCRL2.

9:00 Targeting the Chemokine Receptor CCR2 in Immuno-Oncology: Opportunities and Challenges

Irina Kufareva, PhD, Associate Adjunct Professor, University of California, San Diego

CCR2 is pursued as a target in autoimmunity and immuno-oncology due to its immune-cell trafficking role. This pursuit, however, has not yet yielded any clinical candidates. Failures have been attributed to complexities of CCR2 biology and suboptimal properties of the therapeutic candidates. I will present an overview of CCR2-targeting modalities, discuss the structural principles of their affinity and selectivity, and share recent findings about unexpected side-effects of CCR2 inhibition.

9:30 FLX475: A Potent and Selective CCR4 Antagonist to Target Treg Selectively in the TME

David J. Wustrow, PhD, Senior Vice President Discovery & Preclinical Development, Discovery & Preclinical Development, RAPT Therapeutics

High levels of Treg infiltration in the tumor microenvironment (TME) lead to a poor prognosis in patients. The chemokine receptor CCR4 is highly expressed on Treg where it functions to attract them into the TME where they inhibit immune response. To reduce the prevalence of Treg in the TME we have discovered and developed FLX475 a potent, selective, and orally available CCR4 antagonist.

10:00 Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

PLENARY KEYNOTE PROGRAM

ROOM LOCATION: Constitution A + B

11:00 Plenary Chairperson's Remarks

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

11:05 PLENARY: Pirating Biology to Detect and Degrade Extracellular Proteins

James A. Wells, PhD, Professor, Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco

In contrast to intracellular PROTACs, approaches to degrade extracellular proteins are just emerging. I'll describe our recent progress to harness natural mechanisms such as transmembrane E3 ligases to degrade extracellular proteins using fully genetically encoded bispecific antibodies we call AbTACs. We have also engineered a peptide ligase which can be tethered to cells to detect proteolysis events and target them with recombinant antibodies for greater selectivity for the tumor microenvironment.

11:50 PLENARY: Therapeutic Modalities for Neuroscience Diseases

Anabella Villalobos, PhD, Senior Vice President, Biotherapeutics & Medicinal Sciences, Biogen

Many effective medicines exist to treat neurological diseases, but medical need remains high. We have a unique multi-modality approach to discover novel therapies and our goal is to find the best modality regardless of biological target. With a multi-modality approach, we aim to expand target space, leverage synergies across modalities, and offer options to patients. Opportunities and challenges associated with small molecules, biologics, oligonucleotides, and gene therapy will be discussed.

12:35 pm Enjoy Lunch on Your Own

1:25 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom Foyer)

2:05 Close of GPCR-Based Drug Discovery Conference

Cambridge Healthtech Institute's Inaugural

Neurodegeneration Targets

NEW

Drug Discovery for Brain and Nerve-Related Progressive Disorders

OCTOBER 19-20, 2022

WEDNESDAY, OCTOBER 19

PLENARY KEYNOTE PROGRAM

ROOM LOCATION: Constitution A + B

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12:35 pm Enjoy Lunch on Your Own

1:25 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom Foyer)

ROOM LOCATION: Republic Ballroom B

NEW APPROACHES FOR TARGETING CNS DISEASES

2:05 Welcome Remarks

2:10 Chairperson's Remarks

Heike Wobst, PhD, Senior Scientist, Jnana Therapeutics

2:15 Parkin Activators: Targeting Mitochondrial Health for Parkinson's Disease

Laura Silvian, PhD, Senior Director, Physical Biochemistry, Biogen

Pharmacological activation of the E3 ligase Parkin represents a rational therapeutic intervention for the treatment of Parkinson's disease. We demonstrate how a high-throughput screen with *in vitro* purified components enabled us to identify small molecule positive allosteric modulators that speed up poly-autoUbiquitination of Parkin. Yet they fail to enhance mitophagy in a cellular milieu. We propose the MOA of activators that work primarily on Parkin and not phospho-Parkin.

2:45 Targeting PINK1 and the Mitochondria

Rishi Rakhit, PhD, Director, Translational Medicine, Mitokinin

Mutations in PINK1, a central regulator of mitochondrial quality control, result in Parkinson's disease. We identified MTK458, which selectively binds PINK1 and promotes mitophagy. Published data show that alpha-synuclein aggregation induces mitochondrial dysfunction; MTK458 treatment drives clearance of pathologic alpha-synuclein both *in vitro* and *in vivo* models. Lastly, we identified that PINK1-pathway marker pS65 ubiquitin is significantly increased in PD plasma and lowered by MTK458 treatment in mice and rats.

3:15 Sponsored Presentation *(Opportunity Available)*

3:45 Dessert Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

4:25 Retina-Optic Nerve-Brain Connections Preservation and Regeneration

Najam Sharif, PhD, DSc, Vice President & Head, Global Alliances & External Research, Santen, Inc. USA

Ophthalmic neuroprotection and axonal regeneration related to the retina and optic nerve are important components of the neurological diseases and their mitigation. It is important to highlight and cross-educate researchers that the eyes are indeed windows to the brain, and in fact the retina and optic nerve serve very useful surrogate models for the greater CNS pathologies.

4:55 Harnessing the Splicing Machinery to Drive Down Huntingtin Protein Production: A Small Molecule Drug Discovery Story

Anuradha Bhattacharyya, PhD, Executive Director, Biology, PTC Therapeutics, Inc.

I will describe how we identified splicing modifiers that cross the blood-brain-barrier upon oral delivery, and uniformly lower Huntingtin protein levels in the key affected areas of an huntington disease mouse brain. Our technology leverages knowledge of splicing regulation to discover and develop oral systemically distributed small-molecule splicing modifiers. The presentation will describe how these molecules were identified and optimized for improved oral bioavailability, penetration of the blood-brain-barrier and potency.

5:25 Structure, Function, and Small-Molecule Inhibition of SARM1, a Drug Target Against Axon Degeneration

Yun Shi, PhD, Research Fellow, Institute for Glycomics, Griffith University

SARM1 (sterile alpha and TIR motif containing 1) is a key executioner of axon degeneration and a therapeutic target for multiple neurodegenerative conditions. We have solved its oligomeric structures, characterised its enzymatic function of NAD+ cleavage and allosteric activation, and uncovered the molecular mechanism of an orthosteric small-molecule inhibitor that was shown to assist recovery of injured axons.

5:55 Dinner Short Course Registration*

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

9:00 Close of Day

THURSDAY, OCTOBER 20

7:30 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Republic Ballroom B

MODULATING AUTOPHAGY, THE LYSOSOME OR AGGREGATION

7:55 Chairperson's Remarks

Laura Silvian, PhD, Senior Director, Physical Biochemistry, Biogen

Neurodegeneration disease pathologies include inflammatory reactions, functional loss of neurons in the central nervous system, regional patterns of brain shrinkage and abnormal accumulation of proteinaceous material in and around neurons. The speakers of this session will address the interplay of targeted strategies to prevent these neurodegeneration pathologies in Parkinson's disease and amyotrophic lateral sclerosis (ALS).

8:00 FEATURED PRESENTATION: Enhancing Lysosomal Function to Combat Neurodegeneration

Magdalene M. Moran, PhD, President & CSO, Caraway Therapeutics

Multiple lines of evidence support the hypothesis that impaired lysosomal function is a driver of neurodegenerative disease. This talk will focus on the approach Caraway Therapeutics is taking to improve cellular health by modulating the ionic contents of the lysosome using their proprietary TRPML1 agonists. Recent data supporting the utility of these compounds in GBA-Parkinson's disease will be discussed.

8:30 Chaperone-Mediated Autophagy (CMA) and Neurodegeneration

Evris Gavathiotis, PhD, Professor, Biochemistry, Albert Einstein College of Medicine

Chaperone-mediated autophagy (CMA) contributes to cellular quality control and the cellular response to stress through the selective degradation of cytosolic proteins in lysosomes. Proteins of common neurodegenerative disorders have been shown to undergo degradation via CMA. Here, we identified a unique mechanism for selective activation of CMA and a tractable target for developing CMA activators. Our lead CMA activators demonstrated protection against pathologic stress in various neurodegeneration models.

9:00 Development of a LRRK2 Inhibitor for the Treatment of Parkinson's Disease

Steve Wood, PhD, Senior Vice President, Drug Discovery, Neuron23, Inc.

The LRRK2 gene, encoding leucine-rich repeat kinase 2 (LRRK2), is a common genetic cause of Parkinson's disease (PD). Genetic variation in LRRK2 also modifies the risk of inflammatory bowel disorders (IBD) and infectious diseases. In this work we aim to better understand the roles of LRRK2 in immune cell signaling pathways and their potential contribution to inflammatory and infectious disorders.

9:30 Interactive Discussions

Interactive Discussions 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 conference website's Interactive Discussions page for a complete listing of topics and descriptions.

ROOM LOCATION: Republic Ballroom B

IN-PERSON INTERACTIVE DISCUSSION: CNS Drug Discovery Challenges

Rajesh Kumar, PhD, Principal Scientist, Small Molecule Target Protein Science, Biogen

Magdalene M. Moran, PhD, President & CSO, Caraway Therapeutics

10:15 Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

OLD AND NEW TARGETS FOR NEURODEGENERATION

11:00 A Nuclear Transport XPO1 Inhibitor for ALS

Jeffrey Martin, PhD, Scientist II, Drug Discovery, Biogen

Exportin-1 (XPO1) is a therapeutic target in both amyotrophic lateral sclerosis (ALS) and oncology. I will discuss the development and use ofchemical biology tools to measure XPO1 target occupancy and their application to *in vivo* models.

11:30 ABL Kinase Inhibition as a Disease-Modifying Therapy for Parkinson's Disease

Milton Werner, President & CEO, Inhibikase Therapeutics, Inc.

Modeling Parkinson's disease in mice suggests c-Abl activation is required for PD initiation and progression, and therefore inhibition of c-Abl could be a strategy for disease-modification of Parkinson's. IkT-148009 once daily protected neurons, restored function, reduced pathological alpha-synuclein, and suppressed neuroinflammation in models. 12.5 mg to 325 mg for up to seven days was well-tolerated and exhibited linear dose proportionality, high systemic exposure, and no clinically significant adverse events.

12:00 pm TDP-43: Targeting Stress Granules for ALS and Alzheimer's

Benjamin Wolozin, MD, PhD, Co-Founder & CSO, Aquinnah Pharmaceuticals

Increasing evidence suggests that protein aggregates that accumulate in ALS and Alzheimer's disease proceed via stress granule intermediates. Approaches developed by Aquinnah Pharmaceuticals generated pipelines of compounds that target these protein aggregates from an unbiased perspective, with the goal of generating disease modifying therapies. In addition, emerging science around RNA metabolism in stress granule biology identifies additional therapeutic targets for modifying stress granule biology and therefore disease progression.

12:30 Enjoy Lunch on Your Own

1:40 Refreshment Break in the Hall with Poster Viewing (Grand Ballroom)

TARGETING NEUROINFLAMMATION AND MICROGLIA

2:10 Chairperson's Remarks

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

2:15 Phenotypic Screening for CNS-Penetrant Inflammasome Inhibitors for the Treatment of Neuroinflammation

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

The NLRP3 inflammasome has recently emerged as a promising therapeutic target for inflammatory diseases. After activation NLRP3 forms a complex with ASC followed by formation of the inflammasome. We optimized a NLRP3-dependent ASC speck formation assay in a murine macrophage line and

utilized it to screen a small molecule library. Additional assays to investigate NLRP3 form the basis of a project to identify inhibitors for the treatment of neurodegeneration.

2:45 Itanapraced (CSP-1103): A Neuro-Inflammation Inhibitor

Adrian N. Hobden, PhD, President & CEO & Chairman, CereSpir, Inc.

Itanapraced is an inhibitor of AICD. In clinical studies, it reduced TNF alpha and sCD40 ligand concentrations in CSF whilst showing an excellent safety profile. Studies have demonstrated that itanapraced prevents AICD from relocating to the nucleus and acting as a transcriptional regulator. Amongst the genes regulated are Bim, Pink1, and LRRK2. In an LRRK2 mouse model of Parkinson's disease, itanapraced was able to reduce Parkinson like symptoms.

3:15 Identification of a Novel Class of Highly Potent, CNS-Penetrant NLRP3-Specific Inhibitors with Excellent Drug-Like Physical Features

Rusty Montgomery, PhD, Vice President, Biology, BioAge Labs

BioAge is analyzing proprietary human-omics and longitudinal health outcome data to identify novel neurodegeneration drug targets. Our analyses showed that NLRP3 levels rise with age and correlate positively with mortality and cognitive decline. We have synthesized new compounds that inhibit NLRP3 inflammasome *in vitro* and *in vivo*, are as or more potent than known NLRP3 inhibitors, have novel structures and chemical properties, and penetrate the blood-brain barrier.

3:45 Close of Conference

TUESDAY, OCTOBER 18

7:00 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Back Bay C

SCREENING STRATEGIES

7:55 Welcome Remarks

8:00 Chairperson's Remarks

Katherine Upchurch-Ange, PhD, Principal Scientist, Antibody Discovery, Boehringer Ingelheim Pharmaceuticals, Inc.

8:05 Screening Strategy for Targeting Multi-Pass Membrane Protein for Therapeutic Antibody Discovery

Shunsuke Takenaka, PhD, Principal Scientist, Biologics Discovery, Amgen, Canada

Successful screening of human antibody panels requires an understanding of the therapeutic design goals including specificity, functional activity, and affinity. Targeting multi-pass membrane proteins can pose challenges as they can be difficult to over-express in a biologically relevant manner to be used for assays. This talk will discuss strategy for antibody screening for multi-pass protein target using examples from therapeutic antibody discovery work.

8:35 Rapid on-Cell Selection of High-Performance Human Antibodies

Shana Kelley, PhD, Professor, Biochemistry, Pharmaceutical Sciences, Chemistry, and Biomedical Engineering, University of Toronto, Canada

We recently developed µCellect, an on-cell phage display approach that recapitulates the complex *in vivo* binding environment to produce high-performance human antibodies. In a proof-of-concept screen against human Frizzled-7, a key ligand in the Wnt signaling pathway, antibodies with picomolar affinity were discovered in two rounds of selection, outperforming current best-in-class reagents. This approach, termed µCellect, is low-cost, high-throughput, and compatible with a wide variety of cell types.

9:05 Strategies to Screen Anti-AQP4 Antibodies from Yeast Surface Display Libraries

Brandon DeKosky, PhD, Phillip and Susan Ragon Career Development Professor of Chemical Engineering, MIT Core Member, The Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard

In neuromyelitis optica patients, antibody identification against the aquaporin-4 (AQP4) membrane protein traditionally involves labor-intensive single B-cell sorting, cloning, and analysis. To accelerate patient-specific discovery, we compared two approaches to screen anti-AQP4 antibodies using yeast surface display libraries. We found that both cell-based biopanning and solubilized antigen FACS were effective to select for AQP4-binding clones. These established screening techniques will accelerate library-scale antibody discovery against AQP4 and other membrane proteins.

9:35 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

10:25 The Use of Display Technology to Identify Therapeutic Antibodies against Challenging pHLA Complexes

Katherine Upchurch-Ange, PhD, Principal Scientist, Antibody Discovery, Boehringer Ingelheim Pharmaceuticals, Inc.

Many novel tumor-specific targets are intracellular proteins. To efficiently target them, we can assess which are loaded onto HLA receptors and in turn generate antibodies targeting these peptide-HLA complexes. These T cell receptor mimicking (TCRm) antibodies can be highly tumor-specific, however they can be very challenging to generate. My presentation will touch on these challenges and the methods we have used to overcome them.

10:55 *De novo* Design of Epitope-Specific Antibodies to Membrane Proteins Using AI Methodologies

Philip M. Kim, PhD, Professor, Molecular Genetics & Computer Science, University of Toronto

I will present a set of machine learning technologies for the *de novo* design of epitope specific antibodies to membrane protein targets. Our methods encompass structure-based design of CDRs for optimal epitope recognition and sequence-based generative models ensuring favorable developability properties. We show that we obtain nanomolar Fab binders to a specified novel epitope.

11:25 KEYNOTE PRESENTATION: From Structure to Sequence: Antibody Discovery Using cryoEM

Andrew Ward, PhD, Professor, Integrative Structural and Computational Biology, Scripps Research Institute

Viral glycoproteins embedded in the membrane of virions are attractive targets for rational, structure-based vaccine design. The design process is driven by a molecular understanding of antibody recognition of key epitopes within these glycoproteins. To accelerate this process we have devised a novel approach to generate single particle cryoEM reconstructions of heterogeneous polyclonal antibody-antigen complexes at high resolution.

11:55 Opening the Barn Door to Antibody Diversity

OmniAb

Bill Harriman, PhD., SVP, Antibody Discovery, OmniAb

The antibody repertoire generated by an animal in response to immunization results from its recognition of the target antigen, its native genetic diversification and cellular selection mechanisms, and the sequences of its immunoglobulin genes. All of these parameters are profoundly influenced by the host animal species and its genetics. OmniAb accesses the biodiversity of six species to generate high-quality custom repertoires of human antibodies to empower therapeutic antibody discovery.

12:25 pm Transition to Lunch

12:35 Luncheon Presentation: Luncheon Presentation: mRNA and Lipoparticle (VLP) Immunization Strategies to Display Native Epitopes for Functional Monoclonal Antibodies

integral molecular

Joeseph Rucker, PhD, VP Research & Development, Integral Molecular

Multipass membrane proteins remain valuable yet elusive targets for therapeutic antibodies. We describe recent advances to our MPS Antibody Discovery platform for antigen presentation, enabling robust immune responses against the most intractable targets with >95% success. These advances include immunizations with mRNA and Lipoparticles (virus-like particles). We will describe how these approaches have yielded rare and functional antibodies against GPCRs and other complex targets including GPRC5D, SARS-CoV-2 and Kv1.3.

1:05 Session Break

IN VIVO DISCOVERY STRATEGIES

1:25 Chairperson's Remarks

Keenan Taylor, PhD, Senior Scientist, AbbVie, Inc.

1:30 Discovery of Antibody Tools to Study Caspase and Ubiquitin Signaling

Christopher Davies, PhD, Senior Principal Scientific Researcher, Antibody Engineering, Genentech, Inc.

Unstructured regions comprise key functional epitopes within therapeutic proteins and cell signaling proteins. However, the generation of antibodies against unstructured epitopes remains challenging. Here, we will describe two case studies on the discovery of anti-peptide antibodies with novel specificities: strong yet paradoxical degenerate recognition and recognition of a two amino acid motif. We will describe the generation, characterization, and application of these antibodies to reveal new biological insights.

2:00 Using DNA Immunization to Elicit Monoclonal Antibodies against Membrane Protein Targets

Shuying Liu, CSO, NA Biotech Corp.

DNA immunization is effective in stimulating both innate and adaptive immunities to elicit high levels of antibody responses. The *in vivo* expressed proteins can maximally maintain the native structures and go through appropriate post-transcriptional modifications. DNA immunization has been used by us successfully in various host species to elicit monoclonal antibodies (mAbs) against a wide range of targets including those with complex structures such as G-protein-coupled receptors (GPCR).

2:30 Synthetic DNA Technologies Enable the Discovery of G Protein-Coupled Receptor Antibody Ligands

Sean Peterson, PhD., Staff Scientist, Department of Cell Biology, Twist Biopharma

Twist synthetic DNA technologies have enabled the development of precision antibody libraries designed to bind to G protein-coupled receptors (GPCRs). We have employed high throughput binding and functional assays to discover antibodies with agonist and antagonist profiles. This parallel functional screening was successfully employed for the discovery of novel therapeutic antibody ligands for three GPCRs (called GLP1R, APJR and C5AR1).

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

SELECTION PLATFORMS

3:40 Using Solubilized GPCRs for *in vitro* Antibody Discovery

Catharina Steentoft, Senior Scientist, Antibody Technology, Novo Nordisk

Antigen design, expression, and purification remain a challenge when raising mAbs to GPCRs. Here we present a case story, using a GPCR purified in Lauryl Maltose Neopentyl Glycol (LMNG). The purified receptor was applied as a soluble antigen in an *in vitro* Antibody discovery campaign (Adimab). Optimization of antibody selection, as well as characterization of identified hits, will be presented.

4:10 Combination of Membrane Protein Scaffolds and Target Engineering Strategies to Enable GPCR Purification

Keenan Taylor, PhD, Senior Scientist, AbbVie, Inc.

Recombinant production of multi-span transmembrane proteins is frequently challenging due to their complex structure and low target stability. Selection of the appropriate model membrane system and protein engineering strategy can address some of these challenges. The antigen formats, i.e., virus-like-particles, nanodisc, or polymer-extracted membranes must be carefully considered in the application context. In this talk, I will compare several antigen formats and engineering strategies to produce a GPCR.

IN SILICO METHODS 1

4:40 Simulation Studies of Membrane Proteins with Incomplete Structural Information

Po-Chao Wen, PhD, Research Scientist, Biochemistry, University of Illinois, Urbana-Champaign

Compared to soluble proteins, membrane protein structures often suffer from lower resolutions, more missing atoms/residues, and ambiguous electron densities attributed to ligand or lipid/detergent molecules. Moreover, they sometimes deviate from the necessary membrane contexts. Here we will showcase some examples of structural and functional studies of membrane proteins that used molecular dynamics simulations to remedy the shortcomings of their incomplete structures.

5:10 Interactive Discussions

Interactive Discussions 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 conference website's Interactive Discussions page for a complete listing of topics and descriptions.

ROOM LOCATION: Back Bay C

IN-PERSON INTERACTIVE DISCUSSION: Considerations when Producing Recombinant Membrane Proteins for Biologics Drug Discovery

Keenan Taylor, PhD, Senior Scientist, AbbVie, Inc.

5:55 Welcome Reception in the Exhibit Hall with Poster Viewing (Grand Ballroom)

6:55 Close of Day

WEDNESDAY, OCTOBER 19

7:30 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Back Bay C

IN SILICO METHODS 2

7:55 Chairperson's Remarks

Meredith A. Skiba, PhD, Postdoctoral Fellow, Biological Chemistry and Molecular Pharmacology, Harvard Medical School

8:00 An *in silico* Method to Assess Antibody Fragment Polyreactivity

Meredith A. Skiba, PhD, Postdoctoral Fellow, Biological Chemistry and Molecular Pharmacology, Harvard Medical School

Synthetic antibody libraries facilitate the rapid discovery of monoclonal antibodies for virtually any target. However, synthetic methods lack *in vivo* filtering for broad reactivity. To overcome this limitation, we created machine learning models that quantitatively assess synthetic camelid antibody fragment ('nanobody') polyreactivity and predict amino acid substitutions to decrease polyreactivity. Using our model, we decreased the polyreactivity of a GPCR targeting nanobody without compromising its functional properties.

8:30 Genetic Immunization and Single Cell Screening – Advanced Tools for Antibody Discovery

Andreas Weise, Senior Account Manager, Genovac

Successful antibody discovery against challenging targets requires robust immunization and advanced screening technologies. Genovac has 20+ years of genetic immunization experience, successfully completing over 3,500 projects. In this session, Dr. Andreas Weise will cover:
• Defining characteristics and strategies for challenging targets
• Overview of various antigens and immunization approaches
• Advantages of genetic immunization
• Case studies showing the power of genetic immunization

TARGETING STRATEGIES

9:00 Strategies for Targeting Cell Surface Proteins Using Multivalent Conjugates and Chemical Biology

Ross Cheloha, PhD, Investigator, Chemical Biology of Signaling Section, Laboratory of Bioorganic Chemistry, National Institutes of Health

Single-domain antibodies (nanobodies) offer signature advantages for targeting cell surface proteins, including GPCRs. However, it remains difficult to identify nanobodies that directly activate receptor function. We have devised methodology to link nanobodies with GPCR ligands. Nanobody linkage improves the pharmacological properties of ligands for different GPCRs. This technology will be applied to GPCRs and other cell surface receptors whose function are difficult to address with antibodies or chemistry alone.

9:30 Co-Receptor Signaling Dynamics During B Cell Activation

Katherine Susa, PhD, Postdoctoral Fellow, Blacklow and Kruse Labs, Harvard Medical School

10:00 Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

PLENARY KEYNOTE PROGRAM

ROOM LOCATION: Constitution A + B

11:00 Plenary Chairperson's Remarks

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

11:05 PLENARY: Pirating Biology to Detect and Degrade Extracellular Proteins

James A. Wells, PhD, Professor, Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco

In contrast to intracellular PROTACs, approaches to degrade extracellular proteins are just emerging. I'll describe our recent progress to harness natural mechanisms such as transmembrane E3 ligases to degrade extracellular proteins using fully genetically encoded bispecific antibodies we call AbTACs. We have also engineered a peptide ligase which can be tethered to cells to detect proteolysis events and target them with recombinant antibodies for greater selectivity for the tumor microenvironment.

11:50 PLENARY: Therapeutic Modalities for Neuroscience Diseases

Anabella Villalobos, PhD, Senior Vice President, Biotherapeutics & Medicinal Sciences, Biogen

Many effective medicines exist to treat neurological diseases, but medical need remains high. We have a unique multi-modality approach to discover novel therapies and our goal is to find the best modality regardless of biological target. With a multi-modality approach, we aim to expand target space, leverage synergies across modalities, and offer options to patients. Opportunities and challenges associated with small molecules, biologics, oligonucleotides, and gene therapy will be discussed.

12:35 pm Enjoy Lunch on Your Own

1:25 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom Foyer)

2:05 Close of Antibodies Against Membrane Protein Targets – Part 1 Conference

WEDNESDAY, OCTOBER 19

PLENARY KEYNOTE PROGRAM

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12:35 pm Enjoy Lunch on Your Own

1:25 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom Foyer)

ROOM LOCATION: Back Bay C

TARGETING GPCRs

2:05 Welcome Remarks

2:10 Chairperson's Remarks

Christel Menet, PhD, CSO, Confo Therapeutics

2:15 Autoantibody and Hormone Activation of the Thyrotropin G Protein-Coupled Receptor

Bryan Faust, PhD, Deal Analyst, Andreessen Horowitz, Bio + Health

The Thyrotropin receptor (TSHR) is a central regulator of growth and metabolism. Euthyroid states are marked by synthesis and secretion of thyroid hormones upon TSHR activation. However, aberrant TSHR activity plays a major etiological role in autoimmune thyroid diseases. How TSHR autoantibodies modulate receptor activity has remained elusive. Using cryo-EM, molecular dynamics, and signaling assays, we determined principles of TSHR activation and a hormone-mimicry mechanism employed by a patient-derived autoantibody.

2:45 Identifying CCR5 Coreceptor Populations Permissive for HIV-1 Entry and Productive Infection: Implications for *in vivo* Studies

Yutaka Tagaya, MD, PhD, Head, Cell Biology Lab and Head, IHV Flow CORE, Institute of Human Virology, University of Maryland School of Medicine

Defining the virus-host interactions responsible for HIV-1 transmission facilitates the development of novel HIV-1 therapeutics. We observed that not all CCR5 mAbs reduce HIV-1 infection, suggesting that some CCR5 subpopulations are permissive for HIV-1 entry/infection. We visualized and quantified different CCR5 subpopulations via super-resolution microscopy using a dual CCR5 staining. Identification of CCR5 conformational subpopulations permissive for HIV-1 infection contributes to development of inhibitors that block CCR5 usage by HIV-1.

3:15 Diversity, Resolution, Throughput: Leveraging Synergistic Approaches for Antibody Discovery Against Membrane Targets

Mariya Shapiro, PhD, Scientist II, Team Lead, Single B Cell Discovery, Abveris, A Division of Twist Bioscience

To enable antibody discovery against challenging targets on tight timelines, efficient yet effective approaches are needed for screening, functional characterization, and lead candidate selection. This presentation will distill lessons from dozens of cell surface target campaigns, leveraging function-forward discovery workflows paired with the broad epitopic diversity of hyperimmune mouse models and high-throughput tools for downstream validation to accelerate progression from target to clinic.

3:45 Dessert Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

4:25 The Discovery of Agonistic Therapeutic Antibodies against GPCRs

Christel Menet, PhD, CSO, Confo Therapeutics

ConfoBodies are single-chain antibody stabilizing desired conformational states of a GPCR and enabling conformation-directed drug screening. We will present the unique potential of ConfoBody-stabilized GPCR conformations to facilitate *de novo* discovery of therapeutic antibodies exhibiting nM potency to human GPCRs. We will show *in vitro* and *in vivo* data with monovalent and Fc formatted VHH, confirming the agonist pharmacology of these antibodies.

4:55 Selective Anti-GPCR Antibodies for Fibrosis and Cancer

Kiyoshi Takayama, PhD, Founder & President, Research Center, NB Health Laboratory Co. Ltd.

The GPCRs for lipid mediators such as prostaglandins and lysophosphatidic acid are promising targets for various diseases including inflammation, fibrosis, pain, and immune-oncology. The generation of therapeutic mAb targeting GPCR for lipid mediator ligands is more difficult than mAb for chemokine and peptide GPCRs due to many aspects. NBHL established MoGRAA discovery engine which unlocks the generation of the therapeutic mAbs targeting lipid mediator GPCR.

5:25 Designing Discovery Strategies to Maximize Molecular Recognition to Find Agonist Antibodies

Mas Handa, PhD, Director, Antibody Discovery, Merck & Co.

GPCR agonist antibody discovery is challenging due to the complexities of receptor activation. Leveraging partners, we employed non-traditional discovery approaches to create an agonist antibody. Chicken immunization for antibody diversity provided an interaction capable of activating a GPCR that no other rodent or human phage display derived antibodies could in the same epitope region—delivering an agonist mAb with robust pharmacodynamic activity, good pharmacokinetics, and minimal pre-development sequence liabilities.

5:55 Dinner Short Course Registration*

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

9:00 Close of Day

THURSDAY, OCTOBER 20

7:30 am Registration and Morning Coffee (Grand Ballroom Foyer)

7:55 Chairperson's Remarks
Catherine Hutchings, PhD, Independent Consultant

ROOM LOCATION: Back Bay C

SPECIAL PRESENTATION

8:00 Pipeline Update for Antibody-Based Therapeutics against GPCR, Ion Channel, and Transporter Targets
Catherine Hutchings, PhD, Independent Consultant
Multi-pass transmembrane proteins represent some of the most important drug target classes across a wide range of therapeutic areas. An update on antibody-based therapeutics in the GPCR, ion channel, and transporter pipeline will be provided outlining the breadth and diversity of the target landscape, progress in preclinical and clinical development, including next-generation modalities.

TARGETING ION CHANNELS

8:30 Cryo-EM Structures of the Leak Channel NALCN Bound to its Auxiliary Subunits Reveal an Unexpected Architecture and Insights into Gating and Disease Mutation
Marc Kschonsak, PhD, Senior Scientist, Structural Biology, Genentech
The NALCN leak channel regulates the resting membrane potential of many neurons. NALCN modulates locomotion, circadian rhythm and respiration, and mutations in NALCN cause severe neuro-developmental disorders. We determined the structure of the NALCN channelosome, an approximately 1-MDa complex consisting of NALCN and four auxiliary subunits. Our findings provide a blueprint to understand the physiology of NALCN and a foundation for drug discovery to treat NALCN channelopathies.

9:00 KEYNOTE PRESENTATION: Ion Channel Signaling Complexes and Their Potential for Biotherapeutic Targeting
James Trimmer, PhD, Distinguished Professor, Physiology and Membrane Biology, University of California, Davis
Selective ion channel modulators (naturally occurring neurotoxins and synthetic small molecule inhibitors) do not exist for most ion channels. I will detail how renewable and recombinant antibodies can be used to control ion channel function. I will focus on the different forms of renewable and recombinant antibodies that have been used and the mechanisms by which they modulate ion channel function, including those that are expressed intracellularly as genetically-encoded intrabodies.

9:30 Interactive Discussions
Interactive Discussions 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 conference website's Interactive Discussions page for a complete listing of topics and descriptions.

ROOM LOCATION: Back Bay C

IN-PERSON INTERACTIVE DISCUSSION: Characterization of Antibodies Against Membrane Proteins
Joseph Rucker, PhD, Vice President, Research and Development, Integral Molecular, Inc.

10:15 Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

11:00 Discovery and Development of Therapeutic Antibodies against Ion Channels
Sara Bonetti, PhD, Scientist, Salipro Biotech AB, Sweden
Membrane proteins are important drug targets (GPCRs, ion channels), yet are notoriously difficult to work with. We'll present the direct extraction of ion channels from crude cells, as well as case studies on Salipro-embedded ion channels (e.g. TRPV3) for phage display, immunization, B cell sorting, and antibody characterization with SPR and high-resolution cryoEM.

11:30 Co-Structures of TRPA1 with Small-Molecule Ligands Reveal Multiple Binding Sites, Biased Agonism, and Mechanism of Antagonism
Alexis Rohou, PhD, Principal Scientist and Director of CryoEM, Structural Biology, Genentech
TRPA1, a nonselective calcium channel highly expressed in primary sensory neurons and involved in the induction of airway inflammation and hyperreactivity, is a target for inhibition in asthma. Structural studies using cryoEM have unveiled the binding sites and mechanisms of action of two distinct chemical series of antagonists. We characterized a non-covalent agonist and found that it elicits pain responses that are distinct from those of previously described agonists.

12:00 pm Development of High-Affinity Nanobodies Specific for NaV1.4 and NaV1.5 Voltage-Gated Sodium Channel Isoforms
Katharine Wright, PhD, Senior Scientist, Discovery Chemistry, Merck
Voltage-gated sodium channels are responsible for the rapid rise of action potentials in excitable tissues, and NaVchannel mutations have been implicated in several human genetic diseases. We generated high-affinity anti-NaV nanobodies that recognize the NaV1.4 and NaV1.5 channel isoforms. Our work lays the foundation for developing Nbs as anti-NaV reagents to capture NaVs from cell lysates and as molecular visualization agents for NaVs.

12:30 When *in vitro* Libraries are Better than Immunization: Drug-Like Binders Directly from Semi-Synthetic Antibody Libraries
SPECIFICA
Andrew Bradbury, MB BS, PhD, Chief Scientific Officer, Specifica
The Specifica Generation-3 Library Platform is based on highly developable clinical scaffolds, into which natural CDRs purged of sequence liabilities are embedded. The platform directly yields highly diverse, high affinity, developable, drug-like antibodies, as potent as those from immune sources, with minimal need for downstream optimization. This talk will discuss extension of the Platform to VHH libraries and lead antibody improvement, with simultaneous enhancement of both affinity and developability.

1:00 Transition to Lunch

1:10 LUNCHEON PRESENTATION: Simultaneous Quantification of Absolute Concentration and Affinities of Membrane Protein Targets without Purification
Fluidic Analytics
Molly Coseno, PhD, Field Applications Specialist, Sales and Business Development, Fluidic Analytics

We introduce a membrane protein affinity and concentration assay for working with unpurified membrane proteins in a native lipid-bilayer environment. To demonstrate our approach, we determined both the concentration of endogenous HER2 from a breast cancer cell line and its affinity to trastuzumab, a therapeutic antibody. The method only takes a few hours to complete and has the potential to be expanded from cell lines to tissues and tumor biopsies.

1:40 Refreshment Break in the Hall with Poster Viewing (Grand Ballroom)

TARGETING TRANSPORTERS

2:10 Chairperson's Remarks

Rosemary Cater, PhD, Postdoctoral Researcher, Physiology & Cellular Biophysics, Columbia University

2:15 Structural Insights into the Inhibition of Glycine Reuptake to Inform Design of GlyT1 Inhibitors

Roger Dawson, PhD, CEO, Linkster Therapeutics AG

Prolonged glycine signaling has long been a therapeutic goal to improve cognitive impairment and the negative symptoms in patients with schizophrenia. Partially effective, it remained unclear how inhibitors of the glycine transporter 1 (GlyT1) bind to restore normal levels of glycine. Using structure biology, we create an understanding of the binding mode of a benzoylpiperazine chemotype inhibitor bound to GlyT1 and enable the rational design of novel chemotypes.

2:45 Structural Basis of MFSD2A-Mediated Omega-3 Fatty Acid Transport across the Blood-Brain Barrier

Rosemary Cater, PhD, Postdoctoral Researcher, Physiology & Cellular Biophysics, Columbia University

Docosahexaenoic acid is an essential omega-3 fatty acid that is transported across the blood-brain barrier by MFSD2A. Here we solved the cryo-EM structure of MFSD2A in complex with an Fab and lysolipid substrate. Together with functional assays and molecular dynamics simulations, this structure reveals details of how MFSD2A interacts with substrates and releases them into the membrane through a lateral gate. These findings have the potential to aid neurotherapeutic delivery.

3:15 Bioelectronic Measurement of Target Engagement to a Membrane-Bound Transporter

William Martinez, PhD, Co-Founder & CEO, Avalor Therapeutics

The ability to characterize label-free drug binding to SLC transporters is of growing interest in academic and industrial drug discovery labs. However, SLC purification and binding characterization to SLC targets of interest are extremely challenging. Here, we selected MCT1, an SLC target of interest in the oncology field, as a case study to perform label-free measurement of target engagement to integral MCT1 in its native cell membrane environment.

3:45 Close of Conference

TUESDAY, OCTOBER 18

7:00 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Back Bay B

KRAS INHIBITORS (G12C AND BEYOND)

7:55 Welcome Remarks

8:00 Chairperson's Remarks
Daniel A. Erlanson, PhD, Senior Vice President, Innovation and Discovery, Frontier Medicines Corporation

8:05 KEYNOTE PRESENTATION: Fragment-Based Exploration of KRAS Pockets
Stephen W. Fesik, PhD, Professor of Biochemistry, Pharmacology, & Chemistry; Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University
KRAS, a GTPase frequently mutated in cancer, has been considered undruggable due to the lack of suitable pockets. For over a decade we applied fragment-based methods to identify ligands for KRAS pockets that can be optimized using structure-based design. I review these efforts, which has led to Boehringer Ingelheim's G12C inhibitor in clinical trials and lead molecules that offer the promise of additional clinically useful KRAS inhibitors.

9:05 RMC-9805, a First-in-Class, Orally Bioavailable, Tri-Complex Covalent KRASG12D(ON) Inhibitor
Les Burnett, PhD, Associate Director, Medicinal Chemistry, Revolution Medicines
$KRAS^{G12D}$ mutant cancers represent a significant unmet medical need with 55,000 new diagnoses annually in the US largely in colorectal, pancreatic, and non-small cell lung cancers. RMC-9805, a potent, selective, orally bioavailable, covalent $KRAS^{G12D}$(ON) inhibitor, produced deep, durable suppression of tumor KRAS pathway activation *in vivo* following repeat oral administration. Profound tumor regressions were observed in $KRAS^{G12D}$ mutant xenograft models in mice and all dose regimens were well tolerated.

9:35 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

10:25 Discovery of AZD4625: A Covalent Allosteric Inhibitor of KRAS G12C
Doyle Cassar, PhD, Senior Research Scientist, Medicinal Chemistry, AstraZeneca
Knowledge and structure-based design approaches derived a diverse series of covalent inhibitors that selectively target KRASG12C. Key to developing these compounds has been unique structural and conformational insights, identifying and overcoming cross-species PK differences, and solving significant synthetic challenges at scale. This talk will highlight our development of candidate drug AZD4625, a highly potent and selective inhibitor of KRASG12C with anticipated low clearance and high oral bioavailability profile in humans.

10:55 KRAS G12C Inhibitor: GDC-6036
Nicholas F. Endres, PhD, Senior Scientist, Biochemical & Cellular Pharmacology, Genentech, Inc.
Mutations in KRAS are common oncogenic drivers. GDC-6036 is an orally bioavailable, highly potent and selective KRAS G12C inhibitor. GDC-6036 demonstrates greater potency and selectivity compared with other KRAS G12C inhibitors *in vitro*, and complete tumor growth inhibition in multiple KRAS G12C-positive cell lines and in xenograft mouse models. We will present the research program that led to the discovery and optimization of GDC-6036, which is currently in clinical development.

11:25 Enjoy Lunch on Your Own

INHIBITING OTHER GTPases OR RAS PARTNERS

1:25 pm Chairperson's Remarks
Charles W. Johannes, PhD, Vice President, Exploratory Chemistry, FogPharma

1:30 Design and Discovery of MRTX0902: A Potent, Selective, Brain-Penetrant, and Orally-Bioavailable Inhibitor of the SOS1:KRAS Protein-Protein Interaction
John M. Ketcham, PhD, Associate Director, Drug Discovery & Medicinal Chemistry, Mirati Therapeutics, Inc.
KRAS mutations are frequent driver mutations in human cancers. The guanine nucleotide exchange factor, SOS1, regulates the shift of KRAS from the GDP-loaded "off" state to its GTP-loaded "on" state. MRTX0902 is a potent, selective, brain penetrant, and orally bioavailable inhibitor of the $SOS1:KRAS^{G12C}$ protein-protein interaction that causes tumor regressions when dosed with our $KRAS^{G12C}$ inhibitor adagrasib in several preclinical models. The discovery and characterization of MRTX0902 will be presented.

2:00 Probing and Overcoming KRASG12C Inhibitor Resistance
Melanie Wurm, PhD, Senior Scientist, Medicinal Chemistry, Boehringer Inghelheim
KRASG12C inhibitors deliver clinical benefit, most patients who achieved an objective response ultimately progressed. Multiple ongoing trials seek to augment responses to KRASG12C inhibitors through rational combination strategies, including the first-in-class pan-KRAS SOS1 inhibitor BI 1701963. Here we use different preclinical experimental approaches to interrogate KRASG12C inhibitor resistance mechanisms with the aim to identify strategies to overcome resistance.

2:30 Endogenous KRASG12C Degradation by VHL-MRTX849 PROTACs
Michael Bond, PhD, Postdoctoral Fellow, Laboratory of Kimberly Stegmaier, Dana Farber Cancer Institute
The discovery of covalent inhibitors of KRASG12C has reinvigorated the field of KRAS drug discovery. While these compounds have shown promising clinic results, we wanted to explore PROTAC-mediated degradation as a complementary strategy to modulate KRASG12C. We report the development of LC-2, the first PROTAC capable of degrading endogenous KRASG12C. LC-2 induces rapid, sustained KRASG12C degradation and suppresses MAPK signaling. LC-2 demonstrates that PROTAC-mediated degradation can attenuate oncogenic KRAS levels.

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

3:40 Molecular Assemblies of KRAS and Mutants with SOS1
Arthur Laganowsky, PhD, Associate Professor, Chemistry, Texas A&M University
RAS proteins in the mitogen-activated protein kinase (MAPK) signaling pathway are the most frequently mutated oncogenes in cancer. RAS purified from bacteria copurifies with different forms on guanosine nucleotides. Native mass spectrometry is used to study the biochemical properties of RAS along with the molecular complexes they form with Son of Sevenless. We find the intrinsic GTPase activity of oncogenic RAS mutants is dependent on the form of guanosine triphosphate.

4:10 Chemical Strategies Against Mutant K-Ras Driven Cancer

Ziyang Zhang, PhD, Assistant Professor, Chemistry, University of California, Berkeley

Drugs that directly impede the function of driver oncogenes offer exceptional efficacy and therapeutic window for the treatment of cancer. Despite the success targeting the G12C allele, targeted therapy for other hotspot mutants of KRAS have not been developed. I will discuss the discovery of agents that selectively target KRAS mutants beyond G12C, including small molecules that covalently reacts with KRAS G12S and KRAS G12R.

4:40 SUMOylation Inhibition as a Synthetic Lethal Strategy for Cancers with KRAS Mutations

Jiayu Liao, PhD, Professor, Bioengineering, University of California, Riverside

The synthetic lethality strategy has become a very attractive approach for some "non-druggable" genes, such as KRAS and cMyc, in cancer treatment. We developed a quantitative FRET (qFRET)-based HTS to discover a novel SUMOylation inhibitor that shows potent cell death-inducing activities with KRAS mutations at G12 or Q61 in cells and xenograft model. This supports the new strategy to treat cancers with difficult-to-be targeted genes using other approaches.

5:10 Interactive Discussions

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ROOM LOCATION: Back Bay B

IN-PERSON INTERACTIVE DISCUSSION: KRAS and Beyond

Daniel A. Erlanson, PhD, Senior Vice President, Innovation and Discovery, Frontier Medicines Corporation

Charles W. Johannes, PhD, Vice President, Exploratory Chemistry, FogPharma

5:55 Welcome Reception in the Exhibit Hall with Poster Viewing (Grand Ballroom)

6:55 Close of Day

WEDNESDAY, OCTOBER 19

7:30 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Back Bay B

NEW APPROACHES FOR INHIBITING SMALL G PROTEINS

7:55 Chairperson's Remarks

Micah Steffek, Principal Scientist, Biophysics, Denali Therapeutics

8:00 CLAMPing KRAS: Advancing Small Molecule Drug Discovery with Novel Antibody Chaperones

Christopher Davies, PhD, Senior Principal Scientific Researcher, Antibody Engineering, Genentech, Inc.

FDA approval of the first KRAS inhibitor has rejuvenated the field, however, drugging other KRAS mutants remains a challenge. We will describe Conformation Locking Antibodies for Molecular Probe discovery (CLAMPs) that recognize and induce a rare KRAS conformation. We will describe broad application of CLAMPs to detect inhibitor-bound KRAS in cells and tumors, serve as a structural chaperone, and enable a high-throughput screen to discover small-molecule ligands.

8:30 Presentation to be Announced

9:00 A Covalent Fragment-Based Inhibitor of Ral Guanine Exchange Factor Rgl2

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

The Ral-GEF pathway is one of the three major K-RAS signaling pathways. Ral GTPases are difficult targets, but Rgl2, a Ral guanine exchange factor, has several cysteines on its surface. We screened a library of cysteine electrophiles and identified fragments that inhibited Ral GTPase exchange by Rgl2. These allosteric covalent fragment inhibitors provide a starting point for the development of small-molecule covalent inhibitors to inhibit RAS signaling in animal models.

9:30 A Sos Proteomimetic as a Pan-Ras Inhibitor

Paramjit S. Arora, PhD, Professor, Chemistry, New York University

The cellular activity of Ras is modulated by its association with the guanine nucleotide exchange factor Sos, and the high-resolution crystal structure of the Ras–Sos complex provides a basis for the rational design of orthosteric Ras ligands. We constructed a synthetic Sos mimic that engages the wild-type and oncogenic forms of nucleotide-bound Ras and modulates downstream kinase signaling. Chemoproteomic studies illustrate that the proteomimetic engages Ras and other cellular GTPases.

10:00 Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

PLENARY KEYNOTE PROGRAM

ROOM LOCATION: Constitution A + B

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

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James A. Wells, PhD, Professor, Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco

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12:35 pm **Enjoy Lunch on Your Own**

1:25 **Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom Foyer)**

2:05 **Close of Targeting KRAS and Other Small G Proteins Conference**

WEDNESDAY, OCTOBER 19

PLENARY KEYNOTE PROGRAM

ROOM LOCATION: Constitution A + B

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

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James A. Wells, PhD, Professor, Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco
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12:35 pm Enjoy Lunch on Your Own

1:25 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom Foyer)

ROOM LOCATION: Back Bay B

EXPANDING CHEMICAL SPACE: ORAL-BASED PEPTIDE DRUG LEADS

2:05 Welcome Remarks

2:10 Chairperson's Remarks
Kevin Lumb, DPhil, Vice President, Biology, Avilar Therapeutics

2:15 Oral Peptides: Theory and Practice
Lauren G. Monovich, PhD, Director, Global Discovery Chemistry, Novartis Institutes for BioMedical Research, Inc.
Traditionally, permeable macrocyclic peptides have been identified by discrete synthesis and careful side-chain variation of privileged, natural product scaffolds. Recent advances in the principles governing passive permeability were applied to the prospective design of macrocyclic peptides with oral bioavailability. Herein, we present an expanded set of permeability-biased scaffolds and a case study describing the design of a passively permeable, orally available scaffold from a 13-mer PCSK9 ligand.

2:45 MedChem Approaches for Creating Oral Peptides
Jefferson D. Revell, PhD, Principal Scientist, R&D & Discovery Sciences, AstraZeneca
Within this presentation I will discuss the barriers which exclude potential peptide therapeutics from peroral delivery and present some recent strategies in peptidomimetic design which have enabled just a handful of candidates to achieve regulatory approval by the oral route.

3:15 New Trends in the DEL Space: X-Chem's Offerings and Innovations
Paige Dickson, PhD, Senior Research Scientist, Lead Discovery, X-Chem, Inc.
At X-Chem, we push the limits of DEL-enabled drug discovery to empower our clients' pursuit of novel therapeutics. This talk summarizes our lead generation approaches, hit-to-lead services, and our off-the-shelf DEL collection, which provides high-quality, chemically diverse libraries to bolster existing practitioners' collections. As an experienced DEL service provider, X-Chem offers numerous enablement tools, including target tractability assessments, custom library synthesis, and AI-guided drug discovery.

3:45 Dessert Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

DNA-ENCODED LIBRARY APPROACHES

4:25 When to Use DNA-Encoded Libraries?
Timothy L. Foley, PhD, Senior Principal Scientist & Lab Head, DNA Encoded Library Selection & Pharmacology, Pfizer Global R&D Groton Labs
In addition to traditional high-throughput screening, the hit-identification toolbox now includes the screening of fragment and fragment-like libraries, affinity selection mass spectrometry, and selection against DNA-encoded libraries (DELs). I will discuss the unique advantages and limitations of these techniques that make them more, or less, suitable for different target classes or discovery objectives, with an emphasis on those that indicate when DEL makes a good fit for a program.

4:55 Using DEL to Assess Ligand-Ability of New Targets
Elizabeth D'ambrosio, PhD, Investigator, DNA-Encoded Library Technology, GlaxoSmithKline
Encoded Library Technology (ELT) is a hit identification platform using large collections of chemically diverse DNA-encoded small molecules selected against therapeutically relevant protein targets. At GSK, we have integrated *in silico* and experimental methods to rapidly predict small molecule tractability of novel targets. These outcomes allow us to prioritize therapeutically relevant targets based on empirical data and focus small molecule hit identification efforts on those most likely to succeed.

5:25 DNA-Encoded Libraries for Targeting RNA Binding Proteins
Matthew Disney, PhD, Professor, Department of Chemistry, Scripps Research Institute
We will present the development of a solid phase DNA encoded library-based screening platform to identify compounds that bind to RNA fold libraries. Mining the emergent interactions across the human transcriptome identified a bioactive interaction between the DEL-derived ligand and an oncogenic microRNA precursor. The compound affected cancer-associated phenotypes in cells. DNA encoded library screening can therefore be used to inform design of bioactive ligands targeting RNA.

5:55 Dinner Short Course Registration*
**Premium Pricing or separate registration required. See Short Courses page for details.*

9:00 Close of Day

THURSDAY, OCTOBER 20

7:30 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Back Bay B

LEAD GENERATION APPROACHES: INNOVATION AND INTEGRATION

7:55 Chairperson's Remarks

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

8:00 FEATURED PRESENTATION: Leveraging an Integrated Hit-Finding Approach for SMYD3: A Medicinal Chemistry Perspective on Target Invalidation

Beth A. Knapp-Reed, PhD, Director, Medicinal Chemistry, GlaxoSmithKline

Smyd3 is a lysine methyltransferase that is overexpressed in several tumor cell lines. A three-pronged screening approach which included an HTS campaign, ELT screen, and a fragment screen, followed by lead optimization delivered multiple chemical series for key target validation studies. Several compounds exhibited excellent potency in the biochemical and cellular assays and demonstrated target engagement, however, failed to show anti-proliferative activity or changes in downstream pERK signaling.

8:30 switchSENSE for DNA-Encoded Library and Aptamer Selection Hit Validation

Joshua D. Alper, PhD, Scientific Leader, Biophysics, GSK

Encoded Library Technologies enable discovery chemists to identify thousands of hits from screening campaigns with billions of molecules. However fast hit follow-up typically requires extensive chemical syntheses and biophysical and biochemical assays. We present an efficient hit validation method using switchSENSE, which is a DNA-based technology to determine the binding kinetics, to address these issues. We demonstrate the benefits of the method for both resynthesized on-DNA chemical matter and aptamers.

9:00 Small Molecule Inhibitors of TEADs Allosteric Lipid Pocket

Debra Brennan, Senior Director Protein Sciences & Structural Biology, Nimbus Therapeutics

The TEAD family of transcription factors are implicated in cancer but developing a central pocket assay posed a hurdle toward fully understanding inhibition. We have overcome the challenges of TEADs central lipid pocket and developed a robust biochemical assay, used structural elucidation and computational chemistry to understand the MOAs for small molecule inhibitors. We provide hypothesis of different MOAs which could contribute to development of more potent and selective inhibitors.

9:30 Interactive Discussions

Interactive Discussions 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 conference website's Interactive Discussions page for a complete listing of topics and descriptions.

ROOM LOCATION: Back Bay B

10:15 Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

11:00 FEATURED PRESENTATION: Highlighting the Affinity of Affinity-Driven Covalents.

John Quinn, PhD, Distinguished Scientist, Biophysical Group, Biochemical and Cellular Pharmacology, Genentech

Ligandability of affinity-driven inhibitors is inversely correlated with target disorder thereby limiting the discovery of suitable starting points for small molecule lead generation. However, affinity-driven covalent inhibitors, typically characterized by the overall alkylation rate constant, are proving effective in targeting such challenging targets (e.g. Kras G12C) despite extremely weak affinity. However, optimization of early covalent hits should include reversible affinity/kinetic measurements in order to arrive at more optimal leads.

11:30 Cryo-EM Structures of Inhibitory Antibodies Complexed with Arginase1: Insights into Mechanism of Action

Rachel Palte, PhD, Senior Scientist, Structural Chemistry, Merck Research Labs

Human Arginase 1 (hArg1) modulates T cell-mediated immune response. All published hArg1 inhibitors are small molecules usually < 350 Da. Here we report the first cryo-electron microscopy structures of potent and inhibitory anti-hArg antibodies bound to hArg1, and have unambiguously mapped epitopes and paratopes for all five antibodies. This highlights the ability to utilize antibodies as probes in the discovery and development of peptide and small molecule inhibitors for enzymes.

12:00 pm Application of Cryo-EM for Structure-Based Design against Membrane Protein Targets

Seungil Han, PhD, Research Fellow, Head of cryo-EM Lab, Structural Biology & Molecular Sciences, Pfizer Inc.

Cryo-EM has increasingly been implemented in recent years by pharmaceutical companies for structure-based drug design. Highly druggable but challenging or intractable targets for crystallography, most notably integral membrane proteins such as GPCRs, ion channels, and solute carrier proteins (SLCs), which comprise a disproportionate fraction of drug targets, have become much more amenable to structural characterization by cryo-EM I will discuss recent instructive examples from the implementation of cryo-EM at Pfizer.

12:30 Using Cryo-EM to Enable Structure-Based Drug Discovery Efforts for "Difficult" Targets Such as Epigenetic Targets

PROTEROS
REACH RIGHT FASTER

Stephan Krapp, PhD, Head of Structural Biology, Proteros Biostructures

Cryo electron microscopy (cryo-EM) enables access to structures of so called "difficult" pharmaceutical drug targets. We share our recent experiences with solving structures of diverse target classes, such as, membrane proteins, viral receptors, and higher order complexes. We focus on the first 3D views of the multi protein histone deacetylase (HDAC) assemblies and their nucleosome-bound complexes, and how such information can enable structure based drug discovery programs.

12:45 PAC_FragmentDEL – Combining Fragments and DEL to Generate Leads for Challenging Targets

HITGEN

Rod Hubbard, Founding Scientist, Director of Research Collaborations, Vernalis (R&D) Ltd.

PAC-FragmentDEL is a new approach to hit identification which combines the sensitivity of DEL with the power of fragments to sample chemical space. Each DNA-encoded fragment is linked to a diazirine moiety; incubation of the library is followed by photoactivation, washing and subsequent PCR and

sequencing. The approach will be demonstrated with some model studies on a conventional target (PAK4 kinase) and a previously undrugged and challenging target, 2-epimerase.

1:15 Enjoy Lunch on Your Own

1:40 Refreshment Break in the Hall with Poster Viewing (Grand Ballroom)

FRAGMENT-BASED AND OTHER HIT-FINDING STRATEGIES

2:10 Chairperson's Remarks
Chaohong Sun, PhD, Senior Director, Lead Discovery, AbbVie, Inc.

2:15 Fragment-Based Design of Methionine Adenosyl Transferase (MAT2a) Inhibitors with Anti-tumour Effect
Marianne Schimpl, PhD, Associate Principal Scientist, Structural Biology, AstraZeneca
The methionine adenosyltransferase MAT2a is an emerging target for the treatment of MTAP-deleted cancers. Here, I present the design and *in vivo* evaluation of a series of potent inhibitors of this enzyme, starting from a weak fragment hit determined by X-ray crystallography to bind to an allosteric site. I will detail the biophysical screening cascade, selection of fragment hits, and structure- and computationally-supported design of key compounds through fragment merging.

2:45 Liganding the Cytokinome at AbbVie: Integrating Hit-Finding and Hit-Confirming Strategies for IL-17, IL-36, and TNFa
Brad Shotwell, PhD, Director, Medicinal Chemistry, AbbVie, Inc.
At AbbVie we find that multipronged small molecule hit finding strategies yield the most diverse chemotypes, wherein multiple complementarity screening platforms are paired with multiple robust biophysical confirmation tools prior to execution on a hit. Here we present several case studies which include hit-finding through *in vivo* POC for a series of cytokine targets within our exploratory portfolio.

3:15 Fragment Screening Combined with Corporate Compound Collection Searching: Delivering a Novel Inhibitor of the KEAP1:NRF2 Interaction
David Norton, PhD, Director, Medicinal Chemistry, Astex Pharmaceuticals Ltd.
A successful fragment screening campaign against KEAP1 provided key starting points and information to generate a highly potent series against this PPI. To develop a second potent series, the key pharmacophoric elements were used to search the GSK collection. An SBDD campaign on the resulting hits generated a second potent series suitable for lead optimisation.

3:45 Close of Conference

Cambridge Healthtech Institute's Inaugural

Artificial Intelligence in Drug Discovery – Part 1

AI/ML for Optimizing Drug Targets and Leads | OCTOBER 18-19, 2022

NEW

TUESDAY, OCTOBER 18

7:00 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Republic Ballroom A

AI/ML FOR DRUG DESIGN & OPTIMIZATION

7:55 Welcome Remarks

8:00 Chairperson's Remarks
Patrick Riley, PhD, Senior Vice President, Artificial Intelligence, Computation Department, Relay Therapeutics, Inc.

8:05 Automated Chemical Design in Drug Discovery
Patrick Riley, PhD, Senior Vice President, Artificial Intelligence, Computation Department, Relay Therapeutics, Inc.
I'll cover a framework we call ACD (Automated Chemical Design) Levels for describing the level of autonomy for AI-powered systems that design molecules. This framework allows relevant distinctions to be drawn and can help teams better understand the claimed capabilities of a system and ask more insightful questions to understand their function. Using these definitions, we will discuss the challenges and opportunity for AI-powered design of molecules in drug discovery.

8:35 Combining Generative AI Models and Reinforcement Learning for *de novo* Drug Discovery
Parthiban Srinivasan, PhD, Professor, Data Science and Engineering, Indian Institute of Science Education and Research
Generative Adversarial Networks (GANs) and Reinforcement Learning (RL) have been successfully applied for *de novo* drug design. Multiple such frameworks have been explored and shared by many AI researchers. We review these models and discuss the features of these techniques in terms of generating novel molecules with desired properties.

9:05 How AI Is Redefining How Potential Drug Targets Are Discovered causaly
Richard Harrison, Chief Scientist, Causaly
It is well known that 90% of drugs entering clinical trials fail to make it to market. Furthermore, a failure to link the target to a disease in preclinical research is the major reason for these failures. Using AI to machine-read and comprehend all scientific literature, we will demonstrate how Causaly Cloud can uncover hidden mediators for several diseases, ensuring the identification of candidates with the greatest chance of success.

9:35 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

10:25 CACHE: An Experimental Platform to Benchmark and Reveal the Future of Virtual Screening Methods
Matthieu Schapira, PhD, Principal Investigator, Structural Genomics Consortium
The Critical Assessment of Computational Hit-Finding Experiments (CACHE) is an international competition where computational chemists and AI experts submit their predicted compounds which are procured and tested experimentally at CACHE against a pre-defined target. The first two challenges, finding hits for the Parkinson's disease target LRRK2 and the SARS-CoV-2 helicase NSP13, are ongoing. ~50% of participants combined physics-based and deep-learning techniques. Do these hybrid methods already out-perform more traditional approaches?

10:55 Solubility Prediction by Deep Learning of Quantum Information Embedded in a Novel Molecular Representation
Tonglei Li, PhD, Allen Chao Chair & Professor, Industrial & Physical Pharmacy, Purdue University
Solubility can be a challenging, time-consuming, material intensive property to measure correctly. To accurately predict solubility values of drug-like compounds, we have recently developed a novel molecular featurization scheme based on local electronic properties within the framework of conceptual density functional theory. Our effort shows promise in solubility prediction with an accuracy outperforming most of the reported models. Our approach is being applied to predictions of other drug developability properties.

11:25 PANEL DISCUSSION: Key Learnings from AI-Driven Early Drug Discovery
Moderator: Patrick Riley, PhD, Senior Vice President, Artificial Intelligence, Computation Department, Relay Therapeutics, Inc.
Panelists:
Anthony Bradley, PhD, Director of Design Development, Exscientia Ltd.
Jörg Wegner, PhD, Associate Scientific Director, In Silico Discovery and External Innovation, Janssen Research & Development, LLC

11:55 How to Leverage New AI Technologies Alongside Traditional HTS to Better Validate Hit Compounds for GPCRs eurofins | DiscoverX
Carleton Sage, PhD, Vice President, Computational Sciences, Eurofins Discovery
Based on predictive crystal structures made available by Google's DeepMind AlphaFold project, Eurofins Discovery will explore the potential of computational chemistry alongside HTS procedures to present examples of diverse and complementary approaches to hit discovery using two ongoing GPCR discovery projects. We will discuss target selection rationale in a virtual screening approach and a parallel effort of an HTS campaign to address the challenges of hit confirmation and validation.

12:10 pm Enjoy Lunch on Your Own

UNDERSTANDING THE CAVEATS OF AI PREDICTIONS

1:25 Chairperson's Remarks
Anthony Bradley, PhD, Director of Design Development, Exscientia Ltd.

1:30 Patient-first AI: Exscientia's Approach
Anthony Bradley, PhD, Director of Design Development, Exscientia Ltd.
Exscientia's patient-first approach to drug discovery has produced industry-leading productivity. In this talk, we outline how we leverage the power of physics and informatics in our AI algorithms. We exemplify this through high-throughput structural target assessment, delivery of novel and class-leading potential anti-viral programme for SARS-CoV-2, and in delivering automated and *de novo* potent hits in the first cycle of design for a kinase.

2:00 Opportunities and Challenges on "Which Compounds to Make" and "How to Make Them" – A Scalability Perspective
Jörg Wegner, PhD, Associate Scientific Director, In Silico Discovery and External Innovation, Janssen Research & Development, LLC
We will showcase how data analytics/AI is being used in business processes and how this improves decision-making for drug design teams. We will present retro- and prospective studies to highlight the value proposition of the innovation integration of novel science and technology into business processes. A key differentiator for enabling analytics/AI is to decide which science and technology contributes to the business and only lift those to enterprise level.

2:30 Logica: Reimagining Drug Discovery, Getting Medicines to Patients Faster!

charles river

Ronald Dorenbos, Executive Director Business Development, Logica

Charles River Laboratories and Valo Health have launched Logica, an artificial intelligence (AI) powered drug solution that directly translates clients' biological insights into optimized preclinical assets. Logica leverages Valo's AI-powered Opal Computational Platform and Charles River's leading preclinical expertise, providing clients with transformed drug discovery with a single integrated offering seamlessly translating targets to candidate nomination.

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

3:40 FEATURED PRESENTATION: How AI Is Accelerating Drug Discovery


Petrina Kamya, PhD, Head of AI Platforms, Department of Business Development, Insilico Medicine
Alex Zhavoronkov, PhD, Founder & CEO, Insilico Medicine

Bringing just one drug to market through traditional research and discovery is a decade-long process that costs over $2 billion and the vast majority of drugs in development fail. I will discuss how artificial intelligence is ushering in a new era of accelerated drug discovery. *In silico* medicine is a global pioneer in end-to-end AI-driven drug discovery with the first AI-discovered and AI-designed drug for idiopathic pulmonary fibrosis.

4:25 FEATURED PRESENTATION: The Potential Dark Side of Generative AI for Drug Discovery

Sean Ekins, PhD, Founder & CEO, Collaborations Pharmaceuticals, Inc.

Our recent work describes the use of generative approaches to rapidly develop thousands of virtual molecules, including the nerve agent VX. We will address some of the many AI-related ethical questions we have faced since, including whether we should have published the work in the first place and our motivations behind it. In the process we will propose mechanisms whereby such software, data and models can be securely shared.

5:10 Interactive Discussions

Interactive Discussions 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 conference website's Interactive Discussions page for a complete listing of topics and descriptions.

ROOM LOCATION: Republic Ballroom A

IN-PERSON INTERACTIVE DISCUSSION: Understanding the Caveats of AI Predictions

Anthony Bradley, PhD, Director of Design Development, Exscientia Ltd.
Sean Ekins, PhD, Founder & CEO, Collaborations Pharmaceuticals, Inc.
Petrina Kamya, PhD, Head of AI Platforms, Department of Business Development, Insilico Medicine

- Current trends for the application of AI toward preclinical drug discovery
- The challenge of continuous evolution of models in response to growth of big data, data types, and computational platforms
- What measures should be taken to invest in and effectively use AI at various stages of drug development?

5:55 Welcome Reception in the Exhibit Hall with Poster Viewing (Grand Ballroom)

6:55 Close of Day

WEDNESDAY, OCTOBER 19

7:30 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Republic Ballroom A

AI FOR PROTEIN THERAPEUTICS

7:55 Chairperson's Remarks

Ryan Henrici, MD, PhD, Director of Translational Research, BigHat Biosciences

8:00 Designing Therapeutic Antibodies with Synthetic Biology and Machine Learning

Ryan Henrici, MD, PhD, Director of Translational Research, BigHat Biosciences

BigHat Biosciences is designing safer, more effective antibody therapies for patients using machine learning and synthetic biology. Machine learning guides the search for better molecules by directing and learning from each cycle of our high speed, automated wet lab that synthesizes and characterizes hundreds of antibodies each week. We'll highlight key features of our platform and share several case studies of protein engineering using this novel platform.

8:30 *De novo* Design and Machine Learning Guided Optimization of Antibody Therapeutics

Surge Biswas, PhD, Founder & CEO, Nabla Bio, Inc.

We developed a method for *de novo* antibody design using antigen structure alone. Across multiple antigens, we characterized binding strength for ~10^5 antibody designs and observed 10s-100s of strong binders. All designs were assayed in multiplex for stability and polyspecificity, and this revealed a broad array of binding and developability trade-offs. These results highlight the importance of integrating ML with high-throughput, multi-property measurements for the holistic design of antibody therapeutics.

9:30 Peptide Hit Identification and Lead Optimization Using Artificial Intelligence Approaches

Ewa Lis, PhD, Founder & CTO, Koliber Biosciences

Successful peptide drug discovery programs today require attainment of multiple performance metrics to progress a compound to clinical stage. To aid decision-making, Koliber has developed an AI peptide platform based on state-of-the-art machine learning methods to analyze peptide properties, profile positions, and predict new variants. The capabilities and wet-lab validation of the AI platform will be demonstrated with examples from immunology and antimicrobial peptide discovery and optimization.

10:00 Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

PLENARY KEYNOTE PROGRAM

ROOM LOCATION: Constitution A + B

11:00 Plenary Chairperson's Remarks

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

11:05 PLENARY: Pirating Biology to Detect and Degrade Extracellular Proteins

James A. Wells, PhD, Professor, Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco

In contrast to intracellular PROTACs, approaches to degrade extracellular proteins are just emerging. I'll describe our recent progress to harness natural mechanisms such as transmembrane E3 ligases to degrade extracellular proteins using fully genetically encoded bispecific antibodies we call AbTACs. We have also engineered a peptide ligase which can be tethered to cells to detect proteolysis events and target them with recombinant antibodies for greater selectivity for the tumor microenvironment.

11:50 PLENARY: Therapeutic Modalities for Neuroscience Diseases

Anabella Villalobos, PhD, Senior Vice President, Biotherapeutics & Medicinal Sciences, Biogen

Many effective medicines exist to treat neurological diseases, but medical need remains high. We have a unique multi-modality approach to discover novel therapies and our goal is to find the best modality regardless of biological target. With a multi-modality approach, we aim to expand target space, leverage synergies across modalities, and offer options to patients. Opportunities and challenges associated with small molecules, biologics, oligonucleotides, and gene therapy will be discussed.

12:35 pm Enjoy Lunch on Your Own

1:25 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom Foyer)

2:05 Close of Artificial Intelligence in Drug Discovery – Part 1 Conference

Cambridge Healthtech Institute's Inaugural

Artificial Intelligence in Drug Discovery – Part 2

AI/ML for Genomics and Proteomics Studies | OCTOBER 19-20, 2022

NEW

WEDNESDAY, OCTOBER 19

PLENARY KEYNOTE PROGRAM

ROOM LOCATION: Constitution A + B

11:00 am Plenary Chairperson's Remarks
An-Dinh Nguyen, Team Lead, Discovery on Target, Cambridge Healthtech Institute

11:05 PLENARY: Pirating Biology to Detect and Degrade Extracellular Proteins
James A. Wells, PhD, Professor, Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco
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12:35 pm Enjoy Lunch on Your Own

1:25 Refreshment Break in the Exhibit Hall with Poster Viewing (Grand Ballroom Foyer)

ROOM LOCATION: Constitution A

AI/ML FOR PROTEIN DEGRADATION

2:35 Welcome Remarks

2:40 Chairperson's Remarks
Woody Sherman, PhD, CEO, Psivant Therapeutics

2:45 Accelerating Rational Degrader Design via Computational Prediction of Ternary Structure Ensembles
Woody Sherman, PhD, CEO, Psivant Therapeutics
TPD involves the formation of an induced proximity complex. Here, we address three critical aspects of the TPD process using biophysics, atomistic simulations, and AI: 1) Structural prediction of the ternary complex induced by degrader molecules. 2) Conformational heterogeneity of the ternary complex. 3) Prediction of degradation efficiency via the CRL assembly. We combine HDX-MS, MD, and AI to predict induced proximity ensembles, guide design, and improve degradation efficiency.

3:15 How Artificial Intelligence Enhances Drug Discovery
Sang Eun Jee, PhD, Application Scientist, Xtalpi
AI can cut down the development timeline and cost for drug discovery by answering two significant questions: What molecules should be made next and how are the lead molecules modified? AI technology in drug discovery will be introduced with case studies of how we solved challenging problems with AI. The key to success in AI-driven drug discovery in the future will also be discussed with the lessons learned from history.

3:45 Dessert Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

4:25 Estimating Target Degradability from Protein-Intrinsic Features
Shourya Roy Burman, PhD, Research Fellow, Cancer Biology, Dana-Farber Cancer Institute
Chemo-proteomics profiling of PROTACs designed from pan-class inhibitors revealed a large difference in the degradation frequencies of the target proteins engaged by these molecules. Using protein-intrinsic features, we developed a machine learning classifier that discriminates target proteins based on their observed degradation patterns and highlights properties that dictate their degradability. Using computational structural modeling, we provide mechanistic insight into the predicted features and obtain actionable information for rational PROTAC design.

4:55 Closing the Gap: Heterogeneous Molecular Modeling & Machine Learning for Accurate Modeling
Victor Guallar, PhD, Professor, Barcelona Supercomputing Center and Nostrum Biodiscovery
Combining the state-of-the-art molecular modeling, in heterogeneous data sources and in machine learning techniques, we are dramatically increasing the accuracy in our computational predictions. We will showcase recent successful case studies including virtual screening enrichment, ligase screening for TPD, and ternary complex formation in PROTACs. Overall, the enrichment of machine learning techniques with data augmentation from molecular modeling seems to provide the necessary boost that prediction models might need.

5:25 PANEL DISCUSSION: Challenges with Using AI Predictions for Designing Protein Degraders
Moderator: Woody Sherman, PhD, CEO, Psivant Therapeutics
Panelists:
Shourya Roy Burman, PhD, Research Fellow, Cancer Biology, Dana-Farber Cancer Institute
Victor Guallar, PhD, Professor, Barcelona Supercomputing Center and Nostrum Biodiscovery

5:55 Dinner Short Course Registration*
**Premium Pricing or separate registration required. See Short Courses page for details.*

9:00 Close of Day

THURSDAY, OCTOBER 20

7:30 am Registration and Morning Coffee (Grand Ballroom Foyer)

ROOM LOCATION: Republic Ballroom A

BRIDGING GAPS USING AI PREDICTIONS

7:55 Chairperson's Remarks
Michael Liebman, PhD, Managing Director, IPQ Analytics, LLC

8:00 Defining the Gap in Managing Disease
Michael Liebman, PhD, Managing Director, IPQ Analytics, LLC
Drug discovery has benefitted from the application of AI to enhance the ability to deal with large, diverse data coming from genomics, imaging, EHR'S and claims data. While this has greatly improved operational efficiency, there remains a significant gap between drug discovery and actual management of disease. An introduction to Next-Generation Phenotyping (NGP) in multiple sclerosis will be presented to highlight the challenges and opportunities.

8:30 PANEL DISCUSSION: Understanding Disease vs Designing Drugs: Can AI Bridge the Gap?
Moderator: Michael Liebman, PhD, Managing Director, IPQ Analytics, LLC
Drug discovery has benefitted from the application of AI to enhance the ability to deal with large, diverse data from genomics, imaging, EHRs, and claims data. While this has greatly improved operational efficiency, a significant gap remains between drug discovery and actual understanding of disease processes, involving both diagnosis and treatment. The critical gap remains between correlation and causality and the methods/approaches used to address each and their respective value.
Panelists:
Ryan Henrici, MD, PhD, Director of Translational Research, BigHat Biosciences
Steven E. Labkoff, MD, Global Head, Clinical & Healthcare Informatics, Quantori

9:30 Interactive Discussions
Interactive Discussions 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 conference website's Interactive Discussions page for a complete listing of topics and descriptions.

ROOM LOCATION: Constitution A

IN-PERSON INTERACTIVE DISCUSSION: How Successful Are AI Predictions for Disease Biology?
Michael Cuccarese, PhD, Director, Translational Oncology, Recursion Pharmaceuticals, Inc.
Nicolas Stransky, PhD, Vice President & Head, Data Sciences, Celsius Therapeutics

10:15 Coffee Break in the Exhibit Hall with Poster Viewing (Grand Ballroom)

11:00 Principled Calibration and QA/QC Assessments of AI and Machine Learning Methods within Pathology & Radiology
Arvind Rao, PhD, Associate Professor, Department of Computational Medicine and Bioinformatics, University of Michigan
Given the wide variety of AI tools currently being deployed in radiology and pathology, the calibration of these tools is important. Using the example of tumor segmentation task, we will review a few algorithms and describe their potential modes of failure in addition to scoring rubrics related to data and model veracity. Then using case studies from pathology, we will examine "failure modes" in the performance of AI algorithms.

11:30 Machine Learning Approaches to Identify Targets for Immunotherapy in Glioblastoma
Todd Bartkowiak, PhD, Research Fellow, Department of Cell and Developmental Biology, Vanderbilt University
Immunotherapies have shown limited efficacy in treating glioblastoma. While radiographic tumor contact with the lateral ventricle correlates with worse outcomes; the extent to which ventricle proximity impacts immunobiology in the tumor microenvironment remains unknown. Using CyTOF profiling and machine learning approaches, we identify the suppressive impact of ventricle contact on anti-tumor immunity in the brain and reveal potential clinically actionable immune targets and patient stratification methods for glioblastoma.

12:00 pm Exploring Novel Biologically-Relevant Chemical Space through AI and Automation: The NCATS ASPIRE Program
Danilo Tagle, PhD, Director, Office of Special Initiatives, National Center for Advancing Translational Sciences, National Institutes of Health
NCATS through the ASPIRE (A Specialized Platform for Innovative Research Exploration) program seeks to transform the design-synthesize-test cycle through the development of new algorithms and workflows to capture data from automated chemical synthesis and biological testing systems to predict and inform the next iteration of new chemical entities. ASPIRE will enhance the ability to discover and develop new chemistries towards previously undrugged biological targets across many human diseases and conditions.

12:30 Enjoy Lunch on Your Own

1:40 Refreshment Break in the Hall with Poster Viewing (Grand Ballroom)

AI PREDICTIONS FOR UNRAVELING DISEASE BIOLOGY

2:10 Chairperson's Remarks
Nicolas Stransky, PhD, Vice President & Head, Data Sciences, Celsius Therapeutics

2:15 A Single-Cell RNAseq and Machine Learning Platform to Enable Target ID at Scale
Nicolas Stransky, PhD, Vice President & Head, Data Sciences, Celsius Therapeutics
New genomic technologies hold great promise for the identification of actionable drug targets and associated biomarkers for several complex diseases. However, the discovery of novel targets is often complicated by multigenic effects and the involvement of multiple cell types in disease progression. Our approach uses single-cell RNAseq and machine learning to elucidate the precise cell types involved in the progression of complex diseases and to identify novel therapeutic targets.

2:45 The Application of Artificial Intelligence to Drug Target Identification
Olivier Elemento, PhD, Professor, Physiology, Biophysics & Systems Biology; Director, Englander Institute for Precision Medicine, Weill Cornell Medicine

In this talk, I will describe our continued efforts to use genomics and AI to identify the targets of compounds that may not have entirely known mechanisms of action. I will describe how these approaches can be used to screen libraries of compounds *in silico* to uncover repositioning opportunities. I will then describe the successful application to an anticancer compound, followed by precise clinical positioning in pediatric brain cancers.

3:15 Mapping and Navigating Biology at Scale to Model Complex Disease and Accelerate Discovery

Michael Cuccarese, PhD, Director, Translational Oncology, Recursion Pharmaceuticals, Inc.

Recursion is a clinical-stage pharmatech company, mapping human biology at scale to bring better medicines to patients. Enabled by 14 petabytes of imaging and other omics data, we use deep learning to build biological representations across multiple cell types, a whole-genome CRISPR library, and nearly 1 million compounds. Here, we demonstrate the capability of this platform to model complex disease and identify and optimize compounds as potential cancer therapies.

3:45 Close of Conference

Join Us in Boston!

Conference Venue and Hotel:
Sheraton Boston
39 Dalton Street
Boston, MA 02199

Discounted Room Rate: $289 single/double
Discounted Room Rate Cut-off Date: September 20, 2022

For additional information please go to the Travel Page of DiscoveryOnTarget.com

20th Annual

Register with Confidence

Flexible Registration – Seamlessly switch between In-Person and/or Virtual

Select an in-person or virtual option, and you have the flexibility to switch your preferred event experience at any time leading up to the conference. Our flexible registration is designed to take the uncertainties out of these uncertain times.

Your Safety Is Our Top Priority

To ensure maximum safety, CHI has instituted mandatory health and safety protocols for all attendees, exhibitors, speakers, and staff who attend in person. Attendees who cannot participate because of this policy, or due to travel restrictions, are encouraged to participate using our highly praised virtual event platform. Our virtual events are designed to provide you with an in-person experience at your convenience, anywhere, anytime. We are actively following news and recommendations around COVID-19 and the Omicron variant. These protocols are subject to change as we continue to learn more.

All in-person attendees *must*: Have a negative COVID-19 test result from an FDA-authorized over-the-counter antigen test within 24 hours prior to arriving at the event. You will be asked about your results at registration.

CHI *recommends* all attendees:
Have an updated COVID-19 vaccination and wear a mask in public spaces at the event

Can't Make it to Boston?

Join via our Robust Virtual Platform:

- INTERACTIVE DISCUSSIONS
- INTUITIVE INTERFACE
- LIVE CHAT
- RECORDED SESSIONS
- COMPANY BRANDING
- LIVE SESSIONS
- DOWNLOADS
- POSTER SESSIONS

Cambridge HEALTHTECH Institute
A Division of Cambridge Innovation Institute

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

Please refer to the Registration Code on right:

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

Discovery on TARGET | Pricing & Registration Information

PREMIUM PACKAGE *(Includes in-person or virtual access to 2 conferences, 2 Short Courses and 1 Symposium, plus networking events. In addition, you will receive on-demand access to presentations for one year. You are allowed to move between sessions to attend presentations taking place at the same time.)*

	Commercial	Academic, Government, Hospital-Affiliated
Standard Pricing After September 30	$3,199	$1,549

STANDARD PACKAGE *(Includes in-person or virtual access to 2 conferences & networking events. Does not include Short Courses or Symposium. In addition, you will receive on-demand access to presentations for one year. You are allowed to move between sessions to attend presentations taking place at the same time.)*

Standard Pricing After September 30	$2,649	$1,299

SINGLE CONFERENCE PRICING *(Includes in-person or virtual access to 1 conference & networking events. Does not include Short Courses or Symposium. In addition, you will receive on-demand access to presentations for one year. You are allowed to move between sessions to attend presentations taking place at the same time.)*

Standard Pricing After September 30	$2,199	$999

SYMPOSIUM PRICING

1 Symposium	$999	$599

PRE-CONFERENCE SYMPOSIUM October 17 ▼
S1: Emerging Immune Modulation Strategies

SHORT COURSE PRICING

1 Short Course	$699	$399
2 Short Courses	$999	$599

SHORT COURSES

PRE-CONFERENCE DINNER SHORT COURSES (IN-PERSON ONLY) October 17 ▼	DINNER SHORT COURSES (IN-PERSON ONLY) October 19 ▼
SC1: Protein Degraders: A Focus on PROTACs from a Beyond Rule of Five Space Perspective	SC4: Protein Degraders: A Focus on PROTACs from an ADME-Tox Perspective
SC2: Chemical Biology for Phenotypic Screening and Target Deconvolution	SC5: Biophysical Tools for Membrane Proteins: Drug Discovery Applications
SC3: Best Practices for Targeting GPCRs, Ion Channels, and Transporters with Monoclonal Antibodies	SC6: DNA-Encoded Libraries

CONFERENCE PROGRAMS

October 18-19 ▼	October 19-20 ▼
C1A: PROTACs and Molecular Glues - Part 1	C1B: PROTACs and Molecular Glues - Part 2
C2A: Target Identification and Validation - Part 1	C2B: Target Identification and Validation - Part 2
C3A: Targeting RNA	C3B: New Antivirals
C4A: Small Molecule Immuno-Oncology Targets	C4B: NASH and Fibrosis
C5A: GPCR-Based Drug Discovery	C5B: Neurodegeneration Targets
C6A: Antibodies Against Membrane Protein Targets - Part 1	C6B: Antibodies Against Membrane Protein Targets - Part 2
C7A: Targeting KRAS and Other Small G Proteins	C7B: Drug Lead Generation Strategies
C8A: Artificial Intelligence in Drug Discovery - Part 1	C8B: Artificial Intelligence in Drug Discovery - Part 2

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How to Register:

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

FOR ADDITIONAL REGISTRATION OPTIONS, VISIT OUR EVENT WEBSITE

GROUP DISCOUNTS

Have your colleagues or entire team attend!

Purchase a full price registration and participants from the same organization will receive a 25% discount when registering through the Group Registration page.

For more information on group discounts contact Uma Patel at 781-972-5447.

LEARN MORE

VIRTUAL REAL-TIME OPTIONS

Includes access to virtual conferences and event features including the virtual exhibit hall, poster presentations, facilitated networking, on-demand access and more!

POST-EVENT ON-DEMAND ONLY

Includes post-event recorded access to ALL conferences. Does not include access to live Q&A or networking.

POSTER SUBMISSION

Poster materials are due by September 23, 2022. Once your registration has been fully processed, we will send an email containing a unique link and instructions for submitting your abstract and other materials. If you do not receive your link within 5 business days, please contact jring@healthtech.com.

** CHI reserves the right to publish your poster content in various marketing materials and products.*

Please click here for information on poster materials.