FINAL DAYS to Register!

APRIL 10 - 13, 2023
HILTON BAYFRONT | SAN DIEGO, CA & VIRTUAL

18TH ANNUAL

Drug Discovery Chemistry

Optimizing Small Molecules for Tomorrow's Therapeutics

CONFERENCE PROGRAMS

APRIL 10

- Covalent Modifications & Induced Proximity
- Targeting Transcription Factors

APRIL 11 - 12

- Protein Degraders & Molecular Glues - Part 1
- Fragment-Based Drug Discovery
- RNA-Targeting Small Molecule Drugs
- Artificial Intelligence for Early Drug Discovery - Part 1
- Small Molecule Immuno-Modulators

APRIL 12 - 13

- Protein Degraders & Molecular Glues - Part 2
- Protein-Protein Interactions
- bRo5: Macrocyclics, Degraders & More
- Artificial Intelligence for Early Drug Discovery - Part 2
- Encoded Libraries for Drug Discovery

PLENARY KEYNOTES

Targeting Nodes and Edges in Protein Networks
Michelle Arkin, PhD
Chair and Distinguished Professor, Pharmaceutical Chemistry, University of California, San Francisco

Reflections on a Career as a Medicinal Chemist in Drug Discovery
Nicholas A. Meanwell, PhD
Vice President (recently retired), Small Molecule Drug Discovery, Bristol Myers Squibb Co.

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Drug Discovery Chemistry CONFERENCE AT-A-GLANCE

MONDAY, APRIL 10	TUESDAY, APRIL 11	WEDNESDAY, APRIL 12	THURSDAY, APRIL 13
Covalent Modifications & Induced Proximity	Protein Degraders & Molecular Glues - Part 1	Protein Degraders & Molecular Glues - Part 2	
Targeting Transcription Factors	Fragment-Based Drug Discovery	Protein-Protein Interactions	
Pre-Conference In-Person Dinner Short Courses*	RNA-Targeting Small Molecule Drugs	bRo5: Macrocyclics, Degraders & More	
	Artificial Intelligence for Early Drug Discovery - Part 1	Artificial Intelligence for Early Drug Discovery - Part 2	
	Small Molecule Immuno-Modulators	Encoded Libraries for Drug Discovery	
		In-Person Dinner Short Courses on Wednesday *	

**Premium or Separate Registration Required*

PLENARY KEYNOTES

TUESDAY, APRIL 11

Targeting Nodes and Edges in Protein Networks

Michelle Arkin, PhD, *Chair and Distinguished Professor, Pharmaceutical Chemistry & Director, Small Molecule Discovery Center, University of California, San Francisco*

Michelle Arkin is Professor and Chair of Pharmaceutical Chemistry at the University of California, San Francisco, and co-director of the Small Molecule Discovery Center. Her lab focuses on developing chemical probes and drug leads for novel targets, with a particular interest in protein-protein interactions and protein-degradation networks. Prior to UCSF, Michelle worked at Sunesis Pharmaceuticals, where she helped discover protein-protein interaction inhibitors for IL-2 and LFA-1 (lifitigrast, marketed by Novartis). She is a co-founder of Ambagon and Elgia Therapeutics.

THURSDAY, APRIL 13

Reflections on a Career as a Medicinal Chemist in Drug Discovery

Nicholas A. Meanwell, PhD, *Vice President (recently retired), Small Molecule Drug Discovery, Bristol Myers Squibb Co.*

Dr. Nicholas Meanwell, who retired in October 2022, was a Scientific Vice President in the Department of Small Molecule Drug Discovery at Bristol Myers Squibb. Over his 40-year career at BMS, he has led drug discovery programs in the cardiovascular, neurosciences, and virology therapeutic areas, research that has resulted in the advancement of 33 clinical candidates for the prevention of thrombosis, the treatment of stroke (MaxiPost), and therapy for viral infections, including RSV, HIV-1 (Rukobia), and HCV (Daklinza, Sunvepra, Xymency). He is the author of more than 300 publications and is named as an inventor on more than 140 issued U.S. Patents. Among his many contributions to the medicinal chemistry community and awards received, he is the current Perspectives Editor for the *Journal of Medicinal Chemistry*, he was inducted into the ACS Division of Medicinal Chemistry Hall of Fame in 2015, was the recipient of the 2015 Philip S. Portoghese Medicinal Chemistry Lectureship Award and the 2022 Alfred Burger Award in Medicinal Chemistry. He is a Fellow of the Royal Society of Chemistry and the American Chemical Society.

TRACK-HOPPING

Attendees at Drug Discovery Chemistry are encouraged to "track-hop" between concurrent sessions: Though you register for a particular conference, in reality you gain access to all concurrent conferences. For the best value and to best fit your research needs, select a Premium registration that gives you access to all 10 conferences, 2 symposia, plus 2 short courses over four days of programming. Your registration also includes On-Demand access for one year to access these concurrent conferences.

DINNER SHORT COURSES*

*Premium or Separate Registration Required
Short courses take place in-person only

MONDAY, APRIL 10 6:00-8:30 PM

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

Instructor:

John Erve, PhD, President, 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: Indigo H

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

Instructors:

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

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

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

ROOM LOCATION: Indigo D

SC3: 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, Director, 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: Indigo 202

SC4: Generative and Predictive AI Modeling for Protein Inhibitors and Degraders

Instructors:

Petrina Kamya, PhD, Head of AI Platforms and President of Insilico Medicine, Canada

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

Drug discovery has always been experimenting with new approaches to find novel molecules with desirable properties. Currently, we are witnessing three approaches in the spotlight. The first one is a new set of AI techniques for designing and predicting *in silico* molecules. The next trend is exploring the massive search space of biomolecules and designing peptides with desirable properties. The third trend is the emergence of a new therapeutic modality itself. That is, instead of designing traditional inhibitors, now we can dream about designing molecular glues and PROTACs as target degraders. With these recent developments, this course will cover various AI techniques applied in generative and predictive models for small molecule inhibitors and peptide design. We hope this course will shed light on AI driven molecular design and how that can be applied for PROTACs degrader design.

ROOM LOCATION: Indigo 204

WEDNESDAY, APRIL 12 6:15-8:45 PM

SC5: Protein Degraders: A Focus on PROTACs from an ADME-Tox Perspective

Instructors:

John Erve, PhD, President, Jerve Scientific Consulting

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

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 gives rise to some drug safety issues not seen in small molecules, which will be discussed. Finally, we will explore the possible relevance of circadian rhythm to protein degradation and PROTACs.

ROOM LOCATION: Indigo H

SC6: Principles of Drug Design: Ligand-Receptor Interactions and More

Instructor:

Maricel Torrent, PhD, Principal Research Scientist, Computational Drug Discovery, AbbVie, Inc.

This course provides an overview of protein-ligand interactions and drug design principles. The presentation is targeted to medicinal chemists. The course starts by covering hydrophobic, H-bonding and electrostatic interactions. Then the course moves into coverage of specialized topics such as conformation analysis, pi-stack, cation-pi, halogen bonding, protein-protein interface, and covalent inhibition. Medicinal chemistry case studies are incorporated.

ROOM LOCATION: Indigo D

SC7: DNA-Encoded Libraries

Instructors:

Svetlana Belyanskaya, PhD, Vice President, Biology, Anagenex

Ghotas Evindar, PhD, Senior Vice President, Head of Drug Discovery, 1859, Inc.

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.

ROOM LOCATION: Indigo 202

SC8: 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.

ROOM LOCATION: Indigo 204

Covalent Modifications & Induced Proximity

Innovative Chemistries and Strategies Driving Covalent Drug Discovery

MONDAY, APRIL 10

12:00 pm Pre-Conference Symposium Registration Open (Indigo West Foyer)

1:00 Welcome Remarks

ROOM LOCATION: Indigo D

1:10 Chairperson's Remarks

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

1:15 In-Cell Proteome-Wide Covalent Ligand Discovery

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

Many proteins exist in unique conformations or form interactions present only within their native cellular environment. We have developed proteome-wide cysteine profiling methods and identified covalent fragments with high occupancy for therapeutically relevant targets. Key insights, examples, and lessons learned will be presented.

1:45 FEATURED PRESENTATION: A New Class of Therapeutics Based on Chemically-Induced Proximity

Gerald Crabtree, MD, David Korn Professor of Experimental Pathology & Developmental Biology, Stanford University

With Stuart Schreiber's group we developed chemical inducers of proximity to probe the role of this fundamental physical process in biologic mechanisms such as signal transduction, transcription, epigenetics, protein location, regulation and stability. These early studies used genetically tagged proteins or nonspecific small molecules, but pointed the way to approaches using no genetic tags that capitalize on underlying biologic specificity. I will discuss some of the later in more detail.

2:15 Targeted Covalent Inhibitor Assay Strategies: ADME Perspective

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

Targeted covalent inhibitor (TCI) approaches are an emerging small molecule drug modality where a covalent bond between a drug and a target protein forms by design. TCI drugs are regaining momentum as an attractive small molecule drug modality that can be applied to protein targets which have been previously considered undruggable. This presentation will discuss the challenges and strategies for the development of TCI drugs from ADME perspective.

2:45 Networking Refreshment Break

3:15 A Photocatalytic Toolbox for Mapping Novel Protein Pairings at the Cell Surface

Rob Oslund, PhD, Vice President, Platform Technologies, InduPro, Inc.

Inherent proximity of cell surface protein environments not only influences how proteins function but also informs our ability to effectively target/modulate cell surfaces for therapeutic benefit. This talk will describe the development of a novel light-mediated catalytic proximity labeling toolbox for identifying proximal protein environments for clinically-relevant surface proteins as well as downstream applications of the technology.

ROOM LOCATION: Indigo D

3:45 FEATURED PRESENTATION: Reimagining Druggability Using Chemoproteomic Platforms

Daniel Nomura, PhD, Professor of Chemistry, Molecular and Cell Biology, Nutritional Sciences and Toxicology, University of California, Berkeley

We currently have three major research directions. One of the areas that we focus on uses chemoproteomics-enabled covalent ligand discovery platforms to develop new induced proximity-based therapeutic modalities. This talk will focus on using covalent chemoproteomic strategies for drugging undruggable oncogenic transcription factors and also developing new induced proximity-based therapeutic modalities beyond degradation.

4:15 In-Person Group Discussion

In-Person Group 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 In-Person Group Discussions page on the conference website for a complete listing of topics and descriptions.

IN-PERSON GROUP DISCUSSION: Emerging Covalent and Degradation Strategies for Difficult Drug Targets

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

5:00 Close of Symposium

5:00 Dinner Short Course Registration (Indigo West Foyer)

6:00 Dinner Short Courses*

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

Targeting Transcription Factors

Novel Approaches to Modulate Seemingly Undruggable Targets

MONDAY, APRIL 10

12:00 pm Pre-Conference Symposium Registration Open (Indigo West Foyer)

1:00 Welcome Remarks

ROOM LOCATION: Indigo H

1:10 Chairperson's Remarks
Erica Jackson, PhD, Executive Vice President, Target Biology, Scorpion Therapeutics

1:15 Novel Tools and Strategies for Transcription Factor Drug Discovery
Erica Jackson, PhD, Executive Vice President, Target Biology, Scorpion Therapeutics

Transcription factors (TFs) are critical cancer drivers making them compelling targets for small molecule inhibition. The use of chemical proteomics to screen covalent small molecule libraries in live cells has enabled the identification of compounds that bind in previously unrecognized pockets on TFs. Creative approaches to developing biophysical and functional assays can overcome the challenges of working with recombinant TF proteins and provide a path toward drugging these important targets.

1:45 Potent, Orally-Bioavailable, Efficacious TEAD Inhibitors
Stephen Gwaltney, PhD, Head, Drug Discovery, SpringWorks Therapeutics

Activity of the YAP/TAZ-TEAD complex represents a compelling pharmacologic target. We have identified novel small molecules that bind to the TEAD auto-palmitoylation pocket and these compounds are highly potent, orally bioavailable, and active against multiple cancer cell lines. *In vivo* models of Hippo pathway-altered xenografts showed that our inhibitors deliver consistent monotherapy activity, with dose-dependent and durable tumor regressions achieved at well-tolerated doses.

2:15 FEATURED PRESENTATION: Targeting the Transcription Factor MYC through WDR5
Stephen W. Fesik, PhD, Professor of Biochemistry, Pharmacology, & Chemistry; Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University

One third of all cancer deaths in the United States are attributable to over-expression or activity of the transcription factor MYC. WD repeat domain 5 (WDR5) is a cofactor of MYC that is required for localizing WDR5 and MYC to chromatin. Rather than targeting MYC directly, we have discovered potent WDR5 inhibitors which disrupt MYC's function and show promising activity in a variety of tumors.

2:45 Networking Refreshment Break

3:15 PLX-4107, A Selective IKZF2 Degrader, Reprograms Suppressive Regulatory T Cells in Solid Tumors
Peggy Thompson, PhD, Vice President and Head of Biology, Plexium, Inc.

The transcription factor IKZF2 is required for maintaining stable Tregs. Depletion of IKZF2 converts Tregs into effector-Tcells and loss of suppressive activity. Protein degradation enables targeting undruggable proteins without known ligand binding-sites (i.e. IKZF2). PLX-4107 was designed to induce a novel interaction between IKZF2 and the E3 Cereblon promoting protein degradation. PLX-4107 selectively degrades IKZF2 resulting in Treg conversion into effector-like Tcells, antitumor activity and enhanced immune checkpoint therapy efficacy.

ROOM LOCATION: Indigo D

3:45 FEATURED PRESENTATION: Reimagining Druggability Using Chemoproteomic Platforms
Daniel Nomura, PhD, Professor of Chemistry, Molecular and Cell Biology, Nutritional Sciences and Toxicology, University of California, Berkeley

We currently have three major research directions. One of the areas that we focus on uses chemoproteomics-enabled covalent ligand discovery platforms to develop new induced proximity-based therapeutic modalities. This talk will focus on using covalent chemoproteomic strategies for drugging undruggable oncogenic transcription factors and also developing new induced proximity-based therapeutic modalities beyond degradation.

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IN-PERSON GROUP DISCUSSION: Emerging Covalent and Degradation Strategies for Difficult Drug Targets
Daniel A. Erlanson, PhD, Senior Vice President, Innovation and Discovery, Frontier Medicines Corporation

5:00 Close of Symposium

5:00 Dinner Short Course Registration (Indigo West Foyer)

6:00 Dinner Short Courses*
*Premium Pricing or separate registration required. See Short Courses page for details.

Protein Degraders & Molecular Glues - Part 1

Designing and Optimizing PROTACs and Glues for Pursuing Undruggable Targets

6:00 pm MONDAY, APRIL 10: Dinner Short Course*

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

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

TUESDAY, APRIL 11

7:00 am Registration and Morning Coffee (Indigo West Foyer)

8:00 Welcome Remarks

ROOM LOCATION: Indigo H

STRUCTURAL AND MECHANISTIC CHARACTERIZATION

8:05 Chairperson's Remarks

Matthew Calabrese, PhD, Senior Director & Head, Structural & Molecular Sciences, Pfizer Global R&D

8:10 Structural and Biophysical Studies of Protein Degrader Ternary Complexes

Matthew Calabrese, PhD, Senior Director & Head, Structural & Molecular Sciences, Pfizer Global R&D

Protein degradation using heterobifunctional chimeras is a rapidly growing mechanism to alter protein function. Critical to this mechanism is the formation of a ternary complex in which the target protein is recruited to an E3 ligase. We report structural, biophysical, and cellular studies that expand our understanding of this process - shedding light on different degradation efficiencies for distinct recruitment mechanisms for Bruton's Tyrosine Kinase.

8:40 CoraFluor-Enabled TR-FRET Assay Strategies for Facile PROTAC Profiling

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

The pace of progress in drug discovery is highly dependent on the availability of robust and quantitative assay platforms that allow for straightforward but accurate characterization of the underlying molecular interactions and target abundance. We have developed novel TR-FRET-based assay systems to facilitate the characterization of PROTACs and molecular glue degraders, including the facile measurements of endogenous protein levels, target affinity profiling, and quantitative determination of ternary complex cooperativity.

9:10 Structural and Mechanistic Understanding of Cereblon as a Target of Molecular Glues

Edmond Watson, PhD, Senior Scientist, Bristol Myers Squibb Co.

Cereblon is both a substrate adaptor protein for CRL4-mediated protein destruction, and the target of several novel clinical compounds which redirect this destructive activity to degrade "undruggable" substrates of interest. Though previous crystallographic structures existed, we use Cryo-EM to study the cereblon apoenzyme and directly compare it with several liganded and substrate-engaged states. This ensemble analysis reveals important allosteric changes to the mechanistic cycle of cereblon.

9:40 Navigating Your Chemistry & Exploring the Biology of Protein Degraders

PELAGO BIOSCIENCE

Michael Dabrowski, PhD, Head of Commercial Operations, Pelago Bioscience AB

Protein degradation is a novel modality with the potential to tackle therapeutically interesting proteins previously seen as undruggable. Pelago Biosciences AB will show how CETSA in combination with functional efficacy assays and quantitative proteomics can be applied in various stages of drug discovery to provide data that is both actionable and biologically relevant for targeting protein degradation.

9:55 Quantitative Analysis of Binding Affinities for Small Molecules Targeting STAT Transcription Factors

eurofins | DISCOVERY

Jean Bernatchez, PhD, Senior Scientist and San Diego R&D Group Leader, 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.

10:10 Networking Coffee Break (Indigo West Foyer)

EMERGING DEGRADER STRATEGIES

10:35 Chimeric BRM Degraders and Degrader-Antibody Conjugates

Peter S. Dragovich, PhD, Senior Fellow, Discovery Chemistry, Genentech, Inc.

The BRG1 (SMARCA4) protein is mutated in a subset of NSCLC, and such alterations make the cancers highly dependent on the closely-related BRM (SMARCA2) paralog for growth. The detailed characterization of a potent, heterobifunctional, chimeric BRM degrader compound using NSCLC cells and tumor models will be discussed. The conjugation of a second chimeric BRM degrader molecule to monoclonal antibodies to enhance its *in vivo* activity will also be described.

11:05 Targeted Degradation of Extracellular Proteins with ATACs (ASGPR-Targeting Chimeras)

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

Targeted protein degradation of disease-causing proteins is a promising new therapeutic modality. 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.

11:35 A Unique Covalent Strategy for Protein Degradation Which Co-Opts a Human DNA Repair Protein

Dennis Gillingham, PhD, Professor, Department of Chemistry, University of Basel

Most strategies in protein degradation focus on co-opting E3 ligases directly. Another strategy would be to find a native protein which is potently degraded (naturally or induced) and then hitchhike on that protein. I will present our work on using such an approach to coax the DNA repair protein methylguanine methyltransferase (MGMT) into degrading other target proteins.

12:05 pm Transition to Lunch

12:15 Your Discoveries Elevated

cytiva

Maria Lindgren, Scientist, R&D, Cytiva

Biacore 1 series, the next-generation SPR one needle platform, strikes the perfect balance between flexibility, capacity, and sensitivity to meet today's challenges in drug discovery. Biacore 1S+ provides robustness and reproducibility together with the highest level of sensitivity in the sub-resonance units (mRU) response range needed for working with rare and challenging protein targets. Analysis of fragment screening applications is simplified by Biacore Insight Software combined with Biacore Intelligent Analysis.

12:45 Session Break

Protein Degraders & Molecular Glues - Part 1

Designing and Optimizing PROTACs and Glues for Pursuing Undruggable Targets

PURSUING DIFFICULT DRUG TARGETS

1:30 Chairperson's Remarks

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

1:35 *In cellulo* PROTAC Assembly from Reversibly Interacting Components

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

A significant drawback of PROTACs is their large size, which will likely limit bioavailability, especially to the CNS and in solid tumors. Here we show that rapidly reversible bio orthogonal reactions can be employed to assemble active PROTACs inside of cells from their component target protein and E3 Ub ligase ligands. These much smaller pieces may exhibit superior bioavailability and *in vivo* efficacy for some applications.

2:05 A Functional Zinc Finger Transcription Factor Degrader

Bee Hui Liu, PhD, Senior Scientist, Cancer Science Institute of Singapore, National University of Singapore

The zinc finger transcription factor SALL4 is an ideal target in cancer, but small-molecule therapies against SALL4 are not yet clinically available. We have deduced the crystal structure of the complex of SALL4 bound to DNA via zinc finger cluster 4 (ZFC4), followed by computational predictions and cell-based drug screening identification of a new lead molecule that preferentially targets SALL4 positive cancer cells.

2:35 Discover Protein Degraders for Cancer Therapy: Expect the Unexpected

Yu Shen, PhD, Director, Cancer Biology, AbbVie, Inc.

PROTACs as a nascent technology have shown early promises and the field witnessed an explosion of discovery and development activities recently. In this presentation, we will share some learnings from multiple programs over the last 6 years, including our understanding of potential resistant mechanisms and some unexpected findings on selectivity, toxicity, etc.

3:05 Overcome Challenges in the Characterization of PROTAC Binary and Ternary Complexes to get your Projects Back on Track

Mariano Cardenas, PhD., Product Manager, Product, NanoTemper Technologies

Developing protein degraders is a multi-step and complex process. Using appropriate biochemical and biophysical methods is crucial to selecting the right candidates with confidence. Common roadblocks during the characterization of ternary complexes, cooperativity, and hook effect are low-quality data, immobilization of covalent binders or multimeric molecules, and complex protocols. In this talk, you'll learn how Dianthus, a plate-based screening platform, overcomes these roadblocks from case studies representing difficult drug targets.

3:20 Refreshment Break in the Exhibit Hall with Poster Viewing (Indigo A-G)

ROOM LOCATION: Indigo D+H

PLENARY KEYNOTE SESSION

4:20 Plenary Welcome Remarks from Lead Content Director with Poster Finalists Announced

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

4:35 PLENARY: Targeting Nodes and Edges in Protein Networks

Michelle Arkin, PhD, Chair and Distinguished Professor, Pharmaceutical Chemistry & Director, Small Molecule Discovery Center, University of California, San Francisco

Protein interaction networks consist of protein nodes and interaction edges. We aim to inhibit or stabilize specific protein-protein interactions to dissect these complex networks for chemical biology and therapeutics discovery. Through covalent fragment-based approaches, we discovered compounds that selectively stabilized the chaperone 14-3-3 bound to diverse client proteins and altered their function. Additionally, function-selective inhibitors for the multifunctional enzyme VCP/p97 are providing new tools and drug leads for cancer.

5:30 Welcome Reception in the Exhibit Hall with Poster Viewing (Indigo A-G)

6:30 Close of Day

WEDNESDAY, APRIL 12

7:00 am Registration Open (Indigo West Foyer)

7:45 In-Person Group Discussions with Continental Breakfast

In-Person Group 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 In-Person Group Discussions page on the conference website for a complete listing of topics and descriptions.

IN-PERSON GROUP DISCUSSION: Tools for Structural and Mechanistic Characterization of Protein Degraders

Matthew Calabrese, PhD, Senior Director & Head, Structural & Molecular Sciences, Pfizer Global R&D

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

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

Edmond Watson, PhD, Senior Scientist, Bristol Myers Squibb Co.

- Structural, biophysical, and cellular studies to expand our understanding of protein degradation
- New assay systems to facilitate the characterization of PROTACs and molecular glue degraders
- Chemoproteomic methods to discover additional E3 ligases
- Cryo-EM to study and compare ligand binding and conformational changes

ROOM LOCATION: Indigo H

FRAGMENTS AND TARGETED PROTEIN DEGRADATION APPROACHES

8:30 Chairperson's Remarks

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

8:35 FEATURED PRESENTATION: Fragment Approaches for Discovering Tissue-Specific E3 Ligases and β-Catenin Degraders

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

I will present how we've applied fragment-based methods to discover ligands for tissue-specific E3 ligases. I will also cover our work on

discovering bifunctional degraders for β-catenin. This highly sought-after but difficult-to-drug intracellular target is part of a multi-functional cellular signaling complex whose overactivity contributes to the development of specific cancers and other diseases.

9:35 Coffee Break in the Exhibit Hall with Poster Awards Announced (Indigo A-G)
Poster Award (Sponsorship Opportunity Available)

EXPLORING NEW E3 LIGASES

10:30 Discovery of Novel E3 Ligands for Targeted Protein Degradation
Yue Xiong, PhD, Co-Founder & CSO, Cullgen
Targeted protein degradation separates from other drug discovery modalities by its catalytic mechanism to achieve high efficacy, the ability to target previously undruggable proteins, and its potential to deliver drug activity to selective tissues. All three features depend on the E3 ligands, which are currently limited despite the expression of more than 600 E3 ligases in human cells. I will discuss our rationale and efforts in discovering novel E3 ligands.

11:00 Expanding the Landscape of E3 Ligases for Targeted Protein Degradation
Xiaoyu Zhang, PhD, Assistant Professor, Department of Chemistry, Northwestern University
The field of small molecule-mediated protein degradation has grown tremendously over the past few years. Nonetheless, only a handful of E3 ligases have been identified to support this process. We have developed a chemoproteomic method to discover additional E3 ligases capable of supporting small molecule-mediated protein degradation and identified two novel E3 ligases, DCAF16 and DCAF11, as the targets of electrophilic bifunctional degraders that engage diverse protein substrates.

11:30 Explore the Target Scope of KEAP1 E3 Ligase-Based PROTACs
Guangyan Du, PhD, Scientist II, Department of Chemistry, Blueprint Medicines
A major challenge in the TPD field is the lack of accessible E3 ligase ligands for developing degraders. To expand the E3 ligase toolbox, we sought to convert the KEAP1 inhibitor into a recruitment handle for several targets. We characterize tool compounds to explore KEAP1-mediated ubiquitination and delineate the challenges of exploiting new E3 ligases for generating bivalent degraders.

12:00 pm Close of Protein Degraders & Molecular Glues - Part 1 Conference

Fragment-Based Drug Discovery

Small Molecule Hits to Leads to Drug Candidates via FBDD

6:00 pm MONDAY, APRIL 10: Dinner Short Course*

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

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

TUESDAY, APRIL 11

7:00 am Registration and Morning Coffee (Indigo West Foyer)

8:00 Welcome Remarks

ROOM LOCATION: Indigo D

CASE STUDIES: FRAGMENT-ASSISTED DRUG DISCOVERY

8:05 Chairperson's Remarks
Chaohong Sun, PhD, Senior Director, Lead Discovery, AbbVie, Inc.

8:10 FEATURED PRESENTATION: Inhibiting TEAD Using Fragment Approaches
Timo Heinrich, PhD, Associate Scientific Director, Oncology, EMD Serono
The deeply buried lipidation pocket (P-site) of the TEAD transcription factors is druggable. The SPR-triggered fragment hit discovery and cellular optimization of a P-site binder are described. Utilizing structure-enabled design, based on the established X-ray structures of TEAD1 and TEAD3, on-target potency was improved 4000-fold. The efforts culminated in the TEAD1 selective tool compound MSC-4106, which exhibited desirable potency, mouse PK properties, and *in vivo* efficacy.

8:40 Evolving a Fragment-Like Molecule to Multiple Clinical Candidates: Novel Pan-Metallo-β-Lactamase Inhibitors (MBLi) for Potentiation of β-Lactam-Based Antibiotics
Mihir Mandal, PhD, Principal Scientist, Medicinal Chemistry, Merck
Metallo-ß-lactamases, such as NDM-1, VIM-1, and IMP-1 possess poor homology in their active sites. Despite their poor homology, a class of compounds having a biphenyl tetrazole (BPT) core – identified earlier as a *B. fragilis* metallo-beta-lactamase inhibitor with weak inhibitory activity against NDM-1 in a biochemical assay – was evolved into pan inhibitor first then into multiple clinical candidates.

9:10 Fragment Optimization and Elaboration Strategies – The Discovery of Two Lead Series of PRMT5/MTA Inhibitors from Five Fragment Hits
Chris Smith, PhD, Executive Director, Drug Discovery, Mirati Therapeutics
Here we report the discovery of two lead series from five fragment hits for our PRMT5/MTA program. The hits were identified via an SPR fragment screen followed by X-ray crystallography. We will outline a two-phase process encompassing fragment optimization followed by fragment growing strategies. Access to versatile synthetic intermediates, synthetic traceability, and enablement of structure-based drug design were important success factors.

9:40 Using WAC™ for Identification and Characterization of a Novel Binding Site on the SMARCA4 Bromodomain
Kirill Popov, Head of FBLD, Weak Affinity Chromatography WAC
WAC™ was used to perform a fragment screen towards the bromodomain of SMARCA4. In addition to hits binding to the KAc site, some hits bound to a second site outside the KAc pocket. Here we present hit validation and expansion efforts toward this novel site.

9:55 Efficient Identification of PIM1 Kinase Inhibitors via the LCC 3Discovery Platform
Tony Huxley, Head of Business Development, Business Development, Liverpool ChiroChem Ltd.
A new chemotype targeting PIM1 has been discovered via FBDD and lead optimisation performed using LCC's 3Discovery platform.
LCC's 3Discovery lead-like virtual library is enumerated using 3D-rich fragment library compounds including single enantiomers and enantiopairs with determined absolute stereochemistry, poised for rapid fragment elaboration and hit expansion through parallel synthesis.
This presentation will describe the identification and validation of the initial fragment hit, early lead optimisation and opportunities for further exploration.

10:10 Networking Coffee Break (Indigo West Foyer)

10:35 Attacking Intrinsically Disordered Protein with Fragments
Haihong Wu, PhD, Senior Scientist II, Global Protein Sciences, AbbVie, Inc.
Aggregation of the tau, an intrinsically disordered protein (IDP), into neurofibrillary tangles is one of the hallmarks of Alzheimer's disease (AD). In this presentation, we discuss a fragment-based approach, employing protein NMR, to discover tau binders that could potentially disrupt tau aggregation. Chemical elaboration of fragment hits, driven by both NMR and surface plasmon resonance (SPR), resulted in tau binders with affinities in the low double-digit micromolar range.

11:05 Discovery of Renin Inhibitors via Fragment-Based Drug Design
Tanweer A. Khan, PhD, Director & Head, Discovery Chemistry, ATAI Life Sciences
Renin is an aspartic protease enzyme and the development of renin inhibitors with favorable oral pharmacokinetic profiles has been a longstanding challenge for the pharmaceutical industry. Based on initial BACE1 inhibitors, a repertoire iminopyrimidinones is a novel pharmacophore for aspartyl protease inhibition. This presentation describes how we leverage structural information from the database and modified substitution around this pharmacophore to develop a potent, selective, and orally active renin inhibitor.

11:35 Drug Repurposing via a Fragment-Based Reconstruction Approach
Xavier Morelli, PhD, Director of Research, Cancer Research Center of Marseille, CNRS
The discovery & development of new drugs is a highly costly and slow process while repositioning old drugs to treat other diseases is increasingly becoming an attractive proposition. In this context, at the interface between drug design and drug repositioning, we decided to apply our integrative multidisciplinary drug design approach, DOTS, to deconstruct and optimize an existing drug in a Fragment-Based 'Hit-to-Lead' optimization approach on a newly validated target.

12:05 pm Transition to Lunch

12:15 FragmentDEL-DNA-Encoded Libraries of Fragments for Hit Discovery for Challenging Targets
Rod Hubbard, Professor, Founding Scientist, Director of Research Collaborations, Vernalis (R&D) Ltd.
Combining the sensitivity of DEL and chemical space coverage of fragments is a new approach for identification of hit compounds for challenging targets. This has been demonstrated with PAC-FragmentDEL, where photoactivation

captures the fragment binding to the target. As well as describing additional applications this approach, I will describe the design and use of other ideas for FragmentDELs.

12:45 Session Break

COVALENT FRAGMENTS

1:30 Chairperson's Remarks
Mela Mulvihill, PhD, Director and Senior Principal Scientist, Biochemical & Cellular Pharmacology, Genentech, Inc.

1:35 Drug Discovery Applications of Covalent Fragments in Neuroscience
Jeffrey Martin, PhD, Scientist II, Drug Discovery, Biogen
An overview of reactive cysteines in neuroscience focused research will be discussed. Approaches for covalent fragment screening and drug discovery applications will also be covered.

2:05 Covalent Fragments and Targeting Lysines
Maurizio Pellecchia, PhD, Professor, Biomedical Sciences Division, University of California, Riverside
With the resurgence and the success of Cys-covalent drugs, our studies focus on the identification and the optimization of effective design strategies that widen the available target space beyond cysteine, to include other more abundant residues such as lysine, tyrosine, or histidine. I will report on fragment- and structure-based strategies that include the design of potent and selective Lys- and His-covalent agents targeting oncogenic proteins.

2:35 Reverse Polarity Activity-Based Protein Profiling
Megan L. Matthews, PhD, Assistant Professor, Chemistry, University of Pennsylvania
The polar chemistry of activity-based protein profiling (ABPP) probes was reversed by deploying the nucleophilic hydrazine pharmacophore found in old CNS drugs to show organohydrazines are active-site directed and mechanism-based inhibitors of protein classes that are difficult to drug. Using the first N-nucleophile fragment/probe library, we showed that potent and selective inhibitors can be developed and that reverse-polarity ABPP can advance small molecules that modulate diverse electrophile-dependent functions.

3:05 Leveraging Cryo-Electron Microscopy to Reshape Drug Discovery Landscape
Surajit Banerjee, Dr., Sr. Product Specialist, Life Sciences, Materials & Structural Analysis Division, Thermo Fisher Scientific
Cryo-EM has evolved to a mainstream structural biology method and a game-changing technology for structure-based drug discovery of challenging targets. It was adopted as a well-established technique in the pharmaceutical industry due to its ability to visualize macromolecular assemblies and investigate the intricate interactions between drugs and receptors. How Cryo-EM rapidly overcoming its limitations for more widespread usage through a new wave of technological advances, will be discussed.

3:20 Refreshment Break in the Exhibit Hall with Poster Viewing (Indigo A-G)

ROOM LOCATION: Indigo D+H

PLENARY KEYNOTE SESSION

4:20 Plenary Welcome Remarks from Lead Content Director with Poster Finalists Announced
Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

4:35 PLENARY: Targeting Nodes and Edges in Protein Networks
Michelle Arkin, PhD, Chair and Distinguished Professor, Pharmaceutical Chemistry & Director, Small Molecule Discovery Center, University of California, San Francisco
Protein interaction networks consist of protein nodes and interaction edges. We aim to inhibit or stabilize specific protein-protein interactions to dissect these complex networks for chemical biology and therapeutics discovery. Through covalent fragment-based approaches, we discovered compounds that selectively stabilized the chaperone 14-3-3 bound to diverse client proteins and altered their function. Additionally, function-selective inhibitors for the multifunctional enzyme VCP/p97 are providing new tools and drug leads for cancer.

5:30 Welcome Reception in the Exhibit Hall with Poster Viewing (Indigo A-G)

6:30 Close of Day

WEDNESDAY, APRIL 12

7:00 am Registration Open (Indigo West Foyer)

7:45 In-Person Group Discussions with Continental Breakfast
In-Person Group 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 In-Person Group Discussions page on the conference website for a complete listing of topics and descriptions.

IN-PERSON GROUP DISCUSSION: Developments in Fragment-Based Drug Discovery
Ben J. Davis, PhD, Research Fellow, Biology, Vernalis R&D Ltd.
Mela Mulvihill, PhD, Director and Senior Principal Scientist, Biochemical & Cellular Pharmacology, Genentech, Inc.
Justyna Sikorska, PhD, Associate Principal Scientist, Mass Spectrometry & Biophysics, Merck
- Progressing fragments without routine structural data
- How to evolve extremely weak fragments (X-ray crystallography (low cost possible?), cryo-EM)
- Innovations for FBDD (DNA-encoded libraries for fragments?)
- FBDD for challenging targets (RNA, ion channels, complex assemblies, disordered proteins)
- Can fragments speed TPD discovery?
- Covalent fragment applications

ROOM LOCATION: Indigo H

FRAGMENTS AND TARGETED PROTEIN DEGRADATION APPROACHES

8:30 Chairperson's Remarks
Daniel A. Erlanson, PhD, Senior Vice President, Innovation and Discovery, Frontier Medicines Corporation

8:35 FEATURED PRESENTATION: Fragment Approaches for Discovering Tissue-Specific E3 Ligases and β-Catenin Degraders

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

I will present how we've applied fragment-based methods to discover ligands for tissue-specific E3 ligases. I will also cover our work on discovering bifunctional degraders for β-catenin. This highly sought-after but difficult-to-drug intracellular target is part of a multi-functional cellular signaling complex whose overactivity contributes to the development of specific cancers and other diseases.

9:35 Coffee Break in the Exhibit Hall with Poster Awards Announced (Indigo A-G)

Poster Award

ROOM LOCATION: Indigo D

FRAGMENTS, COVALENT INHIBITORS, KRAS

10:30 A New Covalent Fragment Screening Method for Efficient Covalent Drug Discovery

Jim Nonomiya, Scientist IV, Biochemical and Cellular Pharmacology, Genentech, Inc.

The discovery of a targetable cryptic pocket in KrasG12C has ignited interest in covalent targeting and, in particular, fragment-based screening approaches to identify covalent ligands for difficult-to-drug targets. I will introduce a novel screening method that aims to streamline the covalent drug discovery process by simultaneously providing binding site information.

11:00 NMR and KRAS Fragments

Julien Orts, PhD, Assistant Professor, Physical Chemistry Lab, ETH Zurich

The current state-of-the-art in fragment optimization is structure-based drug design, and it is recommended to have a path to 3D structural information. This talk aims to present the current possibilities in NMR when starting a fragment-based drug design discovery campaign. We will therefore present an NMR pipeline from fragment screening to 3D structure, targeting the protein KRAS. We will also present our latest NMR developments for structure-based drug design by NMR.

11:30 Small-Molecule Cyanamide Pan-TEAD·YAP1 Covalent Antagonists

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

TEADs transcription factors bind to co-activators YAP1 or TAZ to promote tumor growth and metastasis. We report isoindoline and octahydroisoindole small molecules with a cyanamide electrophile that form a covalent complex with a cysteine in the TEAD palmitate cavity. Compounds inhibited YAP1 binding to TEADs and cocrystal structures revealed their binding mode. Compounds inhibited TEAD1-4 transcriptional activity in mammalian cells. Several compounds inhibited cell viability in several cancer cell lines.

12:00 pm Biophysical and Structural Biology Methods Enable Fragment-based Covalent Ligand Discovery of Human BTK

Moran Jerabek-Willemsen, Head of Biophysics & Screening, WuXi HitS, WuXi AppTec

Powerful biophysical and structural biology tools enable the study of large numbers of covalent fragments and are opening up new possibilities in the treatment of various diseases. Here we report the results of a covalent FBDD project on Bruton's Tyrosine Kinase (BTK) and show how orthogonal biophysical and structural methods enable rapid identification, characterization, and optimization of covalent fragments.

12:15 Close of Fragment-Based Drug Discovery Conference

6:15 Dinner Short Course*

SC8: Biophysical Tools for Membrane Proteins: Drug Discovery Applications

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

RNA-Targeting Small Molecule Drugs

Novel Strategies to Modulate RNA Structure, Binding, Interactions, and Function

TUESDAY, APRIL 11

7:00 am Registration and Morning Coffee (Indigo West Foyer)

8:00 Welcome Remarks

ROOM LOCATION: Indigo 202
DEVELOPING RNA MODULATORS

8:05 Chairperson's Remarks
Thomas Hermann, PhD, Professor, Department of Chemistry & Biochemistry, University of California, San Diego

8:10 Discovery of Small Molecule mRNA Modulators Using Phenotypic Screening with AI-Driven MoA Elucidation
Iris Alroy, PhD, Co-Founder & CSO, Anima Biotech
Anima's phenotypic screening approach using mRNA Lightning platform systematically evaluates the impact of small molecules on mRNA translation into proteins. Combined with AI-driven MOA elucidation, Anima has identified and validated compounds that are binding to proteins which regulate mRNA translation, offering an opportunity for both tissue-selective and target-specific modulation. Anima's lead programs in fibrosis and oncology have demonstrated efficacy in animal and patient-derived models and are advancing toward preclinical development.

8:40 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.

9:10 Small Molecule Splicing Modulators Targeting Huntington's Disease
Longbin Liu, PhD, Science Director, Medicinal Chemistry, CHDI Foundation, Inc.
We describe the lead optimization of a series of HTT splicing modulators that are structurally distinct from those currently in the clinic and highlight the *in vitro* and *in vivo* PK/PD profiles of a lead compound.

9:40 Discovery of RNA Targeting Small Molecules: Our Toolbox for RNA Drug Discovery
药明康德 WuXi AppTec
Zhifeng Yu, PhD, Director, WuXi Biology, WuXi AppTec
New "DNA-Zipper" DEL technology significantly reduces interference between DNA tags and RNA molecules, addressing a key hurdle in screening scalability when targeting RNA with small molecules. With advances in complementary techniques such as ASMS, fragment screening, and SHAPE-MaP to verify RNA quality and characterize RNA-small molecule interactions, RNA-as-a-target now holds the promise of dramatically increasing the pool of druggable targets.

9:55 Sponsored Presentation *(Opportunity Available)*

10:10 Networking Coffee Break (Indigo West Foyer)

10:35 Discovery of Small Molecule RNA Binders That Selectively Stimulate Target RNA Degradation
Peng Yue, PhD, CoFounder & CEO, ReviR Therapeutics, ReviR Therapeutics
Small molecules present a superior modality that can broadly target tissues and cross the blood brain barrier by oral administration. In this presentation, we will discuss our efforts to selectively target undruggable RNAs with small molecules that induce RNA degradation at meaningful therapeutic concentrations. This presentation will explore the molecular basis for these interactions and examine the functional consequences of target suppression in cellular models of disease.

11:05 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.

11:35 PANEL DISCUSSION: Challenges with Translating RNA-Targeting Small Molecules into Drugs
Moderator: Thomas Hermann, PhD, Professor, Department of Chemistry & Biochemistry, University of California, San Diego
Panelists:
Peng Yue, PhD, CoFounder & CEO, ReviR Therapeutics, ReviR Therapeutics
Kathleen McGinness, PhD, Head of Platform Biology, Arrakis Therapeutics

12:15 pm Enjoy Lunch on Your Own

12:45 Session Break

ROOM LOCATION: Indigo 204
AI FOR TARGETING RNA

1:30 Chairperson's Remarks
Bryce Allen, PhD, Co-Founder & CEO, Differentiated Therapeutics

1:35 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. However, therapeutically targeting RBPs with small molecules has proven challenging. We present an integrated screening campaign integrating fragment-based differentiable design with molecular dynamics enabling the discovery of a novel non-functional RBP binder. We demonstrate the physics-driven optimization of this hit molecule to induce the proximity of an E3 ligase, facilitating the proteosome-specific degradation of an RBP and restoring a tumor-suppressive miRNA.

2:05 Application of Artificial Intelligence to Discover RNA-Targeting Small Molecules
Sridhar Narayan, PhD, Vice President, ReviR Therapeutics
High-throughput screening of RNA-targeting small molecules remains a challenge due to the lack of RNA-focused small molecule libraries. We applied AI-assisted technology to select a suitable small molecule library and carried out compound screening using ALIS. The increased hit rate was significantly higher compared to our previous campaigns, which demonstrates that AI-driven compound selection strategies can accelerate RNA-targeted small molecule drug discovery.

2:35 Unlocking the Druggable Universe of 3D RNA Structures with Artificial Intelligence
Raphael Townshend, PhD, Founder & CEO, Atomic AI
Atomic AI has developed PARSE, the Platform for AI-driven RNA Structure Exploration, which can locate 3D structures at unprecedented speed and accuracy in disease-relevant RNA targets. PARSE builds on our work featured on the cover of Science, and involves a tight integration of high-throughput wet-lab experiments and cutting-edge artificial intelligence capabilities. Through this data-driven approach, Atomic AI is enabling and pursuing drug discovery against undruggable targets.

3:05 Talk Title to be Announced
CDD VAULT Complexity Simplified
Speaker to be Announced

3:20 Refreshment Break in the Exhibit Hall with Poster Viewing (Indigo A-G)

ROOM LOCATION: Indigo D+H
PLENARY KEYNOTE SESSION

4:20 Plenary Welcome Remarks from Lead Content Director with Poster Finalists Announced
Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

4:35 PLENARY: Targeting Nodes and Edges in Protein Networks
Michelle Arkin, PhD, Chair and Distinguished Professor, Pharmaceutical Chemistry & Director, Small Molecule Discovery Center, University of California, San Francisco
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5:30 Welcome Reception in the Exhibit Hall with Poster Viewing (Indigo A-G)

6:30 Close of Day

WEDNESDAY, APRIL 12

7:00 am Registration Open (Indigo West Foyer)

7:45 In-Person Group Discussions with Continental Breakfast
In-Person Group 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 In-Person Group Discussions page on the conference website for a complete listing of topics and descriptions.

IN-PERSON GROUP DISCUSSION: Novel Tools and Strategies for Discovery of Small Molecules Targeting RNA
Thomas Hermann, PhD, Professor, Department of Chemistry & Biochemistry, University of California, San Diego
Ken Hsu, PhD, Stephen F. and Fay Evans Martin Endowed Associate Professor, Department of Chemistry, The University of Texas at Austin
Rabia Khan, PhD, MBA, CEO, Serna Bio
Anthony Mustoe, PhD, Assistant Professor, Department of Biochemistry and Molecular Biology, Baylor College of Medicine
- Emerging techniques to study RNA structure and function
- Chemoproteomic methods for systematic profiling of RNA-protein interactions
- Assays to determine if RNA binding/modulation leads to biological consequences
- Challenges and opportunities for developing small molecules targeting RNA
- Developing novel business models in a non-competitive space to accelerate the field

ROOM LOCATION: Indigo 202
PROBING RNA INTERACTIONS

8:30 Chairperson's Remarks
Ken Hsu, PhD, Stephen F. and Fay Evans Martin Endowed Associate Professor, Department of Chemistry, The University of Texas at Austin

8:35 Chemical Methods for Investigating the RNA Interactome
Ken Hsu, PhD, Stephen F. and Fay Evans Martin Endowed Associate Professor, Department of Chemistry, The University of Texas at Austin
We present an approach that utilizes clickable probes to directly quantify protein-RNA interactions on proteins. Our method facilitated global detection of RNA-interaction sites on RBPs that mediate recognition of coding and noncoding RNA. We performed functional profiling of known RNA-binding domains and discovery of RNA binding activity on proteins without prior RBP annotation. In summary, we present a chemoproteomic method for global quantification of protein-RNA binding activity in living cells.

9:05 Remodeling Oncogenic Transcriptomes by Small Molecules Targeting the RNA-binding Protein NONO
Stefan Kathman, PhD, Scientist, Early Discovery, Vividion Therapeutics
We have discovered compounds that covalently engage the RNA-binding protein NONO. These NONO ligands suppress mRNA of several cancer-relevant genes and impair cancer cell proliferation. Surprisingly, these effects were not observed in cells genetically disrupted for NONO, which were instead resistant to NONO ligands. The ligands promote NONO accumulation in nuclear foci and stabilize NONO-RNA interactions, supporting a trapping mechanism that prevents compensatory action of paralog proteins PSPC1 and SFPQ.

9:35 Coffee Break in the Exhibit Hall with Poster Awards Announced (Indigo A-G)
Poster Award (Sponsorship Opportunity Available)

10:30 Mapping the Druggable Transcriptome: AI-Enabled RNA Drug Discovery
Rabia Khan, PhD, MBA, CEO, Serna Bio
While the chemical properties of protein binders are increasingly understood and interrogated, the field of RNA-targeted drugs is relatively new and the properties of small molecules that drive specific and selective targeting of RNA, and associated assays, are yet to be developed. At Serna Bio [previously Ladder Therapeutics] we are using an AI enabled, data-first approach to write the rules that define RNA-small molecule interactions.

11:00 Small Molecules Affecting RNA Function: Target Validation and Functional Binding Assays
Thomas Hermann, PhD, Professor, Department of Chemistry & Biochemistry, University of California, San Diego
Targeting of RNA by small molecule drugs requires modification of RNA function or stability induced by ligand binding. Approaches that assess target performance upon structure modification in the context of biological function, and screening assays that couple ligand binding and structure modification are powerful tools to assess targeting RNA domains. I will discuss examples from targeting structured domains in human mRNA and viruses including HCV, Zika virus, and SARS CoV-2.

11:30 Discovering and Targeting Functional RNA Structures
Anthony Mustoe, PhD, Assistant Professor, Department of Biochemistry and Molecular Biology, Baylor College of Medicine
RNA structures play essential roles in directing RNA function and are key therapeutic targets. I will discuss our ongoing efforts to develop single-molecule chemical probing technologies to measure complex RNA and RNA-protein structures at high-resolution in living cells. I will further describe new RNA structural mechanisms revealed by these technologies, and our preliminary efforts to target RNA structures to control gene expression.

12:00 pm Close of RNA-Targeting Small Molecule Drugs Conference

AI for Early Drug Discovery - Part 1

Early Decision-Making for Driving Drug Design and Lead Optimization

6:00 pm MONDAY, APRIL 10: Dinner Short Course*

SC4: Generative and Predictive AI Modeling for Protein Inhibitors and Degraders

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

TUESDAY, APRIL 11

7:00 am Registration and Morning Coffee (Indigo West Foyer)

8:00 Welcome Remarks

ROOM LOCATION: Indigo 204

AI FOR DRUG DESIGN

8:05 Chairperson's Remarks
Tudor Oprea, MD, PhD, CSO, Expert Systems Inc.

8:10 AI and Informatics Navigation of Huge Chemical Spaces
Mark Seierstad, PhD, Senior Principal Scientist, Computer Aided Drug Discovery, Johnson & Johnson Pharmaceutical R&D
In recent years, the size of virtual libraries has greatly expanded by including not just already-available ligands but also ligands expected to be readily synthesizable from already-available building blocks. Within Janssen, we are expanding this space even further by identifying readily synthesizable building blocks as starting points for virtual libraries. This presentation will discuss early work in this area, recent successful implementations, and future-looking efforts.

8:40 3D Pride without 2D Prejudice: Bias-Controlled Generative Models for Structure-Based Design
Marcel Verdonk, PhD, Senior Director, Computational Chemistry & Informatics, Astex Pharmaceuticals
Generative models for structure-based molecular design hold significant promise for drug discovery, however, data sparsity and bias are two main roadblocks to the development of 3D-aware models. We present a first-in-kind protocol for bias control and data efficiency, combining large 2D medicinal chemistry data resources with datasets of 3D ligand-protein complexes. We will illustrate how this framework is used to deliver augmented interactive drug design to modelers and medicinal chemists.

9:10 Applying AI to Precision Engineer Medicines
Someina Khor, BSc, Associate Director, Computational Drug Design, Exscientia
Exscientia's motivation to produce better drugs faster has led to the pioneering approach of patient-first, AI-driven drug discovery, design, and development. This presentation will demonstrate how automation and multiple data types are incorporated in every step of our end-to-end pipeline and will showcase our variety of proprietary toolkits and how they are integrated into a design and optimisation workflow.

9:40 Makya and Modern Virtual Hit-Finding: Ultra-Large Libraries, Scaffold-Hopping, and Ensuring Synthesizability with Spaya
Brian Atwood, PhD, Application Scientist, Iktos
Makya is a generative design platform that makes use of reinforcement learning to optimize virtual molecules. We have used Makya in virtual hit-finding efforts to optimize not only predicted activity but also predicted ADME properties. Makya can now be used to find optimal compounds from within ultra-large libraries and scaffold hop with chemistry-focused algorithms. Makya also designs novel compounds with a focus on synthesizability thanks to our retrosynthesis tool Spaya.

10:10 Networking Coffee Break (Indigo West Foyer)

FEATURED SESSION: SEPARATING HOPE AND HYPE

10:35 Can Humans Learn from Machine Learning in Drug Discovery?
Tudor Oprea, MD, PhD, CSO, Expert Systems Inc.
Acquiring high-quality data is critical to the success of ML model deployment. Building such a knowledge graph based on genes, diseases and drugs informed an ML model which led to the identification of five novel genes associated with Alzheimer's disease. In addition to shortening the time from idea to cure, ML models can evaluate synthetic drug complexity with focus on sustainability. These lessons from ML model development will be discussed.

11:05 Repurposing and Machine Learning for COVID Drug Discovery
Sean Ekins, PhD, Founder & CEO, Collaborations Pharmaceuticals, Inc.
The small molecules approved for treating COVID are limited. Our machine learning efforts to repurpose molecules for Ebola led to novel molecules for COVID. We additionally explored developing machine learning models with quantum computing. We have progressed several molecules through *in vitro* and *in vivo* testing and identified several inhibitors of SARS-CoV-2. We also identified additional antiviral activities. The challenges and opportunities for this strategy will be presented.

11:35 End-to-End Drug Discovery Using AI and Robotics
Petrina Kamya, PhD, Head of AI Platforms and President of Insilico Medicine, Canada
Recent advances in AI technologies allowed for the development of end-to-end drug discovery platforms spanning multi-model target discovery, multiparameter molecular optimization, synthetic route planning, prediction of clinical trial outcomes, and many other steps. In this talk, we will show several case studies of end-to-end approaches and acceleration of target discovery using laboratory robotics.

February 2023 Speaker Interview with Dr. Kamya:
Watch Interview Online

12:05 pm Transition to Lunch

12:15 Introducing Promethium: Next-Gen Chemistry Simulation Software
Alicia Rae Welden, Technical Account Manager, QC Ware
This session will introduce Promethium, a revolutionary chemistry simulation platform developed by QC Ware, that will significantly accelerate the drug, material, and chemical discovery process. With its exceptional speed, accuracy, and system size capabilities, Promethium has the potential to transform the industry and bring immediate value to pharma companies. Join us to learn how Promethium can help you make breakthrough discoveries and take your research to the next level.

12:45 Session Break

ROOM LOCATION: Indigo 204

AI FOR TARGETING RNA

1:30 Chairperson's Remarks
Bryce Allen, PhD, Co-Founder & CEO, Differentiated Therapeutics

1:35 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. However, therapeutically targeting RBPs with small molecules has proven challenging. We present an integrated screening campaign integrating fragment-based differentiable design with molecular dynamics enabling the discovery of a novel non-functional RBP binder. We demonstrate the physics-driven optimization of this hit molecule to induce the proximity of an E3 ligase, facilitating the proteosome-specific degradation of an RBP and restoring a tumor-suppressive miRNA.

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Sridhar Narayan, PhD, Vice President, ReviR Therapeutics

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Speaker to be Announced

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ROOM LOCATION: Indigo D+H

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4:35 PLENARY: Targeting Nodes and Edges in Protein Networks

Michelle Arkin, PhD, Chair and Distinguished Professor, Pharmaceutical Chemistry & Director, Small Molecule Discovery Center, University of California, San Francisco

Protein interaction networks consist of protein nodes and interaction edges. We aim to inhibit or stabilize specific protein-protein interactions to dissect these complex networks for chemical biology and therapeutics discovery. Through covalent fragment-based approaches, we discovered compounds that selectively stabilized the chaperone 14-3-3 bound to diverse client proteins and altered their function. Additionally, function-selective inhibitors for the multifunctional enzyme VCP/p97 are providing new tools and drug leads for cancer.

5:30 Welcome Reception in the Exhibit Hall with Poster Viewing (Indigo A-G)

6:30 Close of Day

WEDNESDAY, APRIL 12

7:00 am Registration Open (Indigo West Foyer)

7:45 In-Person Group Discussions with Continental Breakfast

In-Person Group 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 In-Person Group Discussions page on the conference website for a complete listing of topics and descriptions.

IN-PERSON GROUP DISCUSSION: Challenges with AI Adoption and Implementation for Drug Discovery

Ruben Abagyan, PhD, Professor, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego
Sean Ekins, PhD, Founder & CEO, Collaborations Pharmaceuticals, Inc.
Maria Miteva, PhD, Research Director, Medicinal Chemistry and Translational Research, Inserm
Wenyi Wang, PhD, Principal Scientist, DMPK Department, Genentech, Inc.

- Trends in investing in and effectively using AI for preclinical drug discovery
- The challenge of continuous evolution of models in response to big data, data types, and computational platforms
- Understanding the caveats of AI-driven predictions for drug and target screening
- Machine learning models for predicting ADME-Tox properties of small molecules

ROOM LOCATION: Indigo 204

AI FOR SCREENING & OPTIMIZATION

8:30 Chairperson's Remarks

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

8:35 Giga-Screening for Preclinical Candidates with a Defined Multi-Target Profile

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

Rapid identification of a first-in-class or best-in-class preclinical candidate against a new target, mutant or functional state was always important for computational drug discovery. However, even more challenging is screening for candidates with particular fine-grained specificity, target and property profile which may include multiple desired and undesired activities/properties. The screening of billions of compounds with those complex profiles present an extra barrier. Methods, models, implementations and applications will be discussed.

9:05 Chemistry-Aware Machine Learning on DNA-Encoded Libraries

Polina Binder, Senior Machine Learning Scientist, Compute Team, Anagenex

DNA-encoded libraries (DELs) are used for rapid large-scale screening of small molecules against a protein target. At Anagenex, we employ machine learning techniques that incorporate nuances of chemical data to create improved deep learning these models. These models can be extended to screen external molecules and predict their binding affinity to a target of interest.

9:35 Coffee Break in the Exhibit Hall with Poster Awards Announced (Indigo A-G)

Poster Award (Sponsorship Opportunity Available)

10:30 AI Approach to Predict Inhibitors of Drug Metabolizing Enzymes and Transporters for the Design of Safer Drugs

Maria Miteva, PhD, Research Director, Medicinal Chemistry and Translational Research, Inserm

Drug metabolizing enzymes (DME) and drug transporters strongly influence the drug disposition and can be involved in DDI of a large number of drugs. We will present an AI approach integrating structural bioinformatics and machine learning methodologies to predict interactions of drugs with DME and drug transporters. We focus on the DME: Phase I (cytochrome P450), Phase II conjugate enzymes, sulfotransferase and UDP-glucuronosyltransferase, and on the BCRP transporter.

11:00 Integration of Physics and Machine Learning for Challenging Drug Discovery Targets

Rafal Wiewiora, PhD, Principal, Computational Biophysics, Psivant Therapeutics

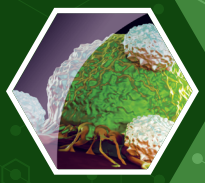
Drug discovery is challenging for many reasons. We developed a flexible toolkit combining best-in-class capabilities in physics-based simulations and machine learning to enable our discovery projects. First, we describe the QUAISAR platform, which combines quantum mechanics, molecular dynamics, and machine learning to predict structure-activity relationships. We then show an example of how molecular simulations on massive GPU resources predict complex biological motions and reveal strategies for small molecule allosteric modulation.

11:30 *In silico* ADME: Application and Impact of QSAR Models in Drug Discovery

Wenyi Wang, PhD, Principal Scientist, DMPK Department, Genentech, Inc.

ADME properties are important considerations for drug discovery. Machine learning models were developed for predicting the ADME properties of small molecules. These models existed for more than a decade and were used on various occasions in lead optimizations. We will discuss the development of these models and the use cases in Genentech.

12:00 pm Close of Artificial Intelligence for Early Drug Discovery – Part 1 Conference



Small Molecule Immuno-Modulators

Combatting Cancer, Autoimmunity and Inflammation with the Immune System

TUESDAY, APRIL 11

7:00 am Registration and Morning Coffee (Indigo West Foyer)

8:00 Welcome Remarks

ROOM LOCATION: Aqua E
INHIBITING KINASES AND GPCRs FOR IMMUNO-ONCOLOGY

8:05 Chairperson's Remarks
Murali Ramachandra, PhD, CEO, Aurigene Discovery Technologies Ltd.

8:10 Selectively Inhibiting Kinase HPK1 for Immuno-Oncology
Ryan McClure, PhD, Senior Scientist, Drug Discovery Science & Technology, AbbVie
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.

8:40 Evolution of HPK1 Clinical Candidate GRC54276: The Journey, Challenges, and Solutions
Pravin S. Iyer, PhD, Senior Vice President & Head of NCE Research, Glenmark Pharmaceuticals Ltd.
HPK1 negatively regulates T & B cell signaling. Our initial HPK1 inhibitor demonstrated a modest TPP. We renewed our efforts with new chemotype designs & refined animal models. Our second-generation candidate showed excellent *in vitro*, immunological & safety profiles. We observed good *in vivo* efficacy, both as a single agent and with immune checkpoint inhibitors. GRC54276 is progressing through a multi-center, Phase I clinical trial in patients with solid tumors.

9:10 FLX475: A Potent and Selective CCR4 Antagonist to Modulate Regulatory T cells in the Tumor Micro-Environment
Omar Robles, PhD, Senior Scientist, Drug Discovery, RAPT Therapeutics
High levels of Regulatory T cells (Treg) accumulation in the tumor micro-environment (TME) have been shown to dampen the antitumor immune response and lead to poor prognosis in patients with various types of cancers. Treg are recruited to the TME through selective interactions of the chemokine receptor CCR4 and chemokines CCL17 and CCL22. The discovery and early clinical development of FLX475, a potent and selective CCR4 antagonist will be described.

9:40 QSP Modeling to Inform R&D Decisions: Differentiation of ASP2453 and Targeted Protein Degrader Strategies

Kas Subramanian, PhD, Executive Director, Modeling, Applied BioMath
ASP2453 is a KRASG12C inhibitor. Preclinical data suggests impressive efficacy yet it was unclear if it would show a more favorable clinical response compared to competitors. A QSP model linked to tumor growth in patients with NSCLC predicted ASP2453 exhibits greater clinical response than AMG 510, supporting potential differentiation and critical thinking for clinical trials. In some instances, pre-built TPD models can be used to more expeditiously assess TPD strategies targeting KRAS.

10:10 Networking Coffee Break (Indigo West Foyer)

TARGETING THE TUMOR MICROENVIRONMENT

10:35 FEATURED PRESENTATION: Discovery of Etrumandenant: A Potent Dual Adenosine Receptor Antagonist for Cancer Immunotherapy
Brandon Rosen, PhD, Senior Scientist, Medicinal Chemistry, Arcus Biosciences
Extracellular adenosine frequently creates an immunosuppressed tumor microenvironment by activating the G protein-coupled A2a and A2b receptors of intratumoral immune cells. Etrumadenant, a novel, selective, and non-brain penetrant small molecule dual A2aR/A2bR antagonist, potently blocks the immunosuppressive effects of high concentrations of adenosine in the tumor microenvironment. I present the design, characterization, and SAR of a series of potent A2aR/A2bR antagonists culminating in the discovery of etrumadenant.

11:05 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.

11:35 Targeting Integrins for Immuno-Oncology
Timothy Machajewski, PhD, Vice President, Head of Chemistry, Pliant Therapeutics
The av integrins (avb1, avb3, avb5, avb6, avb8) are a subset of a family of heterodimeric transmembrane proteins that mediate cell-cell and cell-extracellular matrix signaling. I will discuss the role of integrins in immuno-oncology and will describe the development of our integrin inhibitor library. I will also present the challenges in targeting integrins with small molecule drugs.

12:05 pm Enjoy Lunch on Your Own

INNATE IMMUNITY TARGETS

1:30 Chairperson's Remarks
Bhaumik A. Pandya, PhD, Director, Chemistry Vigil Neuroscience

1:35 Identification of a Novel Class of Highly Potent, CNS-Penetrant, NLRP3-Specific Inhibitors
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.

2:05 Poster Spotlight: Discovery of a SHP1 Specific Covalent Inhibitor for Cancer Immunotherapy
Zihan Eric Qu, Graduate Student, Zhang Group, Purdue University
SHP1 is among the undruggable protein tyrosine phosphatase (PTP) superfamily and negatively regulates the immune responses in T cells and macrophages. Studies revealed that SHP1 deletion in immune cells or whole-body delays tumor progression. From high-throughput screening, we have developed the first-in-class covalent inhibitor that target SHP1 with unprecedented selectivity. The inhibitor is orally bioavailable and inhibits tumor progression via activation of T cells and macrophage activity.

2:35 Targeted Upregulation of STING
Seung Bum Park, PhD, Professor & Associate Dean, Chemistry Department, Seoul National University, Korea (CEO & Founder of SPARK Biopharma)
Stimulator of interferon genes (STING) activation is a promising strategy for immuno-oncology via promoting systemic antitumor immunity. However, from the current clinical investigations of STING agonists, dysregulated STING expression

or poor STING agonist pharmacokinetics pose major challenges that limit the robust antitumor response. Herein, we propose UPPRIS (upregulation of target proteins by protein-protein interaction strategy) to overcome these limitations.

3:05 Targeting PIM3 Kinase with Effective Hit Finding Approaches for Oncology and Immunomodulation

Celine Legros, PhD, Drug Discovery Partnership Director, Eurofins Discovery

Oncoproteins of the serine/threonine kinase PIM family prevent apoptosis while promoting cell survival and protein translocation. Their role in modulating the immune microenvironment and regulation of immune cells has also recently been described for these kinases, facilitating immune evasion in cancer. We will present a comprehensive Hit Finding project to identify innovative and selective PIM3 kinase inhibitors for successful hit-to-lead oncology programs focused on cell survival and immune-modulation pathways.

3:20 Refreshment Break in the Exhibit Hall with Poster Viewing (Indigo A-G)

ROOM LOCATION: Indigo D+H

PLENARY KEYNOTE SESSION

4:20 Plenary Welcome Remarks from Lead Content Director with Poster Finalists Announced

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

4:35 PLENARY: Targeting Nodes and Edges in Protein Networks

Michelle Arkin, PhD, Chair and Distinguished Professor, Pharmaceutical Chemistry & Director, Small Molecule Discovery Center, University of California, San Francisco

Protein interaction networks consist of protein nodes and interaction edges. We aim to inhibit or stabilize specific protein-protein interactions to dissect these complex networks for chemical biology and therapeutics discovery. Through covalent fragment-based approaches, we discovered compounds that selectively stabilized the chaperone 14-3-3 bound to diverse client proteins and altered their function. Additionally, function-selective inhibitors for the multifunctional enzyme VCP/p97 are providing new tools and drug leads for cancer.

5:30 Welcome Reception in the Exhibit Hall with Poster Viewing (Indigo A-G)

6:30 Close of Day

WEDNESDAY, APRIL 12

7:00 am Registration Open (Indigo West Foyer)

7:45 In-Person Group Discussions with Continental Breakfast

In-Person Group 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 In-Person Group Discussions page on the conference website for a complete listing of topics and descriptions.

IN-PERSON GROUP DISCUSSION: What Are Your Small Molecule Lead Generation Challenges?

Susanta Samajdar, PhD, Senior Vice President & Head, Drug Discovery, Aurigene Discovery Technologies Ltd.

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

- TPD strategies and hurdles for cancer & autoimmunity
- Favorite lead generation approach for small molecules: when to use DEL vs. FBDD vs. HTS?
- Pain points

ROOM LOCATION: Indigo H

FRAGMENTS AND TARGETED PROTEIN DEGRADATION APPROACHES

8:30 Chairperson's Remarks

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

8:35 FEATURED PRESENTATION: Fragment Approaches for Discovering Tissue-Specific E3 Ligases and β-Catenin Degraders

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

I will present how we've applied fragment-based methods to discover ligands for tissue-specific E3 ligases. I will also cover our work on discovering bifunctional degraders for β-catenin. This highly sought-after but difficult-to-drug intracellular target is part of a multi-functional cellular signaling complex whose overactivity contributes to the development of specific cancers and other diseases.

9:35 Coffee Break in the Exhibit Hall with Poster Awards Announced (Indigo A-G)

Poster Award

ROOM LOCATION: Aqua E

TPD APPROACHES FOR CANCER

10:30 Discovery and Characterization of NVP-DKY709, a First-In-Class Selective IKZF2 Glue Degrader for Immuno-Oncology Applications

Artiom Cernijenko, PhD, Principal Scientist II, Global Discovery Chemistry, Novartis Institutes for BioMedical Research, Inc.

IKZF2 (Helios) is a member of the Ikaros family of zinc finger transcription factors. IKZF2 genetic knockout in mice was shown to destabilize immune-repressive regulatory T cells and it was hypothesized that selective IKZF2 downregulation might enhance immune responses to tumors. Here, we present the development and characterization of NVP-DKY709, a first-in-class selective molecular glue degrader of IKZF2/4, that is being investigated in human clinical trials as an immunomodulatory drug.

11:00 A Degrader of BTK and IKZF

Mark Noviski, PhD, Principal Scientist, Discovery Biology, Nurix Therapeutics, Inc.

I describe preclinical and clinical data for NX2127, a degrader of Bruton Tyrosine Kinase (BTK), a master regulator of B cells and implicated in cancer. We developed two unique and functionally distinct BTK degraders that harness cereblon (CRBN), an E3 ligase active in hematopoietic cells. I describe the BTK degrader that also has the ability to induce degradation of neosubstrates Ikaros (IKZF1) and Aiolos (IKZF3).

11:30 Targeting CBP/p300 - Inhibition vs Degradation for Potent Anti-tumor Efficacy

Murali Ramachandra, PhD, CEO, Aurigene Discovery Technologies Ltd.

E1A binding protein (p300) and its paralog CREB binding protein (CBP or CREBBP) are key transcriptional co-activators that play a critical role in gene expression in both tumor and immune cells. Our efforts in understanding the distinct advantages of inhibition vs degradation of CBP/p300 for use in cancer therapy resulting from a combination of synthetic lethality, inhibition of pro-tumorigenic signaling and activation of anti-tumor immune response will be presented

12:00 pm Close of Small Molecule Immuno-Modulators Conference

Protein Degraders & Molecular Glues - Part 2

Emerging Degrader Modalities and Screening Strategies

WEDNESDAY, APRIL 12

12:00 pm Registration Open (Indigo West Foyer)

12:45 Dessert Break in the Exhibit Hall with Poster Viewing (Indigo A-G)

1:30 Welcome Remarks

ROOM LOCATION: Indigo H

ADVANCING MOLECULAR GLUES

1:35 Chairperson's Remarks
Jesse Chen, PhD, Co-Founder & CTO, Triana Biomedicines, Inc.

1:40 Expansion of the Druggable Genome through Rational Approaches to Molecular Glue Discovery
Mary Matyskiela, PhD, Vice President, Molecular Sciences, Neomorph, Inc.
Molecular glue degraders offer to significantly expand the druggable genome through their ability to target proteins with no ligand binding sites. Thalidomide analogs offer a case-study in molecular glue mechanisms, with the discovery of neosubstrate degrons enabling prospective searches for on- and off-target activities. Structure-based approaches to molecular glue drug discovery show promise for the rational identification and optimization of novel glue systems, generating a unique and differentiated target space.

2:10 Novel Monovalent Protein Degraders and Molecular Glues in Cancer Drug Discovery
Simon Bailey, PhD, MBA, Executive Vice President & Head of Drug Discovery, Plexium, Inc.
This talk will discuss Plexium's latest approaches to discovering novel molecular glues and monovalent degraders of therapeutically important cancer targets. It will highlight Plexium's unique approach and capabilities to discover monovalent degraders and expand the E3 ligase toolbox.

2:40 System-wide assays to monitor protein activity and function
Hannes Hahne, PhD, CEO, OmicScouts
Proteomics delivers invaluable insights for drug and biomarker discovery and development. At OmicScouts we have a broad portfolio of flexible and scalable (chemo-)proteomic assays to systematically interrogate the cellular and system-wide action of drugs. The presentation will showcase how we support our clients in their drug discovery projects.

3:10 Refreshment Break in the Exhibit Hall with Poster Viewing (Indigo A-G)

4:00 Discovery of Novel CK1a-Selective Molecular Glue Degraders Demonstrating Strong Anti-Tumor Activity
Firoz Jaipuri, PhD, Director, Platform Chemistry, Pin Therapeutics Inc.
CK1a, an isoform of casein kinase 1 (CK1), promotes tumor growth by increasing the negative effects of MDM2 and MDMX on p53. This presentation will discuss our efforts to identify cereblon (CRBN) E3 ligase-mediated CK1a-selective molecular glue degraders, which demonstrated good PK properties and robust pharmacological activities in various preclinical models of AML.

4:30 FEATURED PRESENTATION: Using Covalent Chemoproteomic Platforms to Enable Targeted Protein Degradation
Daniel Nomura, PhD, Professor of Chemistry, Molecular and Cell Biology, Nutritional Sciences and Toxicology, University of California, Berkeley
The Nomura Research Group is focused on reimagining druggability using chemoproteomic platforms to develop transformative medicines. One of the areas that we focus on is using chemoproteomic platforms to expand the scope of targeted protein degradation technologies. This talk will focus on using covalent chemoproteomic strategies for developing next-generation strategies for targeted protein degradation applications using both heterobifunctional and molecular glue-based strategies.

5:00 In-Person Group Discussions (All Session Rooms)
In-Person Group 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 In-Person Group Discussions page on the conference website for a complete listing of topics and descriptions.

IN-PERSON GROUP DISCUSSION: Exploring Innovative Approaches for Developing Molecular Glues
Simon Bailey, PhD, MBA, Executive Vice President & Head of Drug Discovery, Plexium, Inc.
Jesse Chen, PhD, Co-Founder & CTO, Triana Biomedicines, Inc.
Firoz Jaipuri, PhD, Director, Platform Chemistry, Pin Therapeutics Inc.
Mary Matyskiela, PhD, Vice President, Molecular Sciences, Neomorph, Inc.
- Structure-based approaches to molecular glue drug discovery
- Expanding the E3 ligase toolbox
- Covalent chemoproteomic strategies for developing next-gen degraders

5:45 Close of Day

6:15 Dinner Short Course*
SC5: Protein Degraders: A Focus on PROTACs from an ADME-Tox Perspective

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

THURSDAY, APRIL 13

7:15 am Registration Open

7:45 Diversity in Chemistry Breakfast Discussion

IN-PERSON GROUP DISCUSSION: Diversity in Chemistry beyond Molecules: Gender and More
Michelle Arkin, PhD, Chair and Distinguished Professor, Pharmaceutical Chemistry & Director, Small Molecule Discovery Center, University of California, San Francisco
Thomas P. Garner, PhD, Principal Scientist, Biophysics, Genentech, Inc.
Justyna Sikorska, PhD, Associate Principal Scientist, Mass Spectrometry & Biophysics, Merck
Topics may include below, but will be guided by audience input:
- Where does the 'drop-off' of women in the chemistry career progression occur and why?
- How did the pandemic and other sea changes in the past three years bring us closer to or further from equality?
- What issues did you think were solved?
- Diversity in life paths should include us all – how are men and nonbinary scientists being included?

Protein Degraders & Molecular Glues - Part 2

Emerging Degrader Modalities and Screening Strategies

ROOM LOCATION: Indigo D+H

PLENARY KEYNOTE SESSION

8:30 Plenary Welcome Remarks from Lead Content Director with Poster Finalists Announced

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

8:35 PLENARY: Reflections on a Career as a Medicinal Chemist in Drug Discovery

Nicholas A. Meanwell, PhD, Vice President (recently retired), Small Molecule Drug Discovery, Bristol Myers Squibb Co.

A successful drug candidate depends on many factors: creativity of scientists involved, effective collaboration and commitment by the team, and the quality of the compound advanced. I reflect on a 40-year career pursuing the discovery of drug candidates designed to address unmet medical need in the cardiovascular, CNS, and viral diseases therapeutic areas and share undervalued strategies and other synthetic chemistry approaches for overcoming specific medicinal chemistry challenges.

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

ROOM LOCATION: Indigo H

PLATFORMS ENABLING DEGRADER DEVELOPMENT

10:20 Chairperson's Remarks

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

10:25 Enabling Technologies to Determine Absolute Protein Abundance and Degradation Kinetics for PROTACs

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

Proteolysis-targeting chimera (PROTAC) is a frequently used approach for targeted protein degradation. In this talk, we'll present development and application of high throughput technologies to quantitatively measure absolute protein abundance for target protein and E3 ligases, and determine degradation kinetics of PROTACs in cells. Case studies will be included to demonstrate their impact on compound profiling and differentiation for PROTAC projects.

10:55 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

Following clinical proof of concept by thalidomide and related IMiDs, several new molecular entities are entering clinical development. 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.

11:25 Degrader Discovery with Novel POI & E3 Ligases Powered by DELT

Dengfeng Dou, Vice President, Lead Generation Unit, HitGen

DEL is an ideal method for finding potent, specific POI binders, especially for challenging targets. DEL technology allows systematic investigation E3 ligase family proteins. HitGen TPD platform toolboxes for degrader discovery and optimization.

11:40 Enabling Platforms to Accelerate the Development of Degraders for Intracellular and Extracellular Proteins

Weiping Tang, PhD, Professor, Pharmaceutical Sciences and Director, Medicinal Chemistry Center, University of Wisconsin-Madison

I will present our recent progresses for the development of degraders for both intracellular and extracellular proteins. For the former, I will focus on the development of rapid synthesis of PRTAC (Rapid-TAC) platforms. For the latter, I will focus on the development of degraders that recruit different lysosome targeting receptors.

12:10 pm A Chemical Biology Toolbox for Characterizing Novel Protein Degraders

Fiona Pachl, PhD, Senior Scientist, Chemical Biology and Proteomics, AstraZeneca

Targeted protein degradation by small molecules have shown consolidated promise as a new pharmacological approach. We give an overview of our lead generation cascades for the protein degradation modality with focus on proteomics strategies to define degraders selectivity and mechanism of actions. We discuss assay toolboxes and future direction of unbiased discovery of emerging molecular glue degraders and relationship between target and ligase to inform design.

12:40 Transition to Lunch

12:50 Modeling Targeted Protein Degradation via Bifunctional Degraders and Molecular Glues: Recent Case Studies and Developments

Michael Drummond, Scientific Applications Manager, Chemical Computing Group

In recent years, targeted protein degradation has emerged as a new modality to control protein levels *in vivo*. Both bifunctional degraders, such as PROTACs, and monovalent degraders, such as molecular glues, can be developed to selectively and catalytically target a protein-of-interest for degradation. Despite the many advantages of these approaches, numerous challenges still exist in the development of degraders, particularly concerning the rational design of efficacious molecules. This talk will explore the most promising methodologies we have developed to evaluate putative degrader designs. Recent case studies will be presented, demonstrating in particular the utility of these approaches on larger scale degrader investigations. Particular focus will be given to the quality of the predictions as a function of available input knowledge, such as using hydrogen-deuterium exchange (HDX) data to inform protein-protein interface prediction and, ultimately, ternary complex geometry.

1:20 Refreshment Break in the Exhibit Hall with Poster Awards Announced

Poster Award (Sponsorship Opportunity Available)

OPTIMIZING DRUG-LIKE PROPERTIES

2:00 Chairperson's Remarks

Zoran Rankovic, PhD, Director, CBT Chemistry Centers, St. Jude Children's Research Hospital

2:05 Developing Alternative Warheads for CRBN-Directing PROTACs

Zoran Rankovic, PhD, Director, CBT Chemistry Centers, St. Jude Children's Research Hospital

This talk will describe the design, SAR and *in vitro*/*vivo* properties of Phenyl Glutarimide (PG) and Phenyl Dihydrouracil (PD) cereblon ligands, and corresponding BET, JAK and LCK PROTACs. Comparative studies with corresponding IMiD PROTACs, and screening efforts for alternative CRBN binders will also be discussed.

Protein Degraders & Molecular Glues - Part 2

Emerging Degrader Modalities and Screening Strategies

2:35 Targeted Protein Degradation of RET Kinase as a Strategy to Achieve Pan-Mutant and Pan-Fusion Anti-Cancer Activity

Douglas Orsi, PhD, Senior Research Scientist, Medicinal Chemistry, C4 Therapeutics, Inc.

Activating point mutations and chromosomal fusions of the Rearranged During Transfection (RET) receptor tyrosine kinase drive numerous human cancers. Here we describe the medicinal chemistry efforts leading to the orally bioavailable, pan-mutant, and pan-fusion RET heterobifunctional degrader, compound 9. *In vitro*, it promotes potent degradation of wild-type and mutant RET kinase domains. *In vivo*, oral dosing of compound 9 in xenograft models of RET-driven cancers leads to robust tumor regression.

3:05 ORM-5029: A First-in-Class, Tumor-Targeted, Targeted Protein Degradation Therapy for HER2-Positive Breast Cancer

Khuloud Takrouri, PhD, Director of Chemistry & Bioconjugation, Orum Therapeutics

TPD² approach merges the power of protein degraders with the precision of antibodies to deliver molecular glues or hetero-bifunctional degraders intracellularly with cell-specificity and broad therapeutic index. Using the TPD² approach, the dual precision targeted protein degrader platform has been developed using highly specific GSPT1 degraders that show promising efficacy against hematological malignancies and solid tumors. Our first clinical GSPT1 TPD² conjugate, ORM-5029 for breast cancer, will be discussed herein.

3:35 Networking Refreshment Break

ROOM LOCATION: Indigo H

3:55 Bifunctional Degradation Activating Compounds – Overcoming ADME Challenges

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

Targeted Protein Degradation has the potential to transform disease treatment. C4T's TORPEDO platform enables the design of potent, selective, and orally available MonoDAC and BiDAC degraders. The presentation will discuss ADME strategies and challenges in the context of degrader drug discovery. A case study of preclinical ADME properties of CFT8634, a potent, selective, and orally available BiDAC degrader of BRD9 for the treatment of SMARCB1-perturbed cancers will be discussed.

4:25 Direct-to-Biology Accelerates PROTAC Synthesis and the Evaluation of Linker Effects on Permeability and Degradation

Jennifer D. Venable, PhD, Senior Director, Discovery Chemistry Site Head, Janssen La Jolla

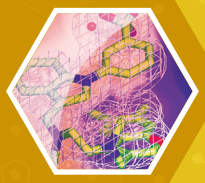
A platform to accelerate optimization of PROTACs has been developed using a direct-to-biology (D2B) approach focusing on linker effects. A large number of linker analogs, with varying length, polarity, rigidity, were rapidly prepared and, without chromatographic purification, characterized in four cell-based assays by streamlining time-consuming steps in synthesis and purification. The expansive dataset informs on linker structure-activity relationships (SAR) for in-cell E3 ligase target engagement, degradation, permeability, and cell toxicity.

4:55 Discovery of FHD-609: A Potent and Selective Heterobifunctional Degrader of BRD9

Matthew Netherton, PhD, Senior Director, Medicinal Chemistry, Foghorn Therapeutics

Synovial sarcoma is a rare, often aggressive malignancy with limited therapeutic options. In preclinical studies, FHD-609 has been shown to selectively degrade bromodomain-containing protein 9 (BRD9), taking advantage of a synthetic lethal relationship with the SS18-SSX translocation. The discovery and optimization of this first-in-class clinical compound will be described.

5:25 Close of Conference



Protein-Protein Interactions

Targeting Molecular Complexes for New Small Molecule Drug Discovery

WEDNESDAY, APRIL 12

12:00 pm Registration Open (Indigo West Foyer)

12:45 Dessert Break in the Exhibit Hall with Poster Viewing (Indigo A-G)

1:30 Welcome Remarks

ROOM LOCATION: Indigo D

PPI INHIBITOR SUCCESS

1:35 Chairperson's Remarks
Justyna Sikorska, PhD, Associate Principal Scientist, Mass Spectrometry & Biophysics, Merck

1:40 MedChem Case Study of HIV Maturation Inhibitor Candidates
Alicia Regueiro-Ren, PhD, Director, Medicinal Chemistry, Bristol Myers Squibb Co.
GSK3640254 is an HIV-1 maturation inhibitor (MI) with antiviral activity towards a wide range of clinically-relevant polymorphic variants, which has demonstrated efficacy in HIV-1 infected patients in Phase IIb clinical trials. In contrast to classical HIV-1 protease inhibitors that act by binding to the viral protease, GSK3640254 binds to the viral Gal-polyprotein, preventing its final processing by the HIV-1 protease and resulting in the release of an immature, non-infectious virus.

2:10 Rational Design and Structural Analysis of Novel Anti-Tubulin Agents
Michel O. Steinmetz, PhD, Lab Head, Laboratory of Biomolecular Research, Division of Biology & Chemistry, Paul Scherrer Institute
Using a combined computational and crystallographic fragment screening approach, we identified novel binding sites in the anticancer target tubulin. Based on our results and using straightforward chemistry, we for the first time fully rationally designed several small molecules, tubulin-tubulin interaction inhibitors that display a unique molecular mechanism of action. We further exploited the conformational switch properties of a designed tubulin inhibitor to assess its unbinding using time-resolved femtosecond serial crystallography.

2:40 Investigating Protein-Protein and Protein-Small Molecule Interactions with Lumit Immunoassays
Ellen Crummy, PhD, Sr Research Scientist, Research & Development, Promega Corporation
Designing small molecule inhibitors and other protein interaction modulators require simple, high-throughput screening methodologies. Lumit Anti-Tag Reagents for Protein Interactions enable *in vitro* homogenous (no wash) bioluminescent immunoassays to measure protein-protein and protein-small molecule interactions using common protein tags. Here, we demonstrate how Lumit immunoassays can be used to compare binding affinities of PROTACs and molecular glues with their targets and to monitor PROTAC-mediated ternary complex formation.

3:10 Refreshment Break in the Exhibit Hall with Poster Viewing (Indigo A-G)

4:00 FEATURED PRESENTATION: Inhibitors of the Bcl-2 Family: A Comparative Chemical Analysis
Andras Kotschy, PhD, Managing Director, Servier Research Institute of Medicinal Chemistry
Cancer cells evade programmed cell death through upregulating Bcl-2 proteins, which sequester the apoptosis-inducing BH3 proteins in high-affinity protein-protein interactions. While the therapeutic potential of inhibiting this interaction and inducing cell death has long been recognized, it took several decades to deliver drug candidates with this mode of action. The presentation describes the inherent difficulties of this discovery process and how we and others overcame them.

4:30 Small Molecule Inhibitors of TEADs Allosteric Lipid Pocket
Debra Brennan, Executive Director, Medicinal Chemistry, 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, using structural elucidation and computational chemistry to understand the MOAs for small molecule inhibitors. We provide hypotheses of different MOAs which could contribute to development of more potent and selective inhibitors.

5:00 In-Person Group Discussions (All Session Rooms)
In-Person Group 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 In-Person Group Discussions page on the conference website for a complete listing of topics and descriptions.

IN-PERSON GROUP DISCUSSION: Strategies and Best Practices in Targeting PPIs
Elisa Barile, PhD, Principal Scientist, Structural Biology & Biophysics, Takeda, San Diego
Phillip Schwartz, PhD, Director, Biophysics, Septerna
Charles Wartchow, PhD, Associate Director, Global Discovery Chemistry, Novartis Institutes for BioMedical Research
- Lead generation strategies – which and when?: DEL, FBDD, HTS, VLS, HCS, FA-tethering, etc.
- Covalent irreversible vs. reversible modalities
- Differing considerations for PPI inhibitors vs. PPI enhancers (glues)
- Best orthogonal biophysical and biochemical approaches: XRC, Cryo-EM, NMR, SPR/GCI, DSF, FRET, MS, FP, and more
- Testing funnels: which techniques to use, and where? (e.g., assessing lead potency vs. tracking PPI affinity shifts...)

5:45 Close of Day

6:15 Dinner Short Course*
SC8: Biophysical Tools for Membrane Proteins: Drug Discovery Applications
*Premium Pricing or separate registration required. See Short Courses page for details.

THURSDAY, APRIL 13

7:15 am Registration Open

7:45 Diversity in Chemistry Breakfast Discussion

Protein-Protein Interactions

Targeting Molecular Complexes for New Small Molecule Drug Discovery

IN-PERSON GROUP DISCUSSION: Diversity in Chemistry beyond Molecules: Gender and More

Michelle Arkin, PhD, Chair and Distinguished Professor, Pharmaceutical Chemistry & Director, Small Molecule Discovery Center, University of California, San Francisco

Thomas P. Garner, PhD, Principal Scientist, Biophysics, Genentech, Inc.

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

Topics may include below, but will be guided by audience input:

• Where does the 'drop-off' of women in the chemistry career progression occur and why?

• How did the pandemic and other sea changes in the past three years bring us closer to or further from equality?

• What issues did you think were solved?

• Diversity in life paths should include us all – how are men and nonbinary scientists being included?

ROOM LOCATION: Indigo D+H

PLENARY KEYNOTE SESSION

8:30 Plenary Welcome Remarks from Lead Content Director with Poster Finalists Announced

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

8:35 PLENARY: Reflections on a Career as a Medicinal Chemist in Drug Discovery

Nicholas A. Meanwell, PhD, Vice President (recently retired), Small Molecule Drug Discovery, Bristol Myers Squibb Co.

A successful drug candidate depends on many factors: creativity of scientists involved, effective collaboration and commitment by the team, and the quality of the compound advanced. I reflect on a 40-year career pursuing the discovery of drug candidates designed to address unmet medical need in the cardiovascular, CNS, and viral diseases therapeutic areas and share undervalued strategies and other synthetic chemistry approaches for overcoming specific medicinal chemistry challenges.

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

ROOM LOCATION: Indigo D

DRUGGING DIFFICULT TARGETS

10:20 Chairperson's Remarks

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

10:25 Identification of the *in vivo* active KRAS G12C Inhibitor BI-0474 via Fragment Based Screening and Optimization of Reversible Binding to KRAS

Joachim Broeker, PhD, Principal Scientist, Medicinal Chemistry, Boehringer Ingelheim RCV GmbH & Co. KG

I describe the discovery of the *in vivo* active KRASG12C inhibitor BI-0474. We identified small molecules that bind reversibly to the Switch II pocket on KRAS. These binders were optimized by growing toward Cys12 and then attaching the Michael acceptor warhead to react with Cys12. Our approach offers an alternative to discover KRASG12C inhibitors and provides a starting point for the discovery of inhibitors against other oncogenic KRAS mutants.

10:55 Fragment Screening Combined with Corporate Compound Collection Searching: Delivering a Novel Inhibitor of the KEAP1:NRF2 Interaction

Marcel Verdonk, PhD, Senior Director, Computational Chemistry & Informatics, Astex Pharmaceuticals

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.

11:25 Structural Basis for Targeting the Nuclear Cap Binding Complex by Potent Anti-inflammatory Drug Candidates

Tazi Jamal, Professor, research, ABIVAX

We have used thermophoresis and cryo-EM to determine the modalities of binding of anti-inflammatory drugs, obefazimod and its metabolically modified metabolite ABX464-N-Glu, to the nuclear Cap Binding Complex (CBC) to trigger the specific and selective expression of the anti-inflammatory microRNA miR-124 *in vitro* and in UC patients. Our results identify a unique interfacial stabilizing mode of action for anti-inflammatory drugs targeting the CBC complex to act selectively on RNA biogenesis.

11:40 Targeting Transcription Factor – BAF Interactions in Cancer

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

Transcription factors (TFs) make for compelling drug targets but have been historically hard to drug. Various TFs work with the BAF remodeling complex to open specific regions of chromatin. Using SPI1 as an example, we will highlight how Foghorn has developed a drug discovery platform to identify and target TF-BAF protein-protein interactions responsible for driving disease.

12:10 pm Platforms for the Rapid Discovery of Helicon Therapeutics

John McGee, Vice President & Scientific Co-Founder, FogPharma

Helically constrained (Helicon) peptides are a drug modality that allows the targeting of undruggable protein-protein interactions in cells. We have developed tandem platforms that enable the *de novo* discovery of helical hits to targets without any prior knowledge of their helix-binding properties, and that enable the rapid optimization of these hits to molecules with drug-like properties via the multiplexed synthesis and screening of thousands of peptides per week.

12:40 Transition to Lunch

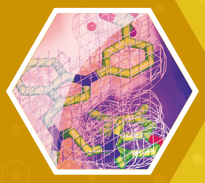
12:50 Employing DNA-Encoded Libraries to Identify Novel Chemical Equity for PPIs and Beyond

Paige Dickson, PhD, Senior Research Scientist, Lead Discovery and Biochemistry, X-Chem, Inc

At X-Chem, we are pushing the limits of DNA-encoded libraries (DEL) to empower our clients' pursuit of novel small molecules. I will review X-Chem's innovative approaches for identification of PPI modulators and describe successful applications of DEL in this area. As an experienced service provider, X-Chem offers tools to support successful small molecule hit identification, including screening X-Chem's diverse set of DELs, target tractability assessments, custom library synthesis, and AI-guided discovery.

1:20 Refreshment Break in the Exhibit Hall with Poster Awards Announced

Poster Award (Sponsorship Opportunity Available)



Protein-Protein Interactions

Targeting Molecular Complexes for New Small Molecule Drug Discovery

BIOPHYSICAL AND OTHER METHODS FOR PPI-TARGETED DISCOVERY

2:00 Chairperson's Remarks

Jon D. Williams, PhD, Senior Principal Research Scientist, Discovery Research, Abbvie, Inc.

2:05 Utilizing the SPR Chaser Assay in a Medicinal Chemistry Assay Cascade

Thomas P. Garner, PhD, Principal Scientist, Biophysics, Genentech, Inc.

Selectivity is a key consideration in medicinal chemistry campaigns. The long residence time of tight complexes can lead to unfavorably long incubation times in many biochemical/biophysical assays causing inaccuracies. Kinetic measurements (SPR) have the advantage of measuring affinities pre-steady state with high accuracy. The "chaser" SPR method allows accurate measurements of very slow dissociation constants, extending the range of measurable affinities with the high accuracy needed for reliable selectivity margins.

2:35 High-Throughput Protein Analysis Enabled by IR-MALDESI-MS

Nathaniel L. Elsen, PhD, Principal Research Scientist, Discovery, AbbVie, Inc.

We have adapted and applied IR-MALDESI-MS, a novel label-free tool, for high-throughput (< 1 sample/sec) biochemical and cellular assays. MALDESI-MS allows direct ambient analysis of complex reaction mixtures in common biochemical buffers and cellular media without sample clean-up. Examples of both cellular and biochemical assays will be given along with other potential applications within the lead discovery space.

3:05 Leveraging the RAPID Chemoproteomics Platform to Unlock PPI Targets (STING Pathway and More)

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.

3:35 Networking Refreshment Break

PPI STABILIZERS AND GLUES

3:55 Small Molecule Mitofusin Activators and Inhibitors

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

Mitofusins reside on the outer mitochondrial membrane and regulate mitochondrial fusion, a physiological process that impacts diverse cellular processes. Using structural and biochemical insights, we developed drug screening strategies and identified the first mitofusin activators and inhibitors that directly increase or inhibit mitofusin activity by modulating mitofusin conformations and oligomerization. Characterization of mitofusin modulators in modulating mitochondrial fusion, function, and signaling and their pharmacological potential in diseases will be discussed.

4:25 Cereblon Covalent Modulation through Structure-based Design of Histidine-Targeting Chemical Probes

Radosław P. Nowak, PhD, Senior Scientist, Center for Protein Degradation, Dana-Farber Cancer Institute

We describe first rational targeting of a specific histidine residue in a protein binding site using sulfonyl exchange chemistry. Using structure-based drug design we incorporated sulfonyl fluoride and triazole reactive group into cereblon binders resulting in potent covalent inhibitors and molecular glues through engagement of His353. Chemical probes and covalent labeling strategy described here will broadly impact this exciting area of therapeutic research.

4:55 Microtubule-Stabilizing 1,2,4-Triazolo[1,5-a]pyrimidines as Candidate Therapeutics for Neurodegenerative Tauopathies

Carlo Ballatore, PhD, Professor, Pharmaceutical Science, University of California San Diego

Normalization of axonal microtubules (MTs) dynamics is a promising strategy to treat neurodegenerative tauopathies, including Alzheimer's disease. Central to this strategy, however, is the identification of MT-stabilizing compounds that could reach effective brain concentrations and doses that would not be systemically toxic. The proposed presentation will provide an overview of structure-activity relationship efforts that led to the identification of selected members of the 1,2,4-triazolo[1,5-a]pyrimidine class as candidates for further development.

5:25 Close of Conference

bRo5: Macrocyclics, Degraders & More

Designing Drug-Like Large Molecules beyond the Rule of Five

WEDNESDAY, APRIL 12

12:00 pm Registration Open (Indigo West Foyer)

12:45 Dessert Break in the Exhibit Hall with Poster Viewing (Indigo A-G)

1:30 Welcome Remarks

ROOM LOCATION: Indigo 202

MAKING MACROCYCLICS

1:35 Chairperson's Remarks
Dean G. Brown, PhD, Vice President & Head, Chemistry, Jnana Therapeutics

1:40 Macrocyclics Traversing the Membrane
Gaurav Bhardwaj, PhD, Assistant Professor, Medicinal Chemistry, University of Washington
Developing macrocyclic binders against intracellular proteins and protein-protein interfaces remains a challenge with current methods and scaffolds. We recently developed computational methods to design peptides with enhanced membrane permeability and oral bioavailability. We are further integrating our computational methods with high-throughput peptide synthesis to design peptide binders for antibiotic, antiviral, and other therapeutic applications. Overall, these methods present avenues for binding intracellular targets currently considered "undruggable" or "difficult to drug."

2:10 Towards Privileged Scaffolds for Macrocyclic Drug Discovery
Andrei K. Yudin, PhD, Professor, Chemistry, University of Toronto
To design passively membrane permeable bioactive macrocycles, chemists have resorted to N-methylated amino acids and/or unnatural amino acids. We replaced select amino acid residues by azole heterocycles in a stepwise manner, which vastly improved the lipophilicity and PAMPA permeability of macrocycles. NMR analysis and molecular dynamics demonstrated permeability did not linearly increase with the addition of heterocycles. This study paves a way to discover privileged macrocyclic scaffolds for drug discovery.

2:40 Modes of Macrocycle Permeation
Adrian Whitty, PhD, Associate Professor of Chemistry, Boston University
Designing macrocycles for passive membrane permeability is a topic of intense research activity. Several different empirical and theoretical approaches have shown promise. I will discuss our recent machine-learning-based approaches for predicting macrocycle permeability, with emphasis on the idea that different classes of compound may have different permeation mechanisms available to them.

3:10 Refreshment Break in the Exhibit Hall with Poster Viewing (Indigo A-G)

4:00 Non-Peptidic Macrocycles for Molecular Glues
Thomas Kodadek, PhD, Professor, Department of Chemistry, University of Florida, Scripps Biomedical Research
This lecture will discuss the development of efficient methods for the solid phase synthesis and on-resin screening of DNA-encoded libraries (DELs) of intrinsically cell-permeable non-peptidic macrocycles of various sizes and compositions. Methods to mine these libraries for highly selective target protein ligands, including molecular glue candidates, will be highlighted.

4:30 A New Technology to Make Cell-Permeable and/or Oral Cyclic Peptide Drugs
Edward Will, PhD Candidate, LPPT, Professor Christian Heinis, EPFL
I will describe our method for synthesizing and screening ten-thousands of macrocyclic compounds at a picomole scale (S. Habeshian et al., Nat Commun. 13, 3823, 2022). Our new platform yields small cyclic peptides (< 700 Da) that have physicochemical properties suited to enter cells or for oral delivery.

5:00 In-Person Group Discussions (All Session Rooms)
In-Person Group 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 In-Person Group Discussions page on the conference website for a complete listing of topics and descriptions.

IN-PERSON GROUP DISCUSSION: Making Large Molecules More Palatable
Katerina Leftheris, PhD, VP Chemistry, Pliant Therapeutics
Cameron Pye, PhD, CEO and Co-Founder, Unnatural Products
Maria Soloveychik, PhD, Co-Founder & CEO, SyntheX
- What is the most likely cell permeable TPD strategy?
- Strategies for oral peptides
- Formulation-based enhancements for oral uptake
- Oral macrocyclics: what can we learn from PCSK9?
- Nanoparticle delivery for bRo5 molecules: lessons from oligo world?

5:45 Close of Day

6:15 Dinner Short Courses*
*Premium Pricing or separate registration required. See Short Courses page for details.

THURSDAY, APRIL 13

7:15 am Registration Open

7:45 Diversity in Chemistry Breakfast Discussion

IN-PERSON GROUP DISCUSSION: Diversity in Chemistry beyond Molecules: Gender and More
Michelle Arkin, PhD, Chair and Distinguished Professor, Pharmaceutical Chemistry & Director, Small Molecule Discovery Center, University of California, San Francisco
Thomas P. Garner, PhD, Principal Scientist, Biophysics, Genentech, Inc.
Justyna Sikorska, PhD, Associate Principal Scientist, Mass Spectrometry & Biophysics, Merck
Topics may include below, but will be guided by audience input:
- Where does the 'drop-off' of women in the chemistry career progression occur and why?
- How did the pandemic and other sea changes in the past three years bring us closer to or further from equality?
- What issues did you think were solved?
- Diversity in life paths should include us all – how are men and nonbinary scientists being included?

ROOM LOCATION: Indigo D+H

PLENARY KEYNOTE SESSION

8:30 Plenary Welcome Remarks from Lead Content Director with Poster Finalists Announced
Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

8:35 PLENARY: Reflections on a Career as a Medicinal Chemist in Drug Discovery
Nicholas A. Meanwell, PhD, Vice President (recently retired), Small Molecule Drug Discovery, Bristol Myers Squibb Co.
A successful drug candidate depends on many factors: creativity of scientists involved, effective collaboration and commitment by the team, and the quality of the compound advanced. I reflect on a 40-year career pursuing the discovery of drug candidates designed to address unmet medical need in the cardiovascular, CNS, and viral diseases therapeutic areas and share undervalued strategies and other synthetic chemistry approaches for overcoming specific medicinal chemistry challenges.

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

ROOM LOCATION: Indigo 202

ORAL PEPTIDES

10:20 Chairperson's Remarks
Adrian Whitty, PhD, Associate Professor of Chemistry, Boston University

10:25 The Surprising Abundance of Passive Permeability in Large Macrocyclic Peptides beyond the World of Natural Products
Scott Lokey, PhD, Professor, Chemistry and Biochemistry, University of California, Santa Cruz
The virtual chemical space that includes synthetically accessible macrocyclic peptides (MCPs) in the 1000-MW range is astronomical. While the proportion of those compounds that are cell permeable may be low, because the space is so vast, the total number of permeable MCPs above 1000 MW is high. I will describe high-throughput synthetic and analytical tools for the discovery of large, passively permeable MCP scaffolds toward ligands against challenging intracellular targets.

10:55 An Integrated Platform for the Structure-Based Design of Orally Bioavailable Macrocycle Therapeutics
Andrew T. Bockus, PhD, Associate Director, Chemistry, Circle Pharma, Inc.
Circle Pharma has established an indication-agnostic peptide macrocycle discovery platform that combines structure-based design, physics-based permeability prediction, and semi-automated synthesis. The integrated workflow enables the rational exploration of vast chemical space to identify potent and permeable macrocycles in rapid iterative design cycles. This platform has produced orally bioavailable macrocyclic inhibitors of intracellular protein-protein interactions that demonstrate *in vivo* efficacy in mouse xenograft tumor models.

11:25 Type IV Macrocyclic Inhibitors of B-Raf Kinase that Block Dimerization and Overcome Paradoxical MEK/ERK activation
Campbell McInnes, PhD, Professor, Drug Discovery & Biomedical Sciences, University of South Carolina
We identified lead macrocyclic compounds that are type IV kinase inhibitors and represent potential next generation BRAF inhibitors. Despite the clinical success of B-Raf inhibitors like vemurafenib in treating metastatic melanoma, resistance has emerged through "paradoxical MEK/ERK signaling" where transactivation of one protomer occurs as a result of drug inhibition of the other partner in the activated dimer. We targeted the dimerization interface to overcome this problem.

11:40 Discovery and Development of Rusfertide (PTG-300), a Hepcidin Mimetic for the Treatment of Polycythemia Vera (PV)
Ashok Bhandari, PhD, Senior Vice President, Discovery Chemistry & Process Research, Protagonist Therapeutics, Inc.
Protagonist utilized its peptide technology platform for the *de novo* drug discovery of first and best-in-class drugs. The peptide technology platform produced novel peptides both oral and injectable clinical assets that include and not limited to rusfertide, PN-943, and PN-235. Will present the discovery and development of rusfertide (PTG-300), an hepcidin mimetic for the Treatment of Polycythemia Vera (PV).

12:10 pm FEATURED PRESENTATION: 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.

12:40 Enjoy Lunch on Your Own

1:20 Refreshment Break in the Exhibit Hall with Poster Awards Announced
Poster Award (Sponsorship Opportunity Available)

ROOM LOCATION: Indigo 202

ENCODED LIBRARIES FOR ORAL MACROCYCLICS

2:00 Chairperson's Remarks
Thomas J. Tucker, Principal Scientist, Medicinal Chemistry, Merck & Co Inc.

2:05 Discovery and Optimization of an Oral PCSK9 Macrocyclic Inhibitor from mRNA Display Screening
Thomas J. Tucker, Principal Scientist, Medicinal Chemistry, Merck & Co Inc.
This talk will highlight the discovery efforts from mRNA display screening hits to a tricyclic peptide PCSK9 inhibitor drug candidate, which demonstrated its pharmacodynamic effects similar to the FDA-approved, parenterally dosed anti-PCSK9 mAb, with the advantage of oral administration using lipidic dosing vehicle Labrasol.

2:35 Improved DNA-Encoded Libraries for Macrocyclic Peptides
Joerg Scheuermann, PhD, Principal Investigator, Department of Chemistry & Applied Biosciences, ETH Zurich
I will discuss my lab's research which touches on macrocycles (DELs) and a strategy we patented for creating super pure DELs which should work out much better in DEL selections by improving signal:noise.

3:05 Libraries and Display Selection for Macrocycles with Better Membrane Permeability
Hiroaki Suga, PhD, Professor Chemistry, Chemical Biology & Biotechnology, University of Tokyo

We design libraries of macrocycles aiming at generating better cell membrane permeability and apply to the RaPID selection against protein target of interest.

3:35 Networking Refreshment Break

MAKING DRUG-LIKE DEGRADERS

ROOM LOCATION: Indigo H

3:55 Bifunctional Degradation Activating Compounds – Overcoming ADME Challenges

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

Targeted Protein Degradation has the potential to transform disease treatment. C4T's TORPEDO platform enables the design of potent, selective, and orally available MonoDAC and BiDAC degraders. The presentation will discuss ADME strategies and challenges in the context of degrader drug discovery. A case study of preclinical ADME properties of CFT8634, a potent, selective, and orally available BiDAC degrader of BRD9 for the treatment of SMARCB1-perturbed cancers will be discussed.

4:25 Direct-to-Biology Accelerates PROTAC Synthesis and the Evaluation of Linker Effects on Permeability and Degradation

Jennifer D. Venable, PhD, Senior Director, Discovery Chemistry Site Head, Janssen La Jolla

A platform to accelerate optimization of PROTACs has been developed using a direct-to-biology (D2B) approach focusing on linker effects. A large number of linker analogs, with varying length, polarity, rigidity, were rapidly prepared and, without chromatographic purification, characterized in four cell-based assays by streamlining time-consuming steps in synthesis and purification. The expansive dataset informs on linker structure-activity relationships (SAR) for in-cell E3 ligase target engagement, degradation, permeability, and cell toxicity.

4:55 Discovery of FHD-609: A Potent and Selective Heterobifunctional Degrader of BRD9

Matthew Netherton, PhD, Senior Director, Medicinal Chemistry, Foghorn Therapeutics

Synovial sarcoma is a rare, often aggressive malignancy with limited therapeutic options. In preclinical studies, FHD-609 has been shown to selectively degrade bromodomain-containing protein 9 (BRD9), taking advantage of a synthetic lethal relationship with the SS18-SSX translocation. The discovery and optimization of this first-in-class clinical compound will be described.

5:55 Close of Conference

AI for Early Drug Discovery - Part 2

Innovative Use of Computational Tools for Finding New Targets and Drugs

WEDNESDAY, APRIL 12

12:00 pm Registration Open (Indigo West Foyer)

12:45 Dessert Break in the Exhibit Hall with Poster Viewing (Indigo A-G)

1:30 Welcome Remarks

ROOM LOCATION: Indigo 204

AI FOR SCREENING & DEGRADATION

1:35 Chairperson's Remarks
Scott Bembenek, PhD, Founder, CEO & CSO, Denovicon Therapeutics

1:40 Differentiable Design: Dynamic Ternary Complex Structure Prediction with Multiscale Generative Diffusion Models
Bryce Allen, PhD, Co-Founder & CEO, Differentiated Therapeutics

Designing bioactive molecules that serve a purpose is central to medicinal chemistry and a common practice in drug discovery. Here we explore a simple, fast, and robust approach to inverse design which combines learned forward simulators based on graph neural networks with gradient-based design optimization. Our approach solves high-dimensional problems with complex physical dynamics, including designing molecules that induce proximity between proteins forming a ternary complex.

2:10 *In silico* Screening for PROTAC Linkers
Shu-Ching Ou, PhD, Scientist, Center for Research Acceleration by Digital Innovation, Amgen, Inc.

With more PROTACs being developed, the importance of linker design and optimization has been broadly recognized. Here we report an approach to virtually screen the linker designs by proactively using the available PROTAC ternary structures. Combined with expansive chemical building blocks, this approach helps us rapidly triage design ideas and expedite the discovery process.

2:40 Synthesizability Orient Mega-size Interactive Chemical Space (SyOMics) PharmaBlock
Liu Liu, Dr., Vice President, Drug Discovery Business Unit, PharmaBlock

Hits identified from recent AIDD campaigns are often lacking structural novelty, particularly synthesizability, with existing chemical spaces. In PharmaBlock, taking advantage of our 160k novel building block inventory and proved synthesis route collections, we established a megasize (1014) interactive virtual chemical space. Supported by our proprietary searching algorithm, we are able to generate structurally diverse hits, which are ready to be synthesized with our building blocks in stock.

3:10 Refreshment Break in the Exhibit Hall with Poster Viewing (Indigo A-G)

4:00 Machine Learning-based Identification of Targets in Cancer for Protein Degradation
Collin Tokheim, PhD, Senior Scientist, Early Oncology Data Science, AstraZeneca Pharmaceuticals

While Targeted Protein Degradation (TPD) can expand druggable targets, how protein degradation is dysregulated in cancer and how TPD drugs counteract this effect is incompletely understood. First, we developed a deep-learning model (deepDegron) to identify mutations that result in loss of protein degradation signals. Second, we developed a machine learning model (MAPD) to predict which protein targets are likely degradable by TPD compounds from unbiased proteomic experiments of the kinome.

4:30 Enhanced Active Learning by Combining Machine Learning and Structure-Based Methods
Scott Bembenek, PhD, Founder, CEO & CSO, Denovicon Therapeutics

We will discuss an approach that applies AI and ML to design, test, and optimize lead molecules rapidly *in silico* and to suggest what compounds to synthesize and screen next in an 'active learning' process. A comprehensive platform approach offers tight integration between the virtual and real cycles (V+R). 3D modeling and simulation methods enhance the accuracy of predictions for drug potency, efficacy, and selectivity, while also addressing multi-target effects.

5:00 In-Person Group Discussions (All Session Rooms)

In-Person Group 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 In-Person Group Discussions page on the conference website for a complete listing of topics and descriptions.

IN-PERSON GROUP DISCUSSION: Emerging Applications of AI/ML Tools in Drug Discovery
Bryce Allen, PhD, Co-Founder & CEO, Differentiated Therapeutics
Collin Tokheim, PhD, Senior Scientist, Early Oncology Data Science, AstraZeneca Pharmaceuticals

- Designing molecules that induce proximity between proteins
- Integrating fragment-based screening with molecular dynamics
- Virtually screening linker designs using available PROTAC ternary structures
- Machine learning to predict which protein targets are likely degradable
- AI and ML models to design, test, and optimize lead molecules rapidly *in silico*

5:45 Close of Day

6:15 Dinner Short Courses*
*Premium Pricing or separate registration required. See Short Courses page for details.

THURSDAY, APRIL 13

7:15 am Registration Open

7:45 Diversity in Chemistry Breakfast Discussion

IN-PERSON GROUP DISCUSSION: Diversity in Chemistry beyond Molecules: Gender and More
Michelle Arkin, PhD, Chair and Distinguished Professor, Pharmaceutical Chemistry & Director, Small Molecule Discovery Center, University of California, San Francisco
Thomas P. Garner, PhD, Principal Scientist, Biophysics, Genentech, Inc.
Justyna Sikorska, PhD, Associate Principal Scientist, Mass Spectrometry & Biophysics, Merck

Topics may include below, but will be guided by audience input:

- Where does the 'drop-off' of women in the chemistry career progression occur and why?
- How did the pandemic and other sea changes in the past three years bring us closer to or further from equality?
- What issues did you think were solved?
- Diversity in life paths should include us all – how are men and nonbinary scientists being included?

AI for Early Drug Discovery - Part 2

Innovative Use of Computational Tools for Finding New Targets and Drugs

ROOM LOCATION: Indigo D+H

PLENARY KEYNOTE SESSION

8:30 Plenary Welcome Remarks from Lead Content Director with Poster Finalists Announced

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

8:35 PLENARY: Reflections on a Career as a Medicinal Chemist in Drug Discovery

Nicholas A. Meanwell, PhD, Vice President (recently retired), Small Molecule Drug Discovery, Bristol Myers Squibb Co.

A successful drug candidate depends on many factors: creativity of scientists involved, effective collaboration and commitment by the team, and the quality of the compound advanced. I reflect on a 40-year career pursuing the discovery of drug candidates designed to address unmet medical need in the cardiovascular, CNS, and viral diseases therapeutic areas and share undervalued strategies and other synthetic chemistry approaches for overcoming specific medicinal chemistry challenges.

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

ROOM LOCATION: Indigo 204

EMERGING AI APPLICATIONS

10:20 Chairperson's Remarks

Ewa Lis, PhD, Founder & CTO, Koliber Biosciences

10:25 Improving Machine Learning Predictions: Focus Is All You Need

Anton Filikov, PhD, Associate Director, Computational Drug Discovery, Arrakis Therapeutics

The mainstream view in improving model predictions is identifying better modeling algorithms and assembling larger training sets curated to get more reliable data. In addition to these approaches we use other measures that are very effective: (1) eliminating data points that confuse the model algorithm, (2) biasing property distributions in training set with the goal to maximize performance metrics. Examples will be given with demonstrated material improvements.

10:55 Fingerprinting Drug Effects and Disease Phenotypes of the CNS Using Deep Functional Readouts of Human iPSC-Derived Neurons

Benjamin Harwood, PhD, Senior Scientist, Q State Biosciences

We built a map of the electrophysiology of human excitatory neurons, with applications to high-throughput screening, drug repurposing, and target deconvolution. We measured several parameters from millions of iPSC-derived neurons perturbed by tool compounds, yielding a database of activity profiles. Then, we used representation learning to distill these data down to concise fingerprints, where similar compounds form neighborhoods and several important tasks (drug repurposing, target deconvolution) reduce to path-matching problems.

11:25 Pragmatic Drug Discovery Acceleration in Place of Dogmatic Automation

Nathan Allen, PhD, Research Fellow and Director of Business Development, Automated Synthetic Chemistry, XtalPi Inc.

Medicinal chemistry synthesis for drug discovery is an expensive and laborious aspect of drug development, often requiring years of effort by skilled chemists. XtalPi is developing a custom robotics and human chemist platform. The goal-deliver productivity and reduce downtime in the development cycle. Real-world complex molecule applications will be presented to demonstrate the progress toward this goal.

11:40 Protein Flexibility and Binding Affinity: What Can AI Predict?

Ponni Rajagopal, PhD, Founder & President, NstructuredesignS, LLC

Accurately predicted binding affinities can be a powerful tool for virtual screening of ligands. Protein flexibility plays an important role in ligand binding. Hence, using parameters that determine protein flexibility will lead to better prediction of binding affinities in ML algorithms. This work will evaluate the use of such independent variables to determine binding affinities.

12:10 pm ASPIRE (A Specialized Platform for Innovative Research Exploration): Lowering the Barrier to Drug Development by Applying Automation, Data Analytics, and AI/Machine Learning to Chemistry and Biology

Sean Gardner, MS, Scientific Program Manager, Office of Special Initiatives, NCATS, National Institutes of Health

NCATS has identified, with the input of the greater scientific community, focus areas that need to be addressed in order to transform the design-synthesize-test cycle to transition to be more data-driven. The ASPIRE Program was created to support the development of AI/ML tools to process captured data to inform the next iteration of the process.

12:50 Enjoy Lunch on Your Own

1:20 Refreshment Break in the Exhibit Hall with Poster Awards Announced

Poster Award (Sponsorship Opportunity Available)

AI FOR HIT IDENTIFICATION

2:00 Chairperson's Remarks

Tonglei Li, PhD, Allen Chao Chair & Professor, Industrial & Physical Pharmacy, Purdue University

2:05 Manifold Embedding of Molecular Surface: A New Dimension in Chemical Deep Learning

Tonglei Li, PhD, Allen Chao Chair & Professor, Industrial & Physical Pharmacy, Purdue University

To chemically differentiate huge quantities of molecules in data-driven drug research, we have developed a low-dimensional representation of molecules and utilize it in deep learning for predicting molecular properties and designing new drugs. The concept centers on transforming a molecule's 3D electronic attributes of local hardness and softness to lower-dimensional manifold embeddings. The representation carries the inherent information of intermolecular interactions by a single molecule.

2:35 The CACHE Computational Hit-Finding Competition: Lessons Learned So Far

Matthieu Schapira, PhD, Principal Investigator, Structural Genomics Consortium

CACHE is a benchmarking exercise modeled after CASP where every four months, computational chemistry and AI experts predict up to 100 compounds for a predefined protein target. Hit candidates are then procured, tested experimentally at CACHE, and all data and a generic description of the methods are released publicly. The emerging landscape of the most successful computational hit-finding approaches so far will be outlined.

3:05 A Unified System for Molecular Property Predictions

David Huang, CEO, Oloren AI

There is no unified API for molecular property predictors (MPPs), which makes it difficult to share, distribute, version, retrain and manage predictors. We present Oloren ChemEngine (OCE), an open-source Python library with a unified, reproducible, and easy-to-integrate API for MPPs. Using OCE, we create models with the best leaderboard performances on 19 ADME/Tox benchmarks with MPP ensembling strategies. Using such API, we integrate model-agnostic uncertainty quantification and interpretability methods.

3:35 Networking Refreshment Break

AI FOR PROTEIN THERAPEUTICS

3:50 Chairperson's Remarks
Ewa Lis, PhD, Founder & CTO, Koliber Biosciences

3:55 FEATURED PRESENTATION: Protein Design Using Deep Learning
David A. Baker, PhD, Henrietta & Aubrey David Endowed Professor, Biochemistry, University of Washington
Proteins mediate the critical processes of life and beautifully solve the challenges faced during the evolution of modern organisms. Our goal is to design a new generation of proteins that address current-day problems not faced during evolution. In this talk, I will describe recent advances in protein design using both traditional physics-based approaches as well as deep learning methods to design sequences predicted to fold into desired structures.

4:25 Designing Therapeutic Antibodies with Synthetic Biology and Machine Learning
Peyton Greenside, PhD, Co-Founder & CSO, 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.

4:55 Peptide Discovery and 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.

5:25 Close of Conference

Encoded Libraries for Drug Discovery

Expanding Chemical Space for New Chemical Entities

WEDNESDAY, APRIL 12

12:00 pm Registration Open (Indigo West Foyer)

12:45 Dessert Break in the Exhibit Hall with Poster Viewing (Indigo A-G)

1:30 Welcome Remarks

ROOM LOCATION: Aqua E

DNA-ENCODED LIBRARY INNOVATIONS

1:35 Chairperson's Remarks

Joerg Scheuermann, PhD, Principal Investigator, Department of Chemistry & Applied Biosciences, ETH Zurich

1:40 FEATURED PRESENTATION: Accelerated Screening and Optimization of DEL-Hits: Cleavable Linker Platform (CLiP)

Timothy L. Foley, PhD, Senior Principal Scientist & Lab Head, DNA Encoded Library Selection & Pharmacology, Pfizer Global R&D Groton Labs

In recent years, we have seen an increase in demand for screening our DNA-Encoded Libraries (DELs) for hit identification across the Pfizer portfolio. To increase efficiency of these campaigns, we optimized our DEL-hit follow-up platform to enable both on-DNA and off-DNA hit confirmation in a seamless manner using cleavable linkers (DEL-CLiP). This talk will detail the operation and application of DEL-CLiP highlighting its impact on expediting the hit-to-lead optimization process.

2:10 Activity-Based and Cellular Analysis Technology for Encoded Libraries

Brian M. Paegel, PhD, Professor, Pharmaceuticals Sciences, University of California, Irvine

I provide updates on activity-based DEL technology, which interfaces solid-phase "OBOC" libraries with HTS-style activity assay. Our recent efforts focus on three thematic areas: 1) the discovery of translation modulators as a general strategy for interrogating the proteome via one universal biochemical activity assay, 2) development of pharmacokinetic assays for analyzing "beyond Rule of 5" libraries, and 3) novel 3D tissue culture strategies to enable cell-based DEL screening.

2:40 Exploration of New Applications of DNA-Encoded Library Technology

HITGEN

Guansai Liu, Vice President and Head of Discovery Chemistry, HitGen

DEL is an advanced and powerful tool for lead compound generation in early drug discovery stage. Here we demonstrate recent advancements and explorations of applications of DEL technology, such as fragment discovery, RNA target selections, hit/lead optimizations, nucleic acid delivery, etc.

3:10 Refreshment Break in the Exhibit Hall with Poster Viewing (Indigo A-G)

4:00 Using DNA-Encoded Libraries to Find Potent and Selective Inhibitors to Phosphodiesterases

Rachael Jetson, PhD, Senior Director, Lead Discovery, Valo Health

Phosphodiesterases (PDEs) play critical roles in cellular signaling, making them desirable therapeutic targets. Finding isoform-specific inhibitors can be essential to limiting adverse side effects in drug discovery. DEL platforms allow for simultaneous interrogation of numerous conditions in parallel making it an ideal platform to find selectivity. This presentation will highlight how we leveraged the Valo DEL platform to find potent and selective inhibitors for a PDE program.

4:30 Expanding the Scope of DNA-Encoded Libraries

Meghan Lawler, PhD, Director, Affinity Technology, Biology, Anagenex

At Anagenex, we are successfully developing methods via both machine learning and in-lab experimental design. Herein, we will discuss how our new methods have enabled us to leverage both active and inactive molecules towards the drug discovery pipeline as well as establish binding compounds for a wide range of protein classes including DNA-binding proteins.

5:00 In-Person Group Discussions (All Session Rooms)

In-Person Group 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 In-Person Group Discussions page on the conference website for a complete listing of topics and descriptions.

IN-PERSON GROUP DISCUSSION: Deploying DEL in Lead Discovery

Meghan Lawler, PhD, Director, Affinity Technology, Biology, Anagenex
Jeff A. Messer, Director, Analytics, Encoded Libraries Technology, GlaxoSmithKline
Brian M. Paegel, PhD, Professor, Pharmaceuticals Sciences, University of California, Irvine

- Improving "off-DNA" hit confirmation rates—or are they good enough?
- Machine learning with DEL data: is it living up to the hype?
- Could more be happening in the pre-competitive space?
- DEL libraries: partnering vs. in-house

5:45 Close of Day

6:15 Dinner Short Course*

SC7: DNA-Encoded Libraries
*Premium Pricing or separate registration required. See Short Courses page for details.

THURSDAY, APRIL 13

7:15 am Registration Open

7:45 Diversity in Chemistry Breakfast Discussion

IN-PERSON GROUP DISCUSSION: Diversity in Chemistry beyond Molecules: Gender and More

Michelle Arkin, PhD, Chair and Distinguished Professor, Pharmaceutical Chemistry & Director, Small Molecule Discovery Center, University of California, San Francisco
Thomas P. Garner, PhD, Principal Scientist, Biophysics, Genentech, Inc.
Justyna Sikorska, PhD, Associate Principal Scientist, Mass Spectrometry & Biophysics, Merck

Topics may include below, but will be guided by audience input:

- Where does the 'drop-off' of women in the chemistry career progression occur and why?
- How did the pandemic and other sea changes in the past three years bring us closer to or further from equality?
- What issues did you think were solved?

• Diversity in life paths should include us all – how are men and nonbinary scientists being included?

ROOM LOCATION: Indigo D+H

PLENARY KEYNOTE SESSION

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

8:35 PLENARY: Reflections on a Career as a Medicinal Chemist in Drug Discovery

Nicholas A. Meanwell, PhD, Vice President (recently retired), Small Molecule Drug Discovery, Bristol Myers Squibb Co.

A successful drug candidate depends on many factors: creativity of scientists involved, effective collaboration and commitment by the team, and the quality of the compound advanced. I reflect on a 40-year career pursuing the discovery of drug candidates designed to address unmet medical need in the cardiovascular, CNS, and viral diseases therapeutic areas and share undervalued strategies and other synthetic chemistry approaches for overcoming specific medicinal chemistry challenges.

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

ROOM LOCATION: Aqua E

NEW DNA-ENCODED LIBRARY APPLICATIONS

10:20 Chairperson's Remarks

Sylvie K. Sakata, PhD, Executive Director & Head, External Research Solutions, Pfizer Inc.

10:25 Utilizing DEL as a Primary Discovery Engine for Targeted Protein Degradation

Christopher B. Phelps, PhD, Vice President and Head, Early Discovery, Nurix Therapeutics, Inc.

Targeted protein degradation has emerged as a promising new modality for addressing previously undruggable targets. DNA-Encoded Libraries offer significant and specific advantages for identifying ligands for bifunctional degraders. Nurix has designed and deployed an integrated DEL discovery pipeline to harness novel ligases and degrade both traditional and challenging targets.

10:55 DEL Selections for Molecular Glues

Audrey E. Tolbert, PhD, Investigator, Encoded Library Technology Biology, GSK

Molecular glues are an established modality for therapeutic intervention. There is high interest in identifying putative molecular glues to modulate protein-protein interactions involved in protein degradation, cellular localization, or activity. DNA-encoded libraries allow for the screening of billions of small molecules as potential molecular glues. These molecular glues are identified via binding enrichment in the presence of both proteins over-enrichment in selections with a single protein.

11:25 We Have your Leads!

Ghotas Evindar, PhD, Senior Vice President, Discovery, Discovery, 1859 Inc.

1859 is transforming how the Life Science industry discovers new medicines by combining custom chemistry capabilities, miniaturized screening technology, and machine learning to generate novel, diverse, and bioactive Lead molecules through iterative drug discovery. With our ability to predict new chemical starting points, our platform can address new therapeutic targets, or find novel matter for those previously explored, to bring new medicines to patients in need.

11:40 DNA-Encoded Libraries for the Identification of Covalent Inhibitors

Xiaojie Bruce Lu, PhD, Professor & Principal Investigator, Chemical Biology Research Center, Chinese Academy of Sciences

DNA-encoded library has witnessed great success in recent years for the identification of hits for many biologically interesting protein targets, however, majority of the reports focused on the reversible binders, and the irreversible covalent inhibitors were less reported. This presentation will focus on the recent development in the design, synthesis, and screening of the DNA-encoded covalent library for the hit identification of irreversible inhibitors.

12:10 pm POSTER SPOTLIGHT: Next-Generation Dual-Display DNA-Encoded Chemical Libraries

Louise Plais, PhD, Post Doctoral Fellow, Pharmaceutical Sciences, ETH Zurich

To facilitate the synthesis of dual-display DNA-encoded chemical libraries (DELs) of unprecedented sizes and designs, we established a DNA platform termed the Large Encoding Design (LED). We used LED to display pairs of macrocyclic molecules built on an original scaffold. Highly combinatorial DELs (counting 6.250.000 and 56.250.000 members) were obtained and screened against diverse targets and their fingerprints showed the advantages of both macrocyclization and dual-display.

12:40 Transition to Lunch

12:50 DNA-Encoded Libraries for the Discovery of Small-Molecule Hits

Alex Satz, PhD, Senior Director DEL Strategy and Operations, WuXi Biology, WuXi AppTec

DNA-Encoded library (DEL) screening is now commonly used in the pharmaceutical industry to find novel chemical matter that modulates protein targets of interest. Point-by-point I will discuss the primary challenges and limitations of DEL screening, and concisely state the current abilities of the technology and then its potential.

1:20 Refreshment Break in the Exhibit Hall with Poster Awards Announced

Poster Award (Sponsorship Opportunity Available)

ROOM LOCATION: Indigo 202

ENCODED LIBRARIES FOR ORAL MACROCYCLICS

2:00 Chairperson's Remarks

Thomas J. Tucker, Principal Scientist, Medicinal Chemistry, Merck & Co Inc.

2:05 Discovery and Optimization of an Oral PCSK9 Macrocyclic Inhibitor from mRNA Display Screening

Thomas J. Tucker, Principal Scientist, Medicinal Chemistry, Merck & Co Inc.

This talk will highlight the discovery efforts from mRNA display screening hits to a tricyclic peptide PCSK9 inhibitor drug candidate, which demonstrated its pharmacodynamic effects similar to the FDA-approved, parenterally dosed anti-PCSK9 mAb, with the advantage of oral administration using lipidic dosing vehicle Labrasol.

2:35 Improved DNA-Encoded Libraries for Macrocyclic Peptides

Joerg Scheuermann, PhD, Principal Investigator, Department of Chemistry & Applied Biosciences, ETH Zurich

I will discuss my lab's research which touches on macrocycles (DELs) and a strategy we patented for creating super pure DELs which should work out much better in DEL selections by improving signal:noise.

3:05 Libraries and Display Selection for Macrocycles with Better Membrane Permeability

Hiroaki Suga, PhD, Professor Chemistry, Chemical Biology & Biotechnology, University of Tokyo

We design libraries of macrocycles aiming at generating better cell membrane permeability and apply to the RaPID selection against protein target of interest.

3:35 Networking Refreshment Break

ROOM LOCATION: Aqua E

CHOOSING DEL'S GREATEST HITS

3:55 Facilitating DEL Hit Triage: Estimating Data Noise Level via Selection Replicate Samples

Hongyao Zhu, PhD, Associate Research Fellow, Machine Learning and Computational Sciences, Pfizer Inc.

An approach to estimating data noise level has been developed by including replicate samples in DEL selections. The noise level is seen to be dependent on sequencing depth and specific selection conditions. The estimated noise cutoff can be used to remove compounds with low sequence reads for DEL hit triage, which greatly reduces (>100-fold) challenges encountered in DEL data analysis without impacting interpretation of the results.

4:25 Transforming DNA-Encoded Library Screening from Qualitative to Quantitative Outcomes

Ching-Hsuan Tsai, PhD, Director, Relay Therapeutics, Inc.

DEL screening has typically classified enriched compounds as binder/not binder, with a highly variable confirmation rate after off-DNA synthesis. A better understanding of the impacts of selection variables on the output of DEL could improve off-DNA confirmation rates and provide more useful datasets for ML. Here, tool compounds of known different affinities are used to validate selection techniques to improve the quantitative prediction of on-DNA affinity from DEL selections.

4:55 Applying Machine Learning to DEL Hit Selection

Patrick Neal, PhD, Analyst, Chemoinformatics, GlaxoSmithKline

Automated structure-activity relationship (SAR) analysis has historically relied on clustering, Quantitative-SAR models, or machine learning to identify potent medicines from high-throughput screening assays. We propose a new straightforward scaffold-based approach for identifying enriched chemical series. Our technique picks chemotypes by breaking down hits into a network of scaffold and scaffold fragments, then uses rank-choice voting to select which scaffolds best represent their exemplars and confer enrichment.

5:25 Close of Conference

HOTEL & TRAVEL

Conference Venue and Host Hotel:
Hilton San Diego Bayfront
1 Park Boulevard
San Diego, CA 92101

Discounted Room Rate: $273
Discounted Room Rate Cut-off Date: March 14, 2023

Visit the Travel page of DrugDiscoveryChemistry.com to make your hotel reservations and for additional information

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Select specific delegates from the pre-registration list to attend a private function at an upscale restaurant or a reception at the hotel. From extending the invitations, to venue suggestions, CHI will deliver your prospects and help you make the most of this invaluable opportunity

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CHI will set up 6-8 in-person meetings during the conference, based on your selections from the advance registration list. Our staff will handle invites, confirmations and reminders, and walk the guest over to the meeting area. This package also includes a meeting space at the venue, complimentary main-conference registrations, branding, an 8'x10' exhibit space, and more.

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Exhibitors will enjoy facilitated networking opportunities with qualified delegates, making it the perfect platform to launch a new product, collect feedback, and generate new leads. Exhibit space sells out quickly, so reserve yours today!

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» Literature Distribution (Tote Bag Insert or Chair Drop)
» Badge Lanyards
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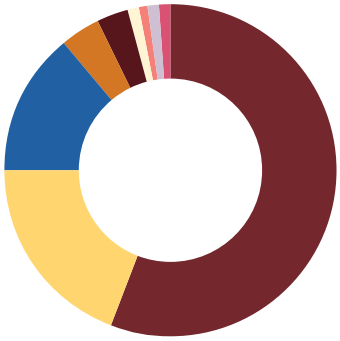
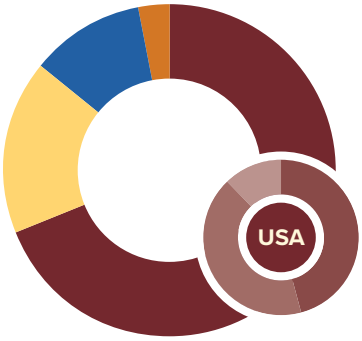
» Padfolios and More...

2022 ATTENDEE DEMOGRAPHICS



COMPANY TYPE

Biotech	56%
Pharma	19%
Academic	14%
Services	4%
Healthcare	3%
Financial	1%
Government	1%
Press	1%
Other	1%

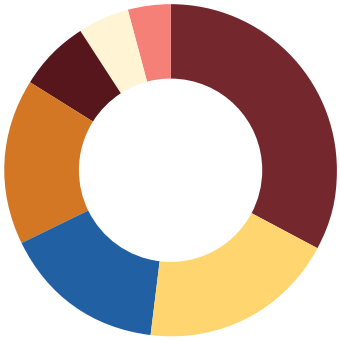


GEOGRAPHIC LOCATION

USA	69%
Europe	17%
Asia	11%
Rest of World	3%

US Breakdown

East Coast	46%
West Coast	42%
Midwest	12%



DELEGATE TITLE

Scientist/ Technologist	33%
Executive	19%
Director	16%
Sales & Marketing	16%
Professor	7%
Manager	5%
Assistant	4%

For more information regarding sponsorship and exhibit opportunities, please contact:

Kristin Skahan
Sr. Business Development Manager | 781.972.5431 | kskahan@healthtech.com

Pricing and Registration Information

CONFERENCE PRICING

	Commercial	Academic, Government, Hospital-Affiliated
PREMIUM CONFERENCE PRICING *BEST VALUE* (Includes access to ALL conferences, in-person short courses, and symposia Monday - Thursday. Plus, On-Demand access for one year.)		
Registrations After March 10, 2023	$3399	$2199
STANDARD CONFERENCE PRICING (Includes access to TWO conferences. Plus, On-Demand access for one year. Excludes short courses and symposia.)		
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One Short Course	$699	$399
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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 Bill Mote at 781-972-5479 or bmote@healthtech.com.

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

POSTER DISCOUNT ($50 Off*) Poster materials are due by **March 3, 2023.** 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.

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APRIL 10 – CONCURRENT SYMPOSIA	APRIL 11-12 – CONCURRENT CONFERENCES	APRIL 12-13 – CONCURRENT CONFERENCES
S1: Covalent Modifications & Induced Proximity	C1A: Protein Degraders & Molecular Glues - Part 1	C1B: Protein Degraders & Molecular Glues - Part 2
S2: Targeting Transcription Factors	C2A: Fragment-Based Drug Discovery	C2B: Protein-Protein Interactions
	C3A: RNA-Targeting Small Molecule Drugs	C3B: bRo5: Macrocyclics, Degraders & More
	C4A: AI for Early Drug Discovery - Part 1	C4B: AI for Early Drug Discovery - Part 2
	C5A: Small Molecule Immuno-Modulators	C5B: Encoded Libraries for Drug Discovery

SHORT COURSES (IN-PERSON ONLY)

April 10

SC1: Protein Degraders: A Focus on PROTACs from a Beyond Rule of Five Space Perspective
SC2: Fragment-Based Drug Design: Advancing Tools and Technologies
SC3: Chemical Biology for Phenotypic Screening and Target Deconvolution
SC4: Generative and Predictive AI Modeling for Protein Inhibitors and Degraders

April 12

SC5: Protein Degraders: A Focus on PROTACs from an ADME-Tox Perspective
SC6: Principles of Drug Design: Ligand-Receptor Interactions and More
SC7: DNA-Encoded Libraries
SC8: Biophysical Tools for Membrane Proteins: Drug Discovery Applications