

**EVENT
FEATURES**

200+
Speakers

14
Conference
Programs

3
Training
Seminars

8
Short
Courses

80+
Exhibiting
Companies

1,300+
International
Attendees

17th Annual

Discovery on TARGET

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

September 16-19, 2019

The Westin Copley Place
Boston, MA

PLENARY KEYNOTE PROGRAM



**Base Editing: Chemistry on a
Target Nucleotide in the Genome
of Living Cells**

David R. Liu, PhD

*Howard Hughes Medical Institute Investigator, Professor of
Chemistry & Chemical Biology, Harvard University*



PROTACs: Past, Present, and Future

Craig M. Crews, PhD

*Professor, Chemistry; Pharmacology; Molecular,
Cellular & Developmental Biology; Yale University*

Plenary Keynote Introduction Sponsored by **Syngene**

**FINAL WEEKS
TO REGISTER**

Organized by
Cambridge **Healthtech** Institute



#BostonDOT19

CONFERENCE PROGRAMS

September 17-18



Target Identification
and Validation



Lead Generation
Strategies



Emerging Ubiquitin and
Autophagy Targets



Targeting NASH



Immuno-Oncology:
Emerging Targets and
Therapeutics **NEW!**



Antibodies Against
Membrane Protein
Targets – Part 1



Antibody Forum –
Part 1



TS: Targeting GPCRs
for Drug Discovery

September 18-19



RNA as a Drug
Target **NEW!**



Kinase Inhibitor
Discovery



PROTACs and
Targeted Protein
Degradation **NEW!**



Targeting Fibrosis
NEW!



GPCR-Based Drug
Discovery



Antibodies Against
Membrane Protein
Targets – Part 2



Antibody Forum –
Part 2



TS: Introduction to Small
Molecule Drug Discovery
and Development



TS: Practical Phenotypic
Screening

DiscoveryonTARGET.com

Final Agenda

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September 16-19, 2019 • The Westin Copley Place • Boston, MA

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Antibodies Against Membrane Protein Targets – Part 1



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GPCR-Based Drug Discovery



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TS: Introduction to Small Molecule Drug Discovery and Development



TS: Practical Phenotypic Screening

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“ Discovery on Target gave us a platform to make real connections with the leading experts in cell & gene therapy to collaborate on their ground-breaking research.

– Marketing & Client Development Manager, Aldevron



HOTEL & TRAVEL

The Westin Copley Place Hotel

10 Huntington Ave
Boston, MA 02169
T: 617-262-9600

Discounted Room Rate: \$329
Reservation Cutoff: August 20, 2019

For more information, visit DiscoveryOnTarget.com

ABOUT THE EVENT

The 17th Annual Discovery on Target (DOT), the industry's preeminent event on novel drug targets and technologies, will convene over 1,300 drug discovery professionals in Boston, MA, on September 16-19, 2019. This event highlights advances in current and emerging "hot" targets and technologies, as well as target validation strategies for the discovery and development of novel therapeutic agents, ranging from biologics to small molecules. Delegates can customize their experience at the event by choosing from 14 conference programs, plus focused training seminars, comprehensive short courses, moderated roundtables and networking functions to meet their own research needs and those of their organizations.

Additions for 2019 include new programming dedicated to PROTACs and their applications, drugs and targets in fibrosis, novel immune-oncology targets, RNA as an emerging target for small molecule drugs, along with expanded coverage of protein engineering and novel biotherapeutics.



EVENT AT-A-GLANCE

Pre-Conference Short Courses

MONDAY
September 16

Immunology Basics: Focusing on Autoimmunity and Cancer

Targeting of Ion Channels with Monoclonal Antibodies

Selection, Screening and Engineering for Affinity Reagents

How to Best Utilize 3D Cells, Spheroids and PDX Models in Oncology

Applications of Artificial Intelligence and Machine Learning in Drug Discovery and Development

Biochemistry and Pharmacology of the Ubiquitin-Proteasome System

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Targeting GPCRs for Drug Discovery

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Kinase Inhibitor Discovery

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Targeted Protein Degradation Using PROTACs, Molecular Glues and More

THURSDAY
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Kinase Inhibitor Discovery

PROTACs and Targeted Protein Degradation

Targeting Fibrosis

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Training Seminars (cont.)

Introduction to Small Molecule Drug Discovery and Development
Practical Phenotypic Screening



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Opportunity includes a 30-minute podium presentation in the main session room. Lunch will be served to all delegates in attendance. A limited number of presentations are available for sponsorship and they will sell out quickly. Sign on early to secure your talk!

Invitation-Only VIP Dinner/Hospitality Suite

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 invitations, to venue suggestions, CHI will deliver your prospects and help you make the most of this invaluable experience.

Exhibit

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!

Additional branding & promotional opportunities include:

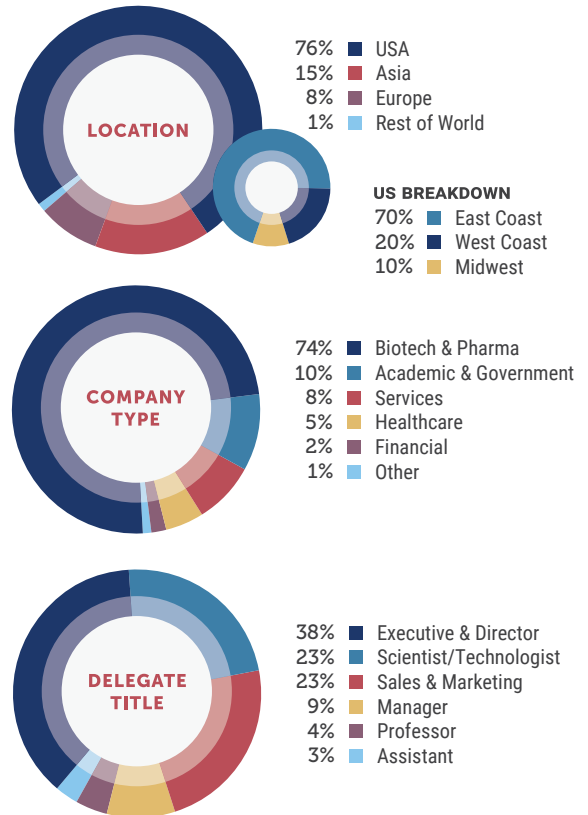
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To learn more about sponsorship and exhibit opportunities, please contact:

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2018 ATTENDEE DEMOGRAPHICS

Attendees included industry leaders, innovators and decision makers from many different backgrounds



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PLENARY KEYNOTE PROGRAM

Join **1,300** of your colleagues for the Discovery on Target Plenary Keynote Program. Bridging both halves of the event, it's the only time our whole community of drug discovery professionals assembles in one room to learn about big-picture perspectives, innovative technologies, and thought-provoking trends from luminaries in the field.

WEDNESDAY, SEPTEMBER 18 | 12:20 - 2:00 PM

12:20 pm Event Chairperson's Opening Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target 2019, Cambridge Healthtech Institute

12:30 Plenary Keynote Introduction

Anjan Chakrabarti, Vice President, Discovery Chemistry, Syngene International Ltd

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12:40 Base Editing: Chemistry on a Target Nucleotide in the Genome of Living Cells

David R. Liu, PhD, Howard Hughes Medical Institute Investigator, Professor of Chemistry & Chemical Biology, Harvard University

Point mutations represent most known human genetic variants associated with disease but are difficult to correct cleanly and efficiently using nuclease-based genome editing methods. I will describe the development, application, and evolution of base editing, a new approach to genome editing that directly converts a target base pair to another base pair in living cells without requiring double-stranded DNA breaks or donor DNA templates. We have recently expanded the scope of base editing by enhancing its efficiency, product purity, targeting scope, and DNA specificity, and have integrated these developments with *in vivo* delivery methods to treat animal models of human genetic diseases.



1:20 PROTACs: Past, Present, and Future

Craig M. Crews, PhD, Professor, Chemistry; Pharmacology; Molecular, Cellular & Developmental Biology; Yale University

The ability to control protein levels using PROTACs is changing how drugs are being developed and is expanding our concept of the druggable target space.

Moreover, PROTACs offer the advantages of siRNA but with more favorable pharmaceutical properties (ADME, biodistribution, routes of administration). For the past 18 years, Professor Crews has pioneered the development of this new modality from concept to clinical trials. Here he will describe the current and future trends in this fast-paced, exciting new therapeutic field.

2:00 Close of Plenary Keynote Program

PLENARY KEYNOTE BIOGRAPHIES:

David R. Liu, PhD

Howard Hughes Medical Institute Investigator, Professor of Chemistry & Chemical Biology, Harvard University

David R. Liu is the Richard Merkin Professor, Director of the Merkin Institute of Transformative Technologies in Healthcare, and Vice-Chair of the Faculty at the Broad Institute of Harvard and MIT; Thomas Dudley Cabot Professor of the Natural Sciences and Professor of Chemistry and Chemical Biology at Harvard University; and Howard Hughes Medical Institute Investigator. Liu graduated first in his class at Harvard in 1994. During his PhD research with Professor Peter Schultz at UC Berkeley, Liu initiated the first general effort to expand the genetic code in living cells. Liu has published ≥ 170 papers and is the inventor of ≥ 65 issued U.S. patents. In 2016 he was named one of the Top 20 Translational Researchers in the world by *Nature Biotechnology*, and in 2017 was named to the "Nature's 10" researchers in the world and to the *Foreign Policy* Leading Global Thinkers. Liu's research integrates chemistry and evolution to illuminate biology and enable next-generation therapeutics. Base editing (named one of four 2017 Breakthrough of the Year finalists by *Science*), phage-assisted continuous evolution (PACE), and DNA-templated synthesis are three examples of technologies pioneered in his laboratory. He is the scientific founder or co-founder of six biotechnology and therapeutics companies, including Editas Medicine, Pairwise Plants, Exo Therapeutics, and Beam Therapeutics.

Craig M. Crews, PhD

Professor, Chemistry; Pharmacology; Molecular, Cellular & Developmental Biology; Yale University

Dr. Crews is the American Cancer Society Professor of Molecular, Cellular and Developmental Biology and holds joint appointments in the departments of Chemistry and Pharmacology at Yale University. He graduated from the University of Virginia with a BA in Chemistry and received his PhD from Harvard University in Biochemistry. Dr. Crews has a foothold in both the academic and biotech arenas; on the faculty at Yale since 1995, his laboratory pioneered the use of small molecules to control intracellular protein levels. His first company, Proteolix, developed the proteasome inhibitor, Kyprolis™ for the treatment of multiple myeloma. His second venture, Arvinas, applies his lab's PROTAC 'induced protein degradation' technology to drug development. He has received numerous awards and honors, including the CURE Entrepreneur of the Year Award (2013), Ehrlich Award for Medicinal Chemistry (2014), Yale Cancer Center Translational Research Prize (2015), a NIH R35 Outstanding Investigator Award (2015), the AACR Award for Outstanding Achievement in Chemistry in Cancer Research (2017), the Khorana Prize from the Royal Society of Chemistry (2018), the Pierre Fabre Award for Therapeutic Innovation (2018), the Pharmacia-ASPET Award for Experimental Therapeutics (2019) and was named an American Cancer Society Professor in 2018.

*For updated Plenary Keynote details, visit:
DiscoveryOnTarget.com/plenary-keynotes





Short Courses*

PRE-CONFERENCE SHORT COURSES MONDAY, SEPTEMBER 16 | 2:00 - 5:00 PM

SC1: Immunology Basics: Focusing on Autoimmunity and Cancer

This short course provides an introduction to immunology and immunology for discovery pharmacologists, biologists and chemists working in the biopharmaceutical industry. It will review how the immune system is organized and gives rise to both normal and pathogenic immune responses. Topics will include pathogen recognition by innate immune cells, antigen generation and presentation to lymphocytes, effector mechanisms of T cells, and therapeutic modulation of the immune responses to control inflammation or promote anti-tumor immunity.

Instructor: Thomas Sundberg, PhD, Senior Research Scientist I, Center for Development of Therapeutics, Broad Institute of MIT and Harvard

SC2: Targeting of Ion Channels with Monoclonal Antibodies

Ion channels are important therapeutic targets and currently represent the second largest target class addressed by therapeutic drugs. Significant opportunities exist for targeting ion channels with antibodies, but to date it has been challenging to discover therapeutic antibodies against them. This course will examine emerging technologies and strategies for enabling the isolation of functional anti-ion channel antibodies and highlight progress via case studies.

Instructor: Trevor Wilkinson, PhD, Associate Director, Antibody Discovery and Protein Engineering, AstraZeneca BioPharmaceuticals Unit, United Kingdom

SC3: Selection, Screening and Engineering for Affinity Reagents

A comprehensive overview of different display technologies as well as screening approaches for the selection of specific binders. In addition, it will discuss engineering strategies including affinity maturation and how to implement these strategies. Classical antibodies and antibody fragments as well as alternative binding scaffolds will also be covered.

*Instructors: Jonas V. Schaefer, PhD, Laboratory Head, Novartis Institutes for BioMedical Research (NIBR), Switzerland
Christian Kunz, PhD, Director, Discovery Alliances & Technologies, MorphoSys AG, Germany*

SC4: How to Best Utilize 3D Cells, Spheroids and PDX Models in Oncology

The course will provide an overview of 3D cell culture and spheroid models currently available and where and how these models are being used, specifically for oncology research. The instructors will share their experiences on how they tested and evaluated various cell culture reagents and growth matrices, what worked, what didn't and what you need to consider when setting up low- and high-throughput screening experiments using 3D cell cultures in your lab. The challenges working with 3D cell cultures, from experimental design to data analysis, will be discussed.

*Instructors: Madhu Lal-Nag, PhD, Program Lead, Research Governance Council, Office of Translational Sciences, Center for Drug Evaluation & Research, U.S. Food and Drug Administration
Geoffrey Bartholomeusz, PhD, Associate Professor and Director, Target Identification and Validation Program, Department of Experimental Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center*

SC5: Applications of Artificial Intelligence and Machine Learning in Drug Discovery and Development

This course aims to educate a diverse group of scientists-chemists, biologists, toxicologists, and those involved in translational and clinical research, about the growing use and applications of AI & ML. Talks start with explaining the basic terminology used and what it means, followed by discussions separating the hope from the hype. It goes into the caveats and

limitations in AI and ML, while exploring ways in which it can be successfully applied in the drug discovery and development pipeline. There will be experts from various areas presenting case studies on how they have used AI/ML tools for lead optimization, target discovery, visualizing and classifying large datasets, patient stratification and more.

*Instructors: Arvind Rao, PhD, Associate Professor, Department of Computational Medicine and Bioinformatics, University of Michigan
Daniel Anderson, PhD, Vice President, Biology, Recursion Pharma
Paul Rohricht MS MBA, Chief Business Officer – Pharma, Nuritas Corporation
Kuan-Fu Ding, MSc, PhD, Chief Science Officer, Sapiens Data Science*

SC6: Biochemistry and Pharmacology of the Ubiquitin-Proteasome System

This course is intended for the audience interested in drug discovery programs aimed to develop proteolysis-targeting chimeric molecules (PROTACs) or molecular degraders, and/or small molecule inhibitors targeting components of the ubiquitin-proteasome system (UPS). The first part of the course will cover basic mechanistic biochemistry/cell biology of the ubiquitin-proteasome system, which includes E1, E2, E3, and deubiquitinating enzymes, and their macromolecular architecture. Subsequently, we will discuss assays and technologies currently available for the UPS system and known enzyme inhibitors. The second part of the course will cover PROTACs and molecular glue molecules, compounds that induce proteasomal degradation of their drug targets.

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

DINNER SHORT COURSES WEDNESDAY, SEPTEMBER 18 | 7:00 - 9:30 PM

SC8: GPCR Structure-Based Drug Discovery

The high-resolution structures of G protein-coupled receptors (GPCRs) determined by X-ray crystallography and recently by cryo-EM are rapidly impacting the pharmaceutical industry. This course will review the structural biology concepts and tools developed to date that enabled successful GPCR structural determination. We will also examine how the elucidated structures have informed our current understanding of GPCR function. Examples will be provided of how GPCR structural information is guiding rational design of subtype selectivity and functional selectivity for small molecules. Perspectives on current gaps in GPCR structure-based drug design will be provided at the end to stimulate deep thinking and discussion on how to overcome these hurdles.

Instructor: Huixian Wu, PhD, Principal Scientist, Structural and Molecular Sciences, Discovery Sciences, Pfizer, Inc.

SC9: Targeted Protein Degradation Using PROTACs, Molecular Glues and More

Targeted protein degradation using molecular glues and bifunctional small molecules known as proteolysis-targeting chimeric molecules (PROTACs) are emerging as a useful tool for drug discovery, and as a new therapeutic modality for chasing previously "undruggable" targets. This course will cover the basic understanding of what these entities are, how they work and how they can be applied to target and degrade specific proteins of interest. Case studies drawn from the work that the instructors have done in their labs will also be presented.

*Instructors: Alexander Statsyuk, PhD, Assistant Professor, Department of Pharmacological and Pharmaceutical Sciences, University of Houston
James Robinson, PhD, Team Leader, Discovery Sciences, AstraZeneca
Stewart Fisher, PhD, CSO, C4 Therapeutics*

*Separate registration required





Training SEMINARS

By Cambridge Healthtech Institute

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

TUESDAY, SEPTEMBER 17: 8:00 AM - 7:10 PM –
WEDNESDAY, SEPTEMBER 18: 8:00 AM - 2:45 PM*

TS1: Targeting GPCRs for Drug Discovery

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



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

WEDNESDAY, SEPTEMBER 18: 12:20 - 6:30 PM –
THURSDAY, SEPTEMBER 19: 7:30 AM - 4:10 PM*

TS3: Introduction to Small Molecule Drug Discovery and Development

This lecture-based interactive seminar focuses on strategies for identifying drug discovery targets, discovering and characterizing small molecule hits, and developing structure-activity relationships to advance hits through lead optimization, preclinical development, and clinical evaluation. Participants will learn the stages and processes required to advance programs from idea to clinic, through examples and case studies. This seminar is intended for scientists in either academia or industry who would like to become more familiar with small molecule drug discovery and development.



Instructor: H. James Harwood Jr., PhD, Founder and CEO, Delphi BioMedical Consultants, LLC

TS4: Practical Phenotypic Screening

Phenotypic drug discovery is experiencing a renaissance in the pharmaceutical industry, based on its successful track record in delivering first-in-class medicines. This approach offers the promise of delivering both novel targets and chemical matter modulating a disease phenotype of interest. Although phenotypic screening may appear at first sight to be similar to target-based screening, there are some significant differences between the two approaches. These need to be properly considered and addressed to ensure the greatest likelihood of success for phenotypic drug discovery programs. This training seminar will cover a range of relevant topics with a goal of providing *practical* information to help prosecute such programs more effectively from assay design all the way to clinical trials.



Instructor: Fabien Vincent, PhD, Associate Research Fellow, Discovery Sciences, Pfizer, Inc.

What is a Training Seminar?

Each CHI Training Seminar offers 1.5 days of instruction with start and stop times for each day shown above and on the Event at-a-Glance published in the onsite Program & Event Guide. Training Seminars will include morning and afternoon refreshment breaks, as applicable, and lunch will be provided to all registered attendees on the full day of the class.

Each person registered specifically for the Training Seminar will be provided with a hard copy handbook for the seminar in which they are registered. A limited number of additional handbooks will be available for other delegates who wish to attend the seminar, but after these have been distributed, no additional books will be available.

Though CHI encourages track hopping between conference programs, we ask that Training Seminars not be disturbed once they have begun. In the interest of maintaining the highest quality learning environment for Training Seminar attendees, and because seminars are conducted differently than conference programming, we ask that attendees commit to attending the entire program, and not engage in track hopping, as to not disturb the hands-on style instruction being offered to the other participants.

*Training Seminar times include Plenary Keynote Program, Interactive Breakout Discussions, and Exhibit Hall Refreshment Breaks.

STUDENT FELLOWSHIP

Full-time graduate and PhD candidates qualify for a student rate. Students are encouraged to present a research poster and receive an additional \$50 off their registration fee. Students with a research poster will be recognized as a student fellow at the event.

Deadline to submit a poster: August 16, 2019



Target Identification and Validation

Leveraging Disease Models, Functional Genomics, Phenotypic Screening & AI

Finding novel, druggable targets for therapeutic intervention remains a top priority for the pharma/biotech industry. It also remains a formidable challenge and companies continue to invest a lot of time and resources in identifying and validating targets that will yield viable drugs. What are the challenges in target discovery today? What new tools and strategies are being used to identify targets and how well are they working? What's being done to adequately validate the targets once they are identified? What efforts are being taken to go after difficult or "undruggable" targets? Cambridge Healthtech Institute's conference on Target Identification and Validation will bring together leading experts to discuss some of these critical issues. This is a unique opportunity to meet and network with biologists and screening groups from around the world to share ideas and set up collaborations.

RECOMMENDED PREMIUM PACKAGE:

Choose 2 Short Courses and 2 Conferences/Training Seminars

- September 16 Pre-Conference Short Course: **SC4: How to Best Utilize 3D Cells, Spheroids and PDX Models in Oncology**
- September 17-18 Conference: **Target Identification and Validation**
- September 18 Dinner Short Course: **SC9: Targeted Protein Degradation Using PROTACs, Molecular Glues and More**
- September 18-19 Training Seminar: **TS4: Practical Phenotypic Screening**

MONDAY, SEPTEMBER 16

1:00 pm Pre-Conference Short Course Registration

Click [here](#) for details on short courses offered.

TUESDAY, SEPTEMBER 17

7:00 am Registration Open and Morning Coffee

TARGET DISCOVERY USING ADVANCED DISEASE MODELS

8:00 Organizer's Welcome Remarks

8:05 Chairperson's Opening Remarks

Roderick Beijersbergen, PhD, Group Leader, Division of Molecular Carcinogenesis and NKI Robotics and Screening Center, The Netherlands Cancer Institute

8:10 Exploring Opportunities – Synergy in Translational Science

Madhu Lal-Nag, PhD, Program Lead, Research Governance Council, Office of Translational Sciences, Center for Drug Evaluation & Research, U.S. Food and Drug Administration

Translation is the process of turning observations in the laboratory, clinic and community into interventions that improve the health of individuals and the public – from diagnostics and therapeutics to medical procedures and behavioral changes. We will explore the challenges and solutions of identifying novel targets for rare diseases.

8:40 FEATURED PRESENTATION: CRISPR Screens in Challenging Model Systems

John Doench, PhD, Associate Director, Genetic Perturbation Platform, Broad Institute of Harvard and MIT

CRISPR screens have become the method of choice for large-scale assessment of gene function, but implementation in complex model systems remains a significant challenge. Here I will present the optimization of mouse models to discover modulators of tumor immunotherapy. Combinatorial screens present similar challenges and will also be discussed.

9:10 Aspartate/Aspergine Beta Hydroxylase (ASPH): A Potential Therapeutic Target for Overcoming HER2 Resistant Metastatic Breast Cancer

Geoffrey Bartholomeusz, PhD, Associate Professor and Director, Target Identification and Validation Program, Department of Experimental Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center

Inflammatory breast cancer (IBC), is a rare and extremely aggressive subtype of breast cancer. Mis-diagnosis and lack of effective therapies further compound the poor clinical outcome of this disease. We observed that Aspartate-beta-hydroxylase (ASPH), known to contribute to the aggressive behavior of cancers, is highly expressed in IBC. Our studies have also suggested that targeting ASPH could potentially improve our ability to treat IBC.

9:40 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

CRISPR SCREENING FOR TARGET & OFF-TARGET IDENTIFICATION

10:25 Off-Target Toxicity is a Common Mechanism-of-Action of Cancer Drugs Undergoing Clinical Trials

Jason Sheltzer, PhD, Principal Investigator, Cold Spring Harbor Laboratory

We have found that cancer cells can tolerate CRISPR-Cas9 mutagenesis of many reported cancer drug targets with no loss in cell fitness. In contrast, RNAi hairpins and small-molecules designed against those targets continue to kill cells, even when their putative target has been knocked out. We suggest that many RNAi constructs and clinical compounds exhibit much greater off-target killing than previously realized, and several dozen clinical trials have been initiated based on irreproducible preclinical research.

10:55 Functional Genomics Screening in Primary Human T Cells to Identify Novel Targets for Autoimmune Diseases

Kristin Rockwell, Senior Scientist, Discovery Sciences, Pfizer

To identify new targets/pathways involved in autoimmune disorders, we have successfully developed two high throughput functional genomics screening platforms based on primary human T-cells, high throughput flow cytometry (HT-FCM) and nucleofection technology. A siRNA screen encompassing 2,000 genes was completed, followed by a CRISPR screen to validate hits. Assay design and optimization as well as the results of these functional genomics screening efforts in primary human T cells will be presented.

11:25 Beyond Viability: Sensor-Based CRISPR Screening

Roderick Beijersbergen, PhD, Group Leader, Division of Molecular Carcinogenesis and NKI Robotics and Screening Center, The Netherlands Cancer Institute

Large scale CRISPR screens have proven their power in many different screening models, predominantly based on read-outs associated with proliferation or survival. Recently, more complex screening models such as co-cultures, cell surface marker expression or reporter gene activation have been applied. The next step is the use of even more sophisticated reporter systems that measure specific biological processes or pathways. The development and application of examples of such systems will be discussed.

11:55 Transcriptome Profiling and Functional Screening to Identify Genes Driving Biological Responses and Disease Progression

Paul Diehl, PhD, COO, Collecta, Inc.

Pooled libraries of heterogenous lentiviral constructs have proven to be an effective approach to individually label cells in a target population with cell-specific barcodes and/or other genetic effectors. NGS analysis of targeted multiplex RT-PCR from cell samples enables parallel

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Target Identification and Validation

Leveraging Disease Models, Functional Genomics, Phenotypic Screening & AI

analysis of differences in gene activation as a result of perturbation. These approaches can be used to gain a more comprehensive understanding of genetic pathways in disease.

12:25 pm Session Break

12:35 Luncheon Presentation: A Blueprint for Translational Integrated Drug Discovery

John Montana, PhD, Corporate Vice President, Integrated Drug Development and Strategic Projects, Charles River

What does the future of your drug discovery program look like? Historically high R&D costs and low success rates have emphasized the need to identify drugs focused on translationally relevant targets in the most cost and time efficient way. There are innovative ways to progress truly translational drug discovery projects in an increasingly complex and competitive environment. These case studies will demonstrate how to optimize operations and build a new model for drug development that emphasizes collaboration and novel approaches.

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 Charles River

1:15 Refreshment Break in the Exhibit Hall with Poster Viewing

GENETICS-BASED TARGET DISCOVERY

1:50 Chairperson's Remarks

Paola G. Bronson, PhD, Scientist II, Human Target Validation Core (Translational Biology), Biogen, Inc.

1:55 Human Genetics-Based Target Identification & Validation for 2x Success in the Clinic

Narender R. Gavva, PhD, Director, Early Target Discovery, Takeda California, Inc.

Most expensive clinical pipeline attrition occurs for lack of efficacy. This could be due to an over-estimation of "effect size" in target validation efforts in preclinical species/models, mismatch of candidate mechanism and clinical indication(s), clinical trial design, etc. Utilization of patient genetics as target validation is yielding targets and mechanisms with higher success in the clinic (estimated at ~2X). This presentation covers different types of human genetics and how to follow up for target validation.

2:25 Genetic Studies of MS for Drug Discovery

Paola G. Bronson, PhD, Senior Scientist, Human Target Validation Core (Translational Biology), Biogen, Inc.

Over 200 loci are associated with multiple sclerosis (MS) susceptibility, but the non-immune component is unknown and the genetic contribution to disease severity is undefined. The goals of this study were: (a) to partition out the non-immune component of MS susceptibility loci; and (b) to evaluate the impact of common genetic variants on disease severity measures (brain atrophy and serum neurofilament light) using MS clinical trial participants. We applied a colocalization strategy to identify neurological targets for MS and potential adverse events, alternate indications, and biomarkers. Our study represents a step toward using objective, quantitative traits to examine the genetics of MS progression.

2:55 SPR Binding Studies of Small Molecule Inhibitors of PRMT5

Rebecca Eells, PhD, Associate Director, Biophysical Assays, Reaction Biology Corporation

Epigenetic modifications are dynamic, reversible processes that regulate gene expression without altering DNA sequence. The proteins involved, epigenetic modifiers, are attractive targets for therapeutic discovery/development since abnormal expression/alteration leads to disease. Reaction Biology offers a suite of services for epigenetic drug discovery, including biophysical assays to directly determine the kinetics/affinity of binding to the target. Here we

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present SPR data for small molecule inhibitors of PRMT5 that engage the target using distinct binding modes.

3:25 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

4:05 Unbiased Compound-Target Interface Mapping through Forward Genetics

Moritz Horn, CEO, Acus Laboratories GmbH, Max Planck Institute for Biology of Ageing

Identifying druggable target structures and understanding an active molecules target space remain challenges in drug development. We established a chemical mutagenesis approach that allows entirely unbiased identification of small molecule targets at amino acid resolution, literally mapping compound-target interaction surfaces. Applied to relevant cellular systems, our screen uncovers specific drug target structures as well as entirely new 'druggable' targets in an unbiased and genome-wide manner.

4:35 An Evolutionary Cross-Species Approach to Context-Specifically Identify Essential Genes Using CRISPR Screens

Raghuvir "Ram" Viswanatha, PhD, Postdoctoral Research Fellow, Blavatnik Institute of Genetics, Harvard Medical School

Insect cell-lines are simple model animal cell-lines, possessing few paralogs while retaining most of the core signaling pathways underlying human disease. My research introduces new CRISPR-based functional screening strategies to insect cell-lines allowing high-resolution, genome-wide dissection of growth and signaling and uncovering new players. I will discuss published and ongoing work related to gene paralogy and redundancy, nuclear steroid hormone transport and signaling, and mTor-dependent control of cell proliferation.

5:05 Interactive Breakout Discussion Groups

Join a breakout discussion group. These are informal, moderated discussions with brainstorming and interactive problem solving, allowing participants from diverse backgrounds to exchange ideas and experiences and develop future collaborations around a focused topic. Visit the conference website for discussion topics and moderators.

6:05 Welcome Reception in the Exhibit Hall with Poster Viewing (Sponsorship Opportunity Available)

7:10 Close of Day

WEDNESDAY, SEPTEMBER 18

7:30 am Registration Open and Morning Coffee

CASE STUDIES USING PHENOTYPIC SCREENING & CHEMICAL BIOLOGY APPROACHES

8:00 Chairperson's Remarks

Jaimeen Majmudar, PhD, Principal Scientist, Chemical Biology, Pfizer, Inc.

8:05 Comparison of Target Identification Approaches Using an IRAK4 Inhibitor

Jeff Martin, PhD, Scientist II, Chemical Biology & Proteomics, Biogen, Inc.

Phenotypic screening is a key starting point for drug discovery that allows for the identification of small molecules that produce a beneficial phenotype in disease relevant models. Target identification of these small molecule hits from phenotypic screens is challenging due to the inherent complexity of the cellular systems involved. Comparison of multiple target identification



Target Identification and Validation

Leveraging Disease Models, Functional Genomics, Phenotypic Screening & AI

approaches will be described in this talk including clickable photoprobes, affinity enrichment, and CETSA.

8:35 Influence of Post-Translational Modifications, Metals and Partner Proteins on the Fe-S Cluster Synthesis Machinery

Jaimeen Majmudar, PhD, Principal Scientist, Chemical Biology, Pfizer, Inc.

Recombinant proteins are routinely utilized for high-throughput screening for identification of lead chemical equity for drug development. While this has proven of immense value, translation of biochemical screens into cellular assays can be challenging. Using the example of the Fe-S cluster machinery proteins NFS1-ISD11-ACP-ISCU2 and FXN, we show that it is critical to understand recombinant systems in the context of metal dependence, complex formation and post-translational modifications.

9:05 Utilizing Integrated Real-World Health and Genomic Data Resources for Discovery

Manjinder Sandhu, CEO, Reader in Global Health & Population Sciences, University of Cambridge, Omnigen Biodata

Large-scale clinical and biodata resources have the potential to spur innovation in drug discovery and target validation and real world data analyses—enabling precision health initiatives and informing health policy to improve the health of individuals and populations. We now have opportunities to create and integrate real-world health and genomic data globally. I outline the value of such resources and approaches to build biodata alongside participants and providers—enabling compliance with data protection and privacy.

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9:35 Coffee Break in the Exhibit Hall with Poster Viewing

10:20 Application of Chemical Proteomics in Drug Discovery: Selectivity Profiling and Target Identification

Hua Xu, PhD, Associate Research Fellow, Medicine Design, Pfizer

Chemical proteomics is a powerful and impactful tool and has been frequently used to address a number of key questions in drug discovery. A few case studies on selectivity profiling and target identification will be described to demonstrate its impact on preclinical and clinical programs at Pfizer.

10:50 - 11:50 BRIDGING LUNCHEON PANEL DISCUSSION: GPCRs: Leveraging Years of Data for Transformative Drug Discovery

This 1-hour panel moderated by *Michel Bouvier, PhD, Principal Investigator & CEO, Institute for Research in Immunology and Cancer (IRIC) and Professor, Department of Biochemistry and Molecular Medicine, Faculty of Medicine, Université de Montréal* will feature two talks related to new horizons in GPCR drug discovery. The talks will be followed by a question and answer session.

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- **GPCR Mutations: Towards a More Personalized Drug Discovery**
Olivier Lichtarge, MD, PhD, Molecular and Human Genetics, Computational and Integrative Biomedical Research Center, Baylor College of Medicine
- **Virtual Screening: A Post-Structural Era**
John Irwin, PhD, Adjunct Professor, Department of Pharmaceutical Chemistry, University of California, San Francisco

11:20 Conference Registration for Programs 1B-7B

11:50 Session Break

PLENARY KEYNOTE PROGRAM

Click [here](#) for full abstracts.

12:20 pm Event Chairperson's Opening Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target 2019, Cambridge Healthtech Institute

12:30 Plenary Keynote Introduction

Anjan Chakrabarti, Vice President, Discovery Chemistry, Syngene International Ltd

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12:40 Base Editing: Chemistry on a Target Nucleotide in the Genome of Living Cells

David R. Liu, PhD, Howard Hughes Medical Institute Investigator, Professor of Chemistry & Chemical Biology, Harvard University



1:20 PROTACs: Past, Present, and Future

Craig M. Crews, PhD, Professor, Chemistry; Pharmacology; Molecular, Cellular & Developmental Biology; Yale University

2:00 Close of Plenary Keynote Program

2:00 Dessert Break in the Exhibit Hall with Poster Viewing

2:45 Close of Target Identification and Validation Conference





Inaugural | September 18-19

RNA as a Drug Target

Expanding the Boundaries of Druggable Targets

NEW

RNA molecules are crucial for delivering cellular information and genetic regulation, but until recently, the drug discovery world has emphasized protein drug targets. Our lack of knowledge in RNA biology prevented us from exploring possibilities of RNA drug targets, but with recent advances in technologies such as sequencing, new therapeutic strategies are being explored. Join us at the Inaugural RNA as a Drug Target conference, part of Discovery on Target, as we discuss RNA as a novel target site for therapeutics.

RECOMMENDED PREMIUM PACKAGE:

Choose 2 Short Courses and 2 Conferences/Training Seminars

- September 16 Pre-Conference Short Course: **SC5: Applications of Artificial Intelligence and Machine Learning in Drug Discovery and Development**
- September 17-18 Conference: **Target Identification and Validation**
- September 18 Dinner Short Course: **SC9: Targeted Protein Degradation Using PROTACs, Molecular Glues and More**
- September 18-19 Conference: **RNA as a Drug Target**

WEDNESDAY, SEPTEMBER 18

11:20 am Conference Registration Open

PLENARY KEYNOTE PROGRAM

Click [here](#) for full abstracts.

12:20 pm Event Chairperson's Opening Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target 2019, Cambridge Healthtech Institute

12:30 Plenary Keynote Introduction

Anjan Chakrabarti, Vice President, Discovery Chemistry, Syngene International Ltd

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Syngene



12:40 Base Editing: Chemistry on a Target Nucleotide in the Genome of Living Cells

David R. Liu, PhD, Howard Hughes Medical Institute Investigator, Professor of Chemistry & Chemical Biology, Harvard University



1:20 PROTACs: Past, Present, and Future

Craig M. Crews, PhD, Professor, Chemistry; Pharmacology; Molecular, Cellular & Developmental Biology; Yale University

2:00 Close of Plenary Keynote Program

2:00 Dessert Break in the Exhibit Hall with Poster Viewing

SMALL MOLECULES TO TARGET RNA

2:45 Organizer's Welcome Remarks

2:50 Chairperson's Opening Remarks

Meizhong Jin, PhD, Senior Director, Chemistry, Arrakis Therapeutics

2:55 FEATURED PRESENTATION: Non-Coding RNA as a Small Molecule Drug Target

Elliott Nickbarg, PhD, Principal Scientist, Pharmacology Department, Merck & Co, Inc.

To understand RNA-small molecule druggability, we have validated an affinity-selection mass spectrometry screening system for detection of RNA-small molecule interactions. This system was used to screen a variety of RNA targets against diverse small molecule collections, functionally annotated compounds, and collections enriched in RNA-binding properties. The system generated

a large dataset of small molecule-ncRNA interactions. Here, we outline our approach and results, and discuss implications for new drug discovery efforts.

3:25 Directly Targeting RNA with Small Molecules

Meizhong Jin, PhD, Senior Director, Chemistry, Arrakis Therapeutics

RNA plays critical roles in gene expression and regulation and, as such, RNA molecules are implicated human disease, often via the undruggable proteins expressed by those RNAs. RNA as a therapeutic target has been validated clinically by oligonucleotide drugs although with limitations. Recent advances in RNA structure and biology point to the exciting potential of directly targeting RNA with drug-like small molecules, offering potential advantages over oligonucleotides.

3:55 Inducing the Biogenesis of Mir-124 by the Drug Candidate ABX464 Opens a Novel Way to Treat Inflammatory Diseases

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Jamal Tazi, PhD, Professor, University of Montpellier; Vice President, Research, ABIVAX; Director, Cooperative Laboratory ABIVAX-CNRS

ABX464 is a first-in-class, clinical-stage, small molecule for oral administration that has shown strong anti-inflammatory effects in patients with moderate to severe Ulcerative Colitis. ABX464 binds to the cap binding complex (CBC) leading to enhancement of the splicing of a single long noncoding RNA to generate the anti-inflammatory miR-124 in patients. The specific ability of ABX464 to generate anti-inflammatory miR-124 may pave the way of a safe and efficient treatment in several inflammatory diseases.

4:25 Refreshment Break in the Exhibit Hall with Poster Viewing

5:00 Precise and Potently Bioactive Small Molecules Interacting with RNA (SMIRNAs)

Suzanne Rzuczek, PhD, Associate Scientific Director, Expansion Therapeutics

The expanding role of RNA in disease has led to exploring RNA as a drug target; however, the ability to selectively target RNA remains challenging. We have assembled technologies and tools to facilitate the identification of specific and potent novel small molecule binders of RNA. We will highlight this generally applicable technology to the design and study of potently bioactive and selective SMIRNAs targeting CUG repeats in Myotonic Dystrophy Type 1 (DM1).

5:30 Targeting Structurally and Functionally Diverse RNAs with Drug-Like Small Molecules

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

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

6:00 Targeting Pre-mRNA Splicing with Small Molecules

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

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

6:30 Dinner Short Course Registration

Click [here](#) for details on short courses offered.





Inaugural | September 18-19

RNA as a Drug Target

Expanding the Boundaries of Druggable Targets

NEW

9:30 Close of Day

THURSDAY, SEPTEMBER 19

7:00 am Registration Open

7:30 Interactive Breakfast Breakout Discussion Groups

Grab a cup of coffee and join a breakout discussion group. These are informal, moderated discussions with brainstorming and interactive problem solving, allowing participants from diverse backgrounds to exchange ideas and experiences and develop future collaborations around a focused topic. Visit the conference website for discussion topics and moderators.

8:30 Transition to Sessions

SMALL MOLECULES TO TARGET RNA CONT.

8:40 Chairperson's Remarks

Razvan Nutiu, PhD, Investigator, Chemical Biology & Therapeutics, Novartis

8:45 Translation Control Therapeutics

Kevin Pong, PhD, Vice President, Business Development, Anima Biotech, Inc.

Anima Biotech is advancing Translation Control Therapeutics, the first platform for the discovery of small molecule drugs that specifically control mRNA translation as a new strategy against many diseases. With novel biology that monitors the translation of proteins and proprietary cloud-based analysis software, we identify drug candidates that modulate a target protein's production. We develop a pipeline across therapeutic areas and partner with Pharma for their targets including our +\$1B collaboration with Lilly. Our approach was further validated with 5 granted patents, 14 peer reviewed publications and 17 scientific collaborations.

RNA-PROTEIN COMPLEXES

9:15 RNA Splicing Modulation... Application to CD33

Tom Chappie, Associate Research Fellow, Pfizer

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

9:45 Modulating the Epitranscriptomic RNA Modifications for Cancer Therapy

Pawel Sledz, PhD, Senior Scientist, Department of Biochemistry, University of Zurich

The modifications of transcriptomic RNA (also called epitranscriptomic modifications) have recently emerged as mechanism of regulation of gene expression, and due to implication in a number of diseases have attracted attention of the drug discovery community. We have pioneered early discovery in epitranscriptomic target space focusing on modulating the protein-RNA interactions (PRIs) and RNA-modifying proteins (RMPs), and delivered lead candidates in two programs. In my talk I will discuss the challenges and opportunities in this target space, as well as provide update on our portfolio: lead generation efforts, preclinical studies, and drug-discovery platform.

10:15 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

FINDING THE DRUGGABLE STRUCTURES

10:55 Enabling Modulation of RNA Biology in Human Disease with Small Molecules

Razvan Nutiu, PhD, Investigator, Chemical Biology & Therapeutics, Novartis
RNA biology is relevant to human disease and drug discovery. To enable drug discovery in the RNA space, several key challenges have to be addressed: what are the most relevant RNA biology phenotypes that affect human disease? What are the molecular interactions that control these phenotypes? What is the chemistry capable of modulating relevant RNA structures and/or RNA/protein complexes? The presentation aims to discuss some of these challenges and to propose an integrated approach to RNA targeted drug discovery using small molecules.

11:25 FEATURED PRESENTATION: Structure-Based Discovery of New Functions in Large RNAs

Kevin Weeks, PhD, Kenan Distinguished Professor of Chemistry, University of North Carolina

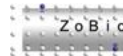
The functions of many RNA molecules – including mRNAs, long non-coding RNAs, and the genomes of RNA viruses – require that an RNA fold back on itself to create intricately and complexly folded structures. This talk will focus on recent progress in our lab with high-resolution RNA structure probing over large scales such that both secondary and tertiary structure elements can be identified and such that these structural data can be used to identify RNA elements likely to have direct and important roles in cellular function and gene regulation.

11:55 Biophysics-Based Drug Discovery for Epitranscriptomics: Fragment Derived Inhibitors of METTL3/METTL14

Stijn Gremmen, Head, Chemistry, ZoBio

Modulation of enzymes that modify RNA (epitranscriptomics) is gaining interest in drug discovery. Gotham Therapeutics and ZoBio are developing inhibitors of METTL3/METTL14, a SAM-dependent methyltransferase that modifies adenosine in mRNA to generate m6A and thereby regulates protein expression. Results from fragment screening and hit evolution that have enabled understanding of the mode of action at atomic resolution will be presented. ZoBio is now well positioned to generate *in vivo* inhibitors that will further Gotham's programs.

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12:25 pm Session Break

12:35 Luncheon Presentation (Sponsorship Opportunity Available) or Enjoy Lunch on Your Own

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

OLIGONUCLEOTIDES AND OTHER NOVEL METHODS TO TARGET RNA

2:05 Chairperson's Remarks

Arthur A. Levin, PhD, Executive Vice President, R&D, Avidity Biosciences

2:10 Oligonucleotide Therapeutics Now on Target: Advances in Antibody Oligonucleotide Conjugates (AOCs)

Arthur A. Levin, PhD, Executive Vice President, R&D, Avidity Biosciences

The ability to utilize genomic information to design oligonucleotide therapeutics is the goal of the industry. Their broader potential as therapeutics has remained untapped because delivery to cells is limited. We are utilizing monoclonal antibodies against internalized cell surface proteins as a delivery mechanism for oligonucleotide therapeutics. We have developed a technology that allows us to successfully delivery oligo payloads to multiple cell types.





Inaugural | September 18-19

RNA as a Drug Target

Expanding the Boundaries of Druggable Targets

NEW

2:40 Cooperative RNA Modulation to Improve Iron Homeostasis Specific to Neurons while Providing Anti-Amyloid Efficacy as a Potential Alzheimer's Disease Therapy

Jack Rogers, PhD, Director of Neurochemistry Laboratory, Associate Professor (HMS), Harvard University; Director of Neurochemistry Massachusetts General Hospital

The project describes an active collaboration between Drs. Jack Rogers, Catherine Cahill, Xudong Huang, Debomoy Lahiri to pursue RNA mediated therapies with the neurotrophin BL-1. This agent represses neuronal Prion Protein (anti amyloid), activates neuronal iron storage in ferritin and it can inhibit phosphorylation of the neurofibrillary associated tau protein.

3:10 PATrOL-Enabled Therapies Targeting Mutant RNA Primary and Secondary Structures

Letha Sooter, PhD, VP of Biology and Bioinformatics, NeuBase Therapeutics, Inc.

NeuBase is developing next-generation gene silencing therapies with a flexible, highly specific synthetic antisense technology. The proprietary peptide-nucleic acid (PNA) antisense oligonucleotide (PATrOL™) platform allows for the rapid development of targeted drugs, increasing the treatment opportunities for the hundreds of millions of people affected by rare genetic diseases, including those that are impossible to treat using traditional antisense approaches. Using PATrOL technology, NeuBase aims to first tackle rare, genetic neurological disorders.

3:40 PANEL DISCUSSION: What Have We Learned and Where Do We Go?

4:10 Close of Conference



Lead Generation Strategies

New Approaches and Biophysical Tools for Small Molecule and Macrocyclic Drug Leads

Finding new drug leads for medical conditions with unmet solutions is one of the biggest hurdles in recent drug discovery as the 'obvious' drug candidates have already been found. Plus, there are more molecular targets to develop new drugs against thanks to the rapid pace of medical research. Many of these new molecular targets are more complex, such as protein-protein interactions (PPIs) or protein-nucleic acid complexes, and move 'drug hunters' into less explored chemical space from which to find or design appropriate lead compounds. Luckily, synthetic chemistry and other innovations have expanded the chemical space new drug leads can occupy while still fitting the properties of a 'good drug'. Join fellow discovery chemists and biologists at the Lead Generation Strategies conference to review the various advances and strategies for finding and creating novel drug leads in today's expanded chemical and molecular universe.

RECOMMENDED PREMIUM PACKAGE:

Choose 2 Short Courses and 2 Conferences/Training Seminars

- September 16 Pre-Conference Short Course: **SC5: Applications of Artificial Intelligence and Machine Learning in Drug Discovery and Development**
- September 17-18 Conference: **Lead Generation Strategies**
- September 18 Dinner Short Course: **SC9: Targeted Protein Degradation Using PROTACs, Molecular Glues and More**
- September 18-19 Conference: **Kinase Inhibitor Discovery**

MONDAY, SEPTEMBER 16

1:00 pm Pre-Conference Short Course Registration

Click [here](#) for details on short courses offered.

TUESDAY, SEPTEMBER 17

7:00 am Registration Open and Morning Coffee

PROGRESSING FROM TARGET HITS TO DRUG LEADS

8:00 Organizer's Welcome Remarks

8:05 Chairperson's Opening Remarks

Robert D. Mazzola, PhD, Director, Chemical Research, Merck Research Labs

8:10 FEATURED PRESENTATION: Interplay between Lead Generation and Target Validation in AbbVie Early Chemistry: A Wild-Type Isocitrate Dehydrogenase 1 Case Study

J. Brad Shotwell, PhD, Senior Principal Scientist, Tool and Lead Generation Chemistry Group Leader, AbbVie

Inhibition of wild type isocitrate dehydrogenase 1 (IDH1), a key source of cytosolic NADPH under conditions of cellular stress, represents an inroad for treatment of VHL-null mutant renal cell carcinomas. We will summarize AbbVie's IDH1 lead-finding activities as they inform both best practices for an integrated hit confirmation approach and the critical interplay between small molecule lead generation and the pharmacological testing of novel target hypotheses.

8:40 Exploiting Pilot Screen Hits to Pressure-Test HTS Screening Triage Funnels

Michael Finley, PhD, Principal Scientist, Screening, Discovery Sciences, Janssen R&D

High-throughput screening (HTS) of small molecule libraries requires careful consideration of potential off-target mechanisms that may contribute to false

positives or mask identification of on-target active compounds. Employing a pilot screen of representative chemotypes of the larger collection provides a means to pressure test a triage strategy with initial hits. We illustrate several examples in which pilot data were used to identify and address gaps in HTS triage.

9:10 Encoded Library Technologies as Integrated Lead Finding Platforms for Drug Discovery

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

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

9:40 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

10:25 Phenotypic Screening Approaches to ALS

Dean G. Brown, PhD, Director, External Chemistry, Hit Discovery, Discovery Sciences, IMED Biotech Unit, AstraZeneca

10:55 Phenotypic Screening and Chemical Biology Strategies to Identify Mechanisms that Regulate Brain Apolipoprotein E Levels

Martin Pettersson, PhD, Research Fellow, Internal Medicine & Medicinal Chemistry, Pfizer

Apolipoprotein E (ApoE) is a 34 kDa protein that functions as a transporter of cholesterol and phospholipids in both the brain and the periphery. In the brain, it is produced primarily by astro-cytes, and plays an important role in neuronal repair, synaptogenesis, and clearance of neurotoxic amyloid β peptides. This presentation will describe phenotypic screening approaches to identify compounds that regulate ApoE secretion. Chemical biology strategies to elucidate mechanism of action will also be discussed.

11:25 CryoEM Applications for Drug Discovery

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

Since the introduction of direct electron detectors, the resolution and range of biological molecules amenable to single particle cryo-EM have significantly widened. The prospects of studying protein-ligand interactions of large macromolecular complexes such as ribosome, viral glycoprotein complexes, ion-channels, gamma-secretase etc. without having to generate single crystal, are definitely appealing. We have started to work on several targets to support the discovery of new drugs and vaccines. I will describe the applications of cryo-EM and progresses we have made.

11:55 Preclinical Approaches to Develop Treatment for Tinnitus

Sylvie Pucheu, CSO, CILcare

Tinnitus is usually perceived as an intermittent or continuous sound. There are many mechanisms inducing tinnitus (acoustic trauma, drug intake, oxidative stress, inflammation), for which there are no approved drugs. This is why CILcare proposes preclinical approaches to help pharmaceutical companies develop new therapies to prevent and treat tinnitus.

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12:10 pm Deep Learning Applied to de novo Drug Design

Yann Gaston-Mathé, CEO, Iktos

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Lead Generation Strategies

New Approaches and Biophysical Tools for Small Molecule and Macrocyclic Drug Leads

Simultaneous optimization of multiple objectives is a major challenge in drug discovery. We present the application of Iktos' AI technology to a complex MPO challenge in a real-life lead optimization project and show that the technology is capable of generating compounds matching all the objectives of the target product profile.

12:25 Session Break

12:35 Grating-Coupled Interferometry's Integration into LeadXpro's Structure-Based Drug Discovery Pipeline

Nicolas Bocquet, PhD, Principal Scientist, leadXpro AG

LeadXpro is a world-class structure based lead (small molecules and biologics) discovery company focusing on challenging membrane protein drug targets, including G-protein coupled receptors (GPCRs), ion channels and transporters. With access to state-of-the-art facilities for structure determination, including the SwissFEL and a single particle cryo-EM system, leadXpro uses the Grating-Coupled Interferometry (GCI) technology to characterize in depth ligand interactions to transmembrane proteins, a significant challenge in the drug discovery "gene-to-lead" process.

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1:15 Refreshment Break in the Exhibit Hall with Poster Viewing

COVALENT FRAGMENTS AS DRUG DISCOVERY TOOLS

1:50 Chairperson's Remarks

Beth Knapp-Reed, PhD, Scientific Leader, NCE-MD Medicinal Chemistry, R&D Platform Technology & Science, GSK

1:55 Use of Chemotype Evolution to Discover Novel, Potent, Irreversible Inhibitors of the Oncogenic G12C Mutant Form of k-RAS

Dan Erlanson, PhD, Co-Founder, Carmot Therapeutics

The protein KRAS has been intensively studied as an oncology target. This presentation will demonstrate how a powerful lead discovery technology, Chemotype Evolution, along with medicinal chemistry and structure-based drug design, were combined to discover novel, irreversible small molecule inhibitors of the oncogenic G12C mutant form of KRAS with potent biochemical and cell-based activity.

2:25 Reactive-Cysteine Profiling for Covalent Ligand Discovery

Eranthie Weerapana, PhD, Associate Professor, Department of Chemistry, Boston College

Reactive and functional cysteine residues provide ideal anchors for covalent ligands. This presentation will focus on the application of a chemical-proteomic technology, known as isoTOP-ABPP, to identify functional cysteines, and monitor proteome-wide selectivity of cysteine-targeted ligands.

2:55 NEW: Poster Spotlight(s): Fragment-Based Molecular Discovery Approach to RAGE Inhibitors

Natalia Kozlyuk, PhD, Postdoctoral Researcher, Structural Biology, Walter Chazin Laboratory, Vanderbilt University

3:25 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

4:05 Covalent Fragments Technology for Drug Lead Generation: Past, Present, and Future

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

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

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

4:35 Applying Covalent Fragment Approaches to E3 Ligase Inhibitor Discovery

Katrin Rittinger, PhD, Professor, Molecular Structure of Cell Signaling, The Francis Crick Institute, UK

Protein ubiquitination is a critical mechanism to regulate almost all biological processes and defects in the ubiquitin system that are associated with many diseases. However, only a limited number of inhibitors against enzymes of the ubiquitin system are available. I will present a fragment-based covalent ligand screening approach to identify inhibitors of thioester-forming E3 ubiquitin ligases and describe the structure-based development of an inhibitor specific for the RBR ligase HOIP.

5:05 Interactive Breakout Discussion Groups

Join a breakout discussion group. These are informal, moderated discussions with brainstorming and interactive problem solving, allowing participants from diverse backgrounds to exchange ideas and experiences and develop future collaborations around a focused topic. Visit the conference website for discussion topics and moderators.

6:05 Welcome Reception in the Exhibit Hall with Poster Viewing (Sponsorship Opportunity Available)

7:10 Close of Day

WEDNESDAY, SEPTEMBER 18

7:30 am Registration Open and Morning Coffee

FRAGMENT-BASED AND ORTHOGONAL APPROACHES

8:00 Chairperson's Remarks

J. Brad Shotwell, PhD, Senior Principal Scientist, Tool and Lead Generation Chemistry Group Leader, AbbVie

8:05 Fragment Screening to Assess Target Ligandability

Fredrik Edfeldt, PhD, Associate Principal Scientist, Discovery Sciences, R&D Biopharmaceuticals, AstraZeneca, Gothenburg, Sweden

Evaluating the ligandability, or chemical tractability, of a protein target is critical when defining hit-finding strategies or to prioritize amongst potential targets. Fragment screening has emerged as a useful approach for this purpose. We demonstrate that thermal shift assays can be used as a simple and generic biophysical method to assess target ligandability. We have applied the method to a set of proteins and show that the assessment is predictive for the success of HTS.

8:35 Fragment-Based Approach to Lactate Dehydrogenase A (LDHA) Inhibitors

Beth Knapp-Reed, PhD, Scientific Leader, NCE-MD Medicinal Chemistry, R&D Platform Technology & Science, GSK

A fragment-based approach was used to identify a unique series of LDHA inhibitors with good ligand efficiencies. Subsequent optimization delivered a novel lead series with LDHA cellular activity of 10 μ M, selectivity against LDHB, and good physicochemical properties. The overall strategy of identification and optimization, lessons learned, and some guiding principles of the FBDD effort will be presented in the context of the discovery of a fragment-derived lead series for the inhibition of LDHA.



Lead Generation Strategies

New Approaches and Biophysical Tools for Small Molecule and Macrocyclic Drug Leads

9:05 CDH and Polipa: Novel Approaches to Overcome Target Expression Challenges for FBDD

Daniel Hothersall, Senior Assay Development Scientist, Domainex Ltd.

Domainex is opening up new frontiers in fragment-based drug design. Our Combinatorial Domain Hunting technology is a proven, high throughput method for unlocking challenging targets for structural elucidation. PoliPa is a new approach to the solubilisation of membrane targets without the use of detergents or the need to resort to stabilising mutations. Our talk will discuss the application of these technologies to aid FBDD, citing a number of case studies.

9:35 Coffee Break in the Exhibit Hall with Poster Viewing

10:20 Fragment-Based Discovery and Characterization of ERK1/2 Inhibitors

Puja Pathuri, PhD, Associate Director, Molecular Sciences, Astex Pharmaceuticals

Using a fragment-based campaign and multiple screening methods, including high throughput crystallography and biophysical assays, we identified and developed novel, orally bioavailable inhibitors of ERK1/2 – key components of the Ras signaling pathway in cancer cells. The inhibitors elicit a similar conformational change to currently available inhibitors but also modulate phosphorylation of ERK. Our series of pERK modulating ERK1/2 inhibitors went through progressive rounds of structure-guided optimization and iterative optimizations. The screening cascade included measurement of pRSK levels and anti-proliferative activity in ras and BRAF mutant cells.

10:50 Drug Discovery Using DNA-Encoded Chemical Libraries

Rachael Jetson, PhD, Senior Research Scientist, Lead Discovery, X-Chem Pharmaceuticals

X-Chem's DNA-encoded chemistry platform provides a method to simultaneously interrogate a diverse chemical library against many targets to identify lead compounds. This presentation will describe the X-Chem platform and highlight case studies leading to the discovery of novel covalent and non-covalent chemical equity to multiple targets.

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PHARMACEUTICALS

11:20 Enjoy Lunch on Your Own

11:20 Conference Registration for Programs 1B-7B

PLENARY KEYNOTE PROGRAM

Click [here](#) for full abstracts.

12:20 pm Event Chairperson's Opening Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target 2019, Cambridge Healthtech Institute

12:30 Plenary Keynote Introduction

Anjan Chakrabarti, Vice President, Discovery Chemistry, Syngene International Ltd

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Syngene



12:40 Base Editing: Chemistry on a Target Nucleotide in the Genome of Living Cells

David R. Liu, PhD, Howard Hughes Medical Institute Investigator, Professor of Chemistry & Chemical Biology,

Harvard University



1:20 PROTACs: Past, Present, and Future

Craig M. Crews, PhD, Professor, Chemistry; Pharmacology; Molecular, Cellular & Developmental Biology; Yale University

2:00 Close of Plenary Keynote Program

2:00 Dessert Break in the Exhibit Hall with Poster Viewing

2:45 Close of Lead Generation Strategies Conference

Share Your Research: Submit a Poster Abstract

Attendees can gain further exposure and networking by presenting their work in the poster sessions. Dedicated poster sessions occur in the Exhibit Hall. Network, collaborate and enhance your time out of the office.

Reasons you should present your research poster at this conference:

- Your poster will be available to 1,300+ delegates
- You'll automatically be entered into our poster competition where two winners each will receive an American Express Gift Certificate
- \$50 off your registration fee
- Your research will be seen by leaders from pharmaceutical, biotech, academic and government institutes



Deadline:
August 16, 2019

Learn more:

DiscoveryOnTarget.com/posters

Kinase Inhibitor Discovery

Emerging Targets, Tools, and Development Strategies

The human kinome is a very large and druggable class of targets with many disease indications. Thus, the kinome targets account for a significant portion of drug discovery efforts. Kinase inhibitor discovery is a very active area as developers explore more deeply into designing immune-modulatory agents as single or combination therapies, tackling chronic disease indications such as inflammation and CNS disorders as well as effectively harnessing allosteric modulators and covalently binding compounds. This year we'll also be discussing PROTACs and the role of artificial intelligence in kinase inhibitor discovery.

RECOMMENDED PREMIUM PACKAGE:

Choose 2 Short Courses and 2 Conferences/Training Seminars

- September 16 Pre-Conference Short Course: **SC5: Applications of Artificial Intelligence and Machine Learning in Drug Discovery and Development**
- September 17-18 Conference: **Emerging Ubiquitin and Autophagy Targets**
- September 18 Dinner Short Course: **SC9: Targeted Protein Degradation Using PROTACs, Molecular Glues and More**
- September 18-19 Conference: **Kinase Inhibitor Discovery**

WEDNESDAY, SEPTEMBER 18

11:20 am **Conference Registration Open**

PLENARY KEYNOTE PROGRAM

Click [here](#) for full abstracts.

12:20 pm Event Chairperson's Opening Remarks

An-Dinh Nguyen, Team Lead, *Discovery on Target 2019*, Cambridge Healthtech Institute

12:30 Plenary Keynote Introduction

Anjan Chakrabarti, Vice President, *Discovery Chemistry*, Syngene International Ltd

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12:40 Base Editing: Chemistry on a Target Nucleotide in the Genome of Living Cells

David R. Liu, PhD, *Howard Hughes Medical Institute Investigator, Professor of Chemistry & Chemical Biology*, Harvard University



1:20 PROTACs: Past, Present, and Future

Craig M. Crews, PhD, *Professor, Chemistry; Pharmacology; Molecular, Cellular & Developmental Biology*, Yale University

2:00 Close of Plenary Keynote Program

2:00 **Dessert Break in the Exhibit Hall with Poster Viewing**

EMERGING CHALLENGES AND OPPORTUNITIES

2:45 **Organizer's Welcome Remarks**

2:50 **Chairperson's Opening Remarks**

Mary M. Mader, PhD, Vice President, *Chemistry, Relay Therapeutics, Inc.*

2:55 **Targeting Human Pseudokinases with Kinase Inhibitors**

Patrick Evers, PhD, *Professor, Cell Signaling, Biochemistry, University of Liverpool*

Protein pseudokinases are atypical (usually inactive) members of the human kinome. The thriving pseudokinase field is strongly placed to benefit from decades of research undertaken on canonical protein kinases, and the

approval of ~50 kinase inhibitors in oncology and inflammatory indications. In this talk, I will focus on the serendipitous discovery of covalent modulators of Tribbles 2 (TRIB2) pseudokinase, which induces a conformation that drives TRIB2 degradation in human cells.

3:25 Brain Penetrant Kinase Chemotherapeutics: Learnings from CNS Discovery

Mary M. Mader, PhD, Vice President, *Chemistry, Relay Therapeutics, Inc.*

Brain penetrance is significantly impacted by the physicochemical properties of the drugs. Compound properties associated with brain penetrance have been analyzed recently for kinase inhibitors in glioblastoma trials, although many of these examples exploit opportunities identified in clinical development rather than specific compound design strategies. An examination of kinase inhibitors that were optimized specifically for CNS indications could provide insight into preferred property space and lead to greater success in neuro-oncology efforts.

3:55 KiPIK, a New Inhibitor-Based Approach to Identify Kinases for Specific Phosphorylation Sites

Jonathan Higgins, DPhil, *Professor of Eukaryotic Molecular Cell Biology, Institute for Cell and Molecular Biosciences, Newcastle University*

There are thousands of known cellular phosphorylation sites, but it remains difficult to identify the kinases responsible for particular phosphorylation events. To address this, we describe a general method that exploits libraries of broadly-profiled protein kinase inhibitors. The inhibition profile for each kinase provides a 'fingerprint' that allows unknown kinases acting on target phosphosites in cell extracts to be identified. The method may be useful in both discovery science and precision medicine.

4:25 **Refreshment Break in the Exhibit Hall with Poster Viewing**

5:00 Discovery and Development of PI4KIII β Inhibitors with a Unique Immuno-Suppressive Phenotype Enabling the Prolongation of Allogeneic Organ Engraftment

Helen Horsley, Senior Principal Scientist, *Medicinal Chemistry, UCB Pharma*

The target of a novel series of immunosuppressive piperazine ureas is the lipid kinase PI4KIII β and a link between inhibition of PI4KIII β and suppression of immune responses *in vitro* and *in vivo* has emerged. Here we detail the identification of UCB9608 and discuss the binding mode and selectivity profile of this novel inhibitor, and the implications this may have on the observed tolerogenic phenotype.

5:30 Targeted Therapy in Patients with PIK3CA-Related Overgrowth Syndrome

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

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

6:00 **Artificial Intelligence in Kinase Inhibitor Discovery**

Istvan J. Enyedy, PhD, *Principal Scientist, Biogen*

Machine learning in combination with automated inhibitor optimization and statistical analysis may be used to accelerate kinase inhibitor discovery. The performance of a prototype artificial intelligence protocol will be presented.

6:30 **Dinner Short Course Registration**



Click [here](#) for details on short courses offered.

9:30 Close of Day

THURSDAY, SEPTEMBER 19

7:00 am Registration Open

7:30 Interactive Breakfast Breakout Discussion Groups

Grab a cup of coffee and join a breakout discussion group. These are informal, moderated discussions with brainstorming and interactive problem solving, allowing participants from diverse backgrounds to exchange ideas and experiences and develop future collaborations around a focused topic. Visit the conference website for discussion topics and moderators.

8:30 Transition to Sessions

APPROVED, IN-CLINIC AND ADVANCED INHIBITORS

8:40 Chairperson's Remarks

Istvan J. Enyedy, PhD, Principal Scientist, Biogen

8:45 Characterization of HER2 Mutations Identified in a Patient with an Initial Response and Acquired Resistance to Neratinib

Ariella B. Harker, PhD, Assistant Professor, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center

HER2 is mutated in 2-4% of breast cancers. We identified a HER2T798I gatekeeper mutation in a patient with HER2L869R-mutant breast cancer with acquired resistance to the HER2 TKI neratinib. Laboratory studies suggested that HER2L869R is a neratinib-sensitive, gain-of-function mutation. The patient exhibited a sustained partial response on neratinib. Upon progression, acquired HER2T798I was detected. Structural modeling and laboratory studies showed that HER2T798I prevented neratinib binding, which was overcome by afatinib.

9:15 Discovery of BLU-667 for RET-Driven Cancers

Jason Brubaker, PhD, Director of Chemistry, Blueprint Medicines

BLU-667 is an oral precision therapy designed for highly potent and selective targeting of oncogenic RET alterations and resistance mutants. Our fully annotated kinase inhibitor library was used to identify several RET inhibitor scaffolds. The optimization of these starting points to lead to the discovery of BLU-667 will be described.

9:45 Targeting PI3K-gamma with IPI-549, a Tumor Macrophage-Reprogramming Small Molecule, in Patients with Advanced Solid Tumors

Jeffery L. Kutok, MD, PhD, CSO, Infinity Pharmaceuticals, Inc.

IPI-549 is a first-in-class, oral, selective PI3K- γ inhibitor that in preclinical studies reprograms tumor macrophages from an immune-suppressive (M2) phenotype, to an immune-activating (M1) phenotype and can overcome intrinsic resistance to checkpoint inhibitors. A Ph 1/1b study IPI-549-01 (NCT02637531) is evaluating the safety, efficacy, tolerability, pharmacokinetics, pharmacodynamics, and immunomodulatory activity of IPI-549 as monotherapy and combined with nivolumab, in over 200 patients with advanced solid tumors.

10:15 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

10:55 Tarloxotinib, a Hypoxia Activated Prodrug for EGFR and HER2 Exon 20 Insertion Mutant NSCLC

Vijaya Tirunagaru, PhD, VP, Head of Biology and Non-Clinical Development,

Research, Rain Therapeutics

EGFR and HER2 exon 20 insertion mutations in non-small cell lung cancers are resistant to current EGFR inhibitors and lack an effective therapy. Similarity of exon20 insertions to WT EGFR in the drug binding pocket limits the therapeutic window for WT EGFR mediated toxicities. Tarloxotinib selectively releases active EGFR inhibitor in the hypoxic tumors and enhances tumor dose intensity while minimizing systemic toxicities.

NEW APPROACHES & APPLICATIONS FOR PROTEIN DEGRADATION

11:25 Orally Active IRAK4 Degraders for Oncology and Autoimmune Diseases

Nello Mainolfi, PhD, Founder and CSO, Kymera Therapeutics, Inc.

Targeted protein degradation combines the power of eliminating a disease-causing protein with the advantages of small molecule circulation in the body. Kymera is pioneering and advancing this technology by designing novel heterobifunctional molecules that engage the target protein and the E3 ligases to direct the target protein to be selectively degraded by the ubiquitin proteasome system. We have utilized this technology to successfully degrade IRAK4, a key node in innate immunity and cancer. This talk will describe the investigation of the pharmacology of IRAK4 degraders, in cellular systems and *in vivo*.

11:55 Sponsored Presentation (Opportunity Available)

12:25 pm Session Break

12:35 Luncheon Presentation: Use of InCELL Pulse™ Cellular Thermal Shift Target Engagement Assays in Early Drug Discovery

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Paul Shapiro, PhD, Group Leader, Assay and Product Development, Research and Development Department, Eurofins DiscoverX

A common problem in early target-based drug discovery is the lack of correlation between potencies, or even rank order of potencies, derived from initial biochemical screens and those observed in cellular assays. In phenotypic screening approaches, often the actual drug target is unknown and needs to be identified and proven. Cellular thermal shift assays for target engagement are of increasing interest because they bridge these gaps, however, existing technologies have been cumbersome and low-throughput. InCELL Pulse™, using Eurofins DiscoverX Enzyme Fragment Complementation technology, is a rapid, homogeneous, cell-based assay based on ligand-induced changes in protein thermal stability and is used to study drug-target engagement in live cells. We have successfully applied InCELL Pulse™ to rapidly measure quantitative cellular target engagement potency values for ligands of diverse intracellular protein classes such as kinases, methyltransferases, and hydrolases.

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

NEW APPROACHES & APPLICATIONS FOR PROTEIN DEGRADATION (CONT.)

2:05 Chairperson's Remarks

Nello Mainolfi, PhD, Founder and CSO, Kymera Therapeutics, Inc.

2:10 KEYNOTE PRESENTATION AND DISCUSSION: Targeting Kinases for Degradation- Challenges and Opportunities

Nathanael S. Gray, PhD, Professor of Biological Chemistry and Molecular Pharmacology, Dana-Farber Cancer Institute

Heterobifunctional molecules that recruit E3 ubiquitin ligases, such as cereblon, for targeted protein degradation represent an emerging pharmacological strategy. A major unanswered question is how generally



applicable this strategy is to all protein targets. In this talks I will discuss our efforts to develop chemoproteomic strategies to identify degradable kinases. Methods to characterize small molecule kinase degraders will also be discussed.

3:10 E3 Ubiquitin Ligases for PROTACs Discovery

Matthieu Schapira, PhD, Principal Investigator, Structural Genomics Consortium and Associate Professor, Pharmacology & Toxicology, University of Toronto

To be active, a PROTAC must induce the formation of a productive complex between a target of interest and a structurally and functionally compatible E3 ubiquitin ligase. Considering that less than ten E3 ligases out of over 600 in the human proteome are exploited by current PROTACs, extending the repertoire of ligands to E3 ligases with a variety of structural properties as well as diverse temporal and spatial expression profiles should considerably expand potential applications of PROTACs for chemical biology, and broaden the horizon for future drug discovery efforts. I will review the classification, ubiquitin-proteasome system association, tissue expression profile and druggability of human E3 ligases.

3:40 Close of Conference



Emerging Ubiquitin and Autophagy Targets

Novel Probes, Assays and Small Molecules Modulators for Protein Degradation

Autophagy and the ubiquitin-proteasome system (UPS) are the two major pathways responsible for protein degradation and maintenance of cellular homeostasis. They consist of well-controlled, selective mechanisms for intracellular protein degradation and turnover. New understanding of the role and molecular mechanisms involved in the dysregulation of autophagy and ubiquitin pathways has revealed its underlying role in cancer, CNS, immunology and other diseases. However, the diversity of substrates and the multi-step processes involved, make it difficult to target these pathways for therapeutic intervention. In recent years, the development of high-quality chemical probes, small molecule modulators, assays and screening platforms have helped identify novel autophagy and ubiquitin targets for drug discovery. Cambridge Healthtech Institute's conference on Emerging Ubiquitin and Autophagy Targets will bring together a diverse group of chemists and biologists to discuss the promise and challenges in this area of research. This conference will be followed by one that focuses exclusively on targeted protein degradation using proteolysis-targeting chimeric molecules (PROTACs) and other molecular entities for hijacking the ubiquitin system.

RECOMMENDED PREMIUM PACKAGE:

Choose 2 Short Courses and 2 Conferences/Training Seminars

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- September 17-18 Conference: **Emerging Ubiquitin and Autophagy Targets**
- September 18 Dinner Short Course: **SC9: Targeted Protein Degradation Using PROTACs, Molecular Glues and More**
- September 18-19 Conference: **PROTACs and Targeted Protein Degradation**

MONDAY, SEPTEMBER 16

1:00 pm Pre-Conference Short Course Registration

Click [here](#) for details on short courses offered.

TUESDAY, SEPTEMBER 17

7:00 am Registration Open and Morning Coffee

PROBING PPI & PROTEIN DEGRADATION

8:00 Organizer's Welcome Remarks

8:05 Chairperson's Opening Remarks

Tanuja Koppal, PhD, Conference Director, Cambridge Healthtech Institute

8:10 New Technologies to Discover E3 Ligase Inhibitors, Activators, Hijackers

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

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

8:40 Drugging the Fbw7 E3 Ligase with a Combined Computational and Fragment-Based Approach

Carles Galdeano, PhD, Serra Hunter Professor, Department of Pharmacy and Pharmaceutical Technology and Physical Chemistry, University of Barcelona

We have developed a multidisciplinary computational and biophysical approach to identify ligands that target E3 ligases, and specifically the Fbw7 E3 ligase. Fbw7 is one of the most commonly deregulated UPS protein in human cancers, which targets some key human onco-proteins including cyclin-E, MYC, Notch and Junk. So far, no potent small molecule directly targeting the Fbw7 complex has been reported. Our approach has allowed us to identify ligands able to bind at the low micromolar level to the Fbw7 protein. Work is on-going to elucidate the binding mode and the potential MOA of these ligands.

9:10 ULK3 Kinase as a Key Regulator of Cancer Associated Fibroblast Conversion

Sandro Goruppi, PhD, Instructor in Dermatology, Harvard Medical School, Cutaneous Biology Research Center, Massachusetts General Hospital

The connection between pathways and the role of microenvironment metabolic alterations in cancer associated fibroblasts (CAFs) activation is unknown. CSL/RBPJ suppress gene expression program(s) leading to CAF activation. GLI signaling also contributes to CAF conversion. I will report on a degradative autophagy mechanism targeting CSL and leading to CAF activation. Then I will outline the identification and targeting of ULK3 kinase, which links CSL and GLI signaling and represent a tool for stroma-focused anti-cancer intervention.

9:40 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

10:25 Analysis of Mammalian ER-Associated Degradation Using Genome-Wide CRISPR Screens

Dara E. Leto, PhD, Basic Life Research Scientist, Departments of Biology, Genetics, Chemical and Systems Biology and Program in Chemistry, Engineering and Medicine for Human Health, Stanford University

Only a handful of ubiquitin-proteasome system (UPS) components have been linked to the recognition and degradation of specific protein quality control substrates. To identify genes required for the destruction of distinct clients of the ER-associated degradation (ERAD) system, we developed a screening approach that combines genome-wide CRISPR-Cas9-mediated gene deletions and a phenotypic selection based on protein turnover kinetics. Our findings show that forward genetic analysis can be used to discover new biochemical pathways in protein quality control.

10:55 Engineering Protein-Protein Interactions to Probe and Rewire Ubiquitin Signaling

Wei Zhang, PhD, Assistant Professor, Molecular and Cellular Biology, University of Guelph

Advances of genomic technologies accelerated the identification of signal transduction cascades essential for initiation and progression of human diseases. In particular, protein-protein interactions in ubiquitin signaling are found to play critical roles in eliciting numerous mis-regulated biological functions. We employ structure-based combinatorial protein design and engineering strategies to develop potent and selective modulators to probe the ubiquitin signaling pathways with unprecedented precision for underlying molecular mechanisms and potential therapeutics.

11:25 Structures of the Substrate-Engaged Proteasome Reveal the Mechanism of Translocation and Activation

Andres Hernandez de la Peña, PhD, Scientist I, Structural and Chemical Biology, Celgene

As the primary eukaryotic proteolytic machine, the 26S proteasome is responsible for ubiquitin-mediated degradation of misfolded, damaged, or obsolete proteins. We determined several structures of the proteasome as it actively translocated substrate. These structures reveal the mechano-chemical coupling of ATP hydrolysis to substrate translocation and gate opening. Additionally, these structures reveal a co-translocational deubiquitination mechanism that positions ubiquitin and the isopeptide scissile bond in the Rpn11 deubiquitinase.



Emerging Ubiquitin and Autophagy Targets

Novel Probes, Assays and Small Molecules Modulators for Protein Degradation

11:55 Presentation to be Announced

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IBM Watson Health.

12:25 pm Session Break

12:35 Luncheon Presentation (*Sponsorship Opportunity Available*) or
Enjoy Lunch on Your Own

1:15 Refreshment Break in the Exhibit Hall with Poster Viewing

DEVELOPING SMALL MOLECULE UBIQUITIN-MEDIATED DEGRADATION

1:50 Chairperson's Remarks

Yue Xiong, PhD, William R. Kenan Professor of the Biochemistry and Biophysics, University of North Carolina; Co-Founder, Cullgen

1:55 SMARCA2/4 Degradation for Cancer Therapy

Susanta Samajdar, PhD, Senior Vice President and Head of Discovery, Aurigene
SMARCA2 and SMARCA4 are ATPases in the SWI/SNF complexes, which function in regulating transcription, DNA replication and repair. SMARCA4 is mutated in a number of cancers, which are dependent on functional SMARCA2. SMARCA4 is also highly expressed without mutation in certain other tumor types, where overexpression contributes to proliferation and survival. In view of these findings, our efforts in developing novel bi-functional molecules inducing proteasome-mediated degradation of SMARCA2/4 for the treatment of cancers will be presented.

2:25 Ubiquitin-Mediated Small Molecule Induced Target Elimination in Cancer

Yue Xiong, PhD, William R. Kenan Professor of the Biochemistry and Biophysics, University of North Carolina; Co-Founder, Cullgen

Development of small molecules to target ubiquitin-dependent degradation of disease-linked proteins represents a promising opportunity for the drug discovery. Multiple such small molecules have been developed based on different E3 ubiquitin ligases. I will discuss the catalytic mechanism, assembly and regulation of cullin-RING E3 ubiquitin ligases (CRLs). I will also present our efforts in developing novel degraders targeting different human cancer protein. Finally, I will share some thoughts on the development of novel E3 ligands.

2:55 Sponsored Presentation (*Opportunity Available*)

3:25 Refreshment Break in the Exhibit Hall with Poster Viewing and
Poster Competition Winner Announced

NOVEL APPROACHES FOR PROTEIN DEGRADATION

4:05 New Ubiquitin Ligases and Novel PROTAC Approaches

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

Ligases that reside primarily in the nucleus are not suited to cytosolic targets, for example, while membrane-associated ligases are required to target GPCRs and other membrane associated targets. Novel E3 ligases and ligands would thus expand the therapeutic potential of PROTACs and provide new IP. I will present data on PROTACs that hijack novel ubiquitin ligases to ubiquitylate targets affecting immune oncology and anti-inflammatory cascades. Degradative versus non-degradative ubiquitylation and relationships between the type of ubiquitylation and PROTAC-targeted function will be discussed.

4:35 Broad-Spectrum Proteome Editing with an Engineered Bacterial Ubiquitin Ligase Mimic

Matthew DeLisa, PhD, William L. Lewis Professor of Engineering, Robert

Frederick Smith School of Chemical and Biomolecular Engineering, Cornell University

Ubiquibodies are comprised of a synthetic binding protein fused to an E3 ubiquitin ligase, thus enabling post-translational ubiquitination and degradation of a target protein independent of its function. Here, we have designed a panel of new ubiquibodies based on E3 ubiquitin ligase mimic from bacterial pathogens that enable selective and customizable removal of proteins of interest. Delivery of synthetic mRNA encoding ubiquibodies caused efficient target depletion in cultured mammalian cells as well as in transgenic mice. Overall, our results suggest that engineered ubiquibodies are a highly modular proteome editing technology with the potential for pharmacologically modulating disease-causing proteins.

5:05 Interactive Breakout Discussion Groups

Join a breakout discussion group. These are informal, moderated discussions with brainstorming and interactive problem solving, allowing participants from diverse backgrounds to exchange ideas and experiences and develop future collaborations around a focused topic. Visit the conference website for discussion topics and moderators.

6:05 Welcome Reception in the Exhibit Hall with Poster Viewing
(*Sponsorship Opportunity Available*)

7:10 Close of Day

WEDNESDAY, SEPTEMBER 18

7:30 am Registration Open and Morning Coffee

EMERGING UBIQUITIN TARGETS & MODULATORS

8:00 Chairperson's Remarks

Mary Matyskiela, PhD, Principal Scientist, Structural and Chemical Biology, Celgene

8:05 Potent Small Molecule Parkin Activators for Treating Neurodegenerative Diseases

Suresh Kumar, PhD, Senior Director R&D, Progenra, Inc.

Parkin, an ubiquitin E3 ligase, is a critical regulator of mitochondrial dynamics and a protector of neuronal health. Inactivating mutations in both Parkin and PINK1 are found in Parkinson's disease patients. Using the UbiPro™ HTS platform we have discovered novel small molecule Parkin activators. Parkin activators promote degradation of mitochondrial and cytosolic Parkin substrates in human neurons. Development of these Parkin activators offers potentially viable therapeutic options to treat Parkinson's and other neurodegenerative diseases.

8:35 A Neurodevelopmental Disorder Caused by USP7 Haploinsufficiency

Ryan Potts, PhD, Associate Member, Department of Cell and Molecular Biology, St. Jude Children's Research Hospital

USP7 is a prominent deubiquitinating enzyme that has a multitude of cellular functions. Most notably its role in regulation of p53 has garnered much attention. This has resulted in tremendous interest in development of USP7 inhibitors for cancer treatment. Here, I will discuss progress in understanding how mutation or deletion of a single copy of USP7 leads to a neurodevelopmental disorder. The implications of these findings in drug development will be discussed.



Emerging Ubiquitin and Autophagy Targets

Novel Probes, Assays and Small Molecules Modulators for Protein Degradation

9:05 Solving a 60 Year Mystery: SALL4 Mediates Teratogenicity as a Thalidomide-dependent Substrate of Cereblon

Mary Matyskiela, PhD, Principle Scientist, Group Leader, Structural and Chemical Biology, Celgene

Targeted protein degradation through small molecule modulation of cereblon offers vast potential for new therapeutics, but cereblon-binding molecules carry the safety risks of thalidomide, which caused an epidemic of severe birth defects in the 1950s. We identify SALL4 as a thalidomide-dependent cereblon substrate whose degradation phenocopies genetic embryopathies caused by SALL4 mutation. This work offers a path towards safer therapeutics through understanding the molecular basis of thalidomide-induced teratogenicity, and expands the scope of cereblon neosubstrates.

9:35 Coffee Break in the Exhibit Hall with Poster Viewing

10:20 FEATURED PRESENTATION: Advancing Targeted Protein Degradation for CNS Proteinopathies

Stephen. J. Haggarty, PhD, Associate Professor, Department of Neurology, Harvard Medical School; Associate in Neuroscience and Director, Chemical Neurobiology Laboratory, Center for Genomic Medicine, Massachusetts General Hospital

Exploiting the control of protein proximity to catalyze targeted protein degradation provides a potentially powerful therapeutic strategy. Recent advances enabling the generation of patient-derived, *ex vivo* models of central nervous system (CNS) proteinopathies and the development of bifunctional molecules capable of selectively targeting pathological protein conformations now allow this strategy to be applied to the context of neurodegeneration. Here we will summarize recent findings focused on targeted degradation of tau, a protein implicated in multiple forms of dementia.

11:20 Enjoy Lunch on Your Own

11:20 Conference Registration for Programs 1B-7B

PLENARY KEYNOTE PROGRAM

Click [here](#) for full abstracts.

12:20 pm Event Chairperson's Opening Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target 2019, Cambridge Healthtech Institute

12:30 Plenary Keynote Introduction

Anjan Chakrabarti, Vice President, Discovery Chemistry, Syngene International Ltd

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Syngene



12:40 Base Editing: Chemistry on a Target Nucleotide in the Genome of Living Cells

David R. Liu, PhD, Howard Hughes Medical Institute Investigator, Professor of Chemistry & Chemical Biology, Harvard University



1:20 PROTACs: Past, Present, and Future

Craig M. Crews, PhD, Professor, Chemistry; Pharmacology; Molecular, Cellular & Developmental Biology; Yale University

2:00 Close of Plenary Keynote Program

2:00 Dessert Break in the Exhibit Hall with Poster Viewing

2:45 Close of Emerging Ubiquitin and Autophagy Targets Conference

Please click [here](#) to continue to the agenda for PROTACs and Targeted Protein Degradation

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Inaugural | September 18-19

PROTACs and Targeted Protein Degradation

Pursuing Undruggable Protein Targets for Drug Discovery and Therapeutics

The ubiquitin-proteasome system (UPS) is a well-controlled, selective mechanism for intracellular protein degradation and turnover, and it acts as a key regulator in cancer, CNS and other diseases. However, the multi-step processes involved and the diversity of substrates make it difficult to target the UPS. Proteolysis-targeting chimeric molecules (PROTACs) are a group of engineered hetero-bifunctional chemical entities that bind to the target and ligase to mediate ubiquitination and subsequent protein degradation. Like PROTACs, other chemical entities and molecular glues, using varied mechanisms-of-action, are being developed to trigger targeted protein degradation. These approaches have a lot of potential in seeking out previously "undruggable" protein targets for applications in drug discovery and for developing new therapeutic modalities. However, some challenges do exist in terms of stability, biodistribution and penetration of these molecules *in vivo*. Cambridge Healthtech Institute's conference on PROTACs and Targeted Protein Degradation will bring together a diverse group of chemists and biologists to discuss the prospects, as well as, the challenges underlying strategies for targeted protein degradation. This will be preceded by a conference that discusses emerging ubiquitin and autophagy targets for therapeutic intervention.

RECOMMENDED PREMIUM PACKAGE:

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- September 18-19 Conference: **PROTACs and Targeted Protein Degradation**

WEDNESDAY, SEPTEMBER 18

11:20 am Conference Registration Open

PLENARY KEYNOTE PROGRAM

Click [here](#) for full abstracts.

12:20 pm Event Chairperson's Opening Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target 2019, Cambridge Healthtech Institute

12:30 Plenary Keynote Introduction

Anjan Chakrabarti, Vice President, Discovery Chemistry, Syngene International Ltd

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12:40 Base Editing: Chemistry on a Target Nucleotide in the Genome of Living Cells

David R. Liu, PhD, Howard Hughes Medical Institute Investigator, Professor of Chemistry & Chemical Biology, Harvard University



1:20 PROTACs: Past, Present, and Future

Craig M. Crews, PhD, Professor, Chemistry; Pharmacology; Molecular, Cellular & Developmental Biology; Yale University

2:00 Close of Plenary Keynote Program

2:00 Dessert Break in the Exhibit Hall with Poster Viewing

OVERCOMING TRANSLATIONAL CHALLENGES

2:45 Organizer's Welcome Remarks

2:50 Chairperson's Opening Remarks

Peter Dragovich, PhD, Staff Scientist, Discovery Chemistry, Genentech

2:55 Translating Cellular Degradation Insights to *in vivo* Models

Stewart Fisher, PhD, CSO, C4 Therapeutics

Targeted protein degradation, through the use of heterobifunctional degraders that act as catalytic activators for an E3 ligase and target protein, has the potential to transform drug discovery. This talk will discuss the application of an enzymology framework to characterize cellular degradation data and the extension of these insights to pharmacodynamic modeling and predictions.

3:25 FEATURED PRESENTATION: Targeting the Undruggables Using PROTACs

Shaomeng Wang, PhD, Warner-Lambert/Parke-Davis Professor of Medicine, Pharmacology and Medicinal Chemistry; Co-Director, Molecular Therapeutics Program and Director, Cancer Drug Discovery Program, University of Michigan

I will present our recent efforts to design potent, selective and highly efficacious degraders to target STAT3 (signal transducers and activators of transcription 3), a classical undruggable target by small molecules. *In vitro* and *in vivo* data demonstrate that our most promising STAT3 degrader is highly potent and effective in inducing degradation of the STAT3 protein and demonstrates absolute selectivity over other STAT members. It achieves complete and long-lasting tumor regression in multiple xenograft models in mice at well tolerated dose-schedules.

3:55 Novel Approaches to PROTAC Drug Discovery

Dahmane Ouazia, PhD, Business Development Manager, LifeSensors, Inc.

Karteek Kadimisetty, PhD, Assistant Director, Research & Development, LifeSensors, Inc.

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Current methods for PROTAC drug discovery are inefficient and full of artifacts. We developed a plate-based methodology for rapid screening of PROTAC-mediated protein ubiquitination, a true measure of PROTAC drug effect. This method is faster, more reproducible and requires less starting material than already used Western blotting and reporter assays.

4:25 Refreshment Break in the Exhibit Hall with Poster Viewing

5:00 Pharmacokinetics Related Challenges of PROTACs

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

PROTACs are bifunctional molecules, designed to bind with target protein and E3 ligase to degrade protein of interest by hijacking cell's ubiquitin proteasome system. Several challenges remain in designing optimal PROTACs that has good PK properties to show efficacy *in vivo*. For example, PROTACs have high MW (beyond rule of 5), low permeability and low oral bioavailability. This presentation will focus on pharmacokinetics related challenges of PROTACs to share/discuss/improve PK properties of PROTACs.

5:30 Targeted Protein Degradation Enters the Clinic: Insights From ARV-110 and Other PROTAC® Degraders

Miklos Bekes, PhD, Research Investigator, Platform Biology, Arvinas, Inc.

The orally bioavailable, androgen receptor-targeted PROTAC protein degrader ARV-110 entered Phase I clinical trials for metastatic, castration-resistant prostate cancer in 1Q19; and is followed by a planned 3Q19 clinical trial initiation for the orally bioavailable, estrogen receptor-targeted PROTAC® protein degrader ARV-471 for ER+ locally advanced or metastatic breast cancer. I will present learnings from these programs. Additionally, I will discuss results for tau-targeted PROTAC protein degraders for potential application in Alzheimer's disease and other tauopathies.





Inaugural | September 18-19

PROTACs and Targeted Protein Degradation

Pursuing Undruggable Protein Targets for Drug Discovery and Therapeutics

NEW

6:00 Antibody-Mediated Delivery of Protein Degraders

Peter Dragovich, PhD, Staff Scientist, Discovery Chemistry, Genentech
Chimeric Chemical Inducers of DEgradation (CIDEs) which effect intracellular degradation of target proteins via E3 ligase-mediated ubiquitination are currently of high interest in medicinal chemistry. However, these entities are relatively large compounds that often possess molecular characteristics which may compromise oral bioavailability, solubility, and/or *in vivo* pharmacokinetic properties. Accordingly, we explored whether conjugation of CIDEs to monoclonal antibodies using technologies originally developed for cytotoxic payloads might provide alternate delivery options for these agents.

6:30 Dinner Short Course Registration

Click [here](#) for details on short courses offered.

9:30 Close of Day

THURSDAY, SEPTEMBER 19

7:00 am Registration Open

7:30 Interactive Breakfast Breakout Discussion Groups

Grab a cup of coffee and join a breakout discussion group. These are informal, moderated discussions with brainstorming and interactive problem solving, allowing participants from diverse backgrounds to exchange ideas and experiences and develop future collaborations around a focused topic. Visit the conference website for discussion topics and moderators.

8:30 Transition to Sessions

IDENTIFYING NEW LIGANDS & TARGETS FOR DEGRADATION

8:40 Chairperson's Remarks

Ye Che, PhD, Head of Computational Design, Discovery Sciences, Pfizer, Inc.

8:45 Targeted Protein Degradation for Treatment of Cancer

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

Targeted protein degradation using bifunctional molecules to remove specific proteins by hijacking the ubiquitin proteasome system has emerged as a novel drug discovery approach. Several challenges remain in designing optimal degraders that also show efficacy *in vivo*. We will present case studies from our ongoing efforts in the design and biological evaluation of novel degraders for selected oncology targets that display *in vivo* activity in mouse models.

9:15 Targeted Degradation of IRAK4 Protein Via Heterobifunctional Small Molecules for Treatment of MYD88 Mutant Lymphoma

Matthew Weiss, PhD, Director, Chemistry, Kymera Therapeutics

KYM-001 is a first-in-class, potent, selective and orally active IRAK4 degrader that causes tumor regression in ABC-DLBCL models. Degradation of IRAK4 removes both the kinase and scaffolding functions of IRAK4 and may be superior to kinase inhibition alone. These data support IRAK4 degraders as a promising new therapeutic opportunity for MYD88-driven lymphoma, both alone and in combination with other targeted approaches such as BTK inhibition.

9:45 Establishing a Platform for High-Throughput Identification and Profiling of Target Degraders

James Robinson, PhD, Team Leader, Discovery Sciences, AstraZeneca

Target degradation can provide additional benefits over target inhibition and can in some cases enable targets that were previously considered intractable.

Here I present our approaches to identify degraders of two high profile drug targets. In the first case we deployed a suite of high throughput plate-based assays to enable profiling and optimisation of a series of PROTACs. In the second case we performed a high throughput screen to identify novel small molecule degraders.

10:15 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

10:55 Computational Design of PROTACs

Ye Che, PhD, Head of Computational Design, Discovery Sciences, Pfizer, Inc.

Orthosteric and allosteric modulators of enzyme function or receptor signaling are well-established mechanisms of drug action. Drugs that promote novel protein-protein interactions and induce protein degradation promise to dramatically expand opportunities for therapeutic intervention. This approach is more difficult for rational design due to the extensive contact surfaces that must be perturbed antagonistically. Here, I will highlight recent applications of computational methods in the design and optimization of targeted protein degraders.

11:25 Structure-Based Design of Degraders

Radoslaw Nowak, PhD, Scientist, Laboratory of Dr. Eric Fischer, Department of Cancer Biology, Dana-Farber Cancer Institute, Harvard Medical School

Small molecule degraders have shown considerable promise as a new pharmacological modality. With the mounting structural information on degrader mediated ligase-substrate interactions we are beginning to understand the rationale for target recruitment and selectivity. This presentation will describe a recently developed framework for use of computational tools, such as protein-protein docking, for accelerating degrader design.

11:55 *In silico* Modeling of PROTAC-Mediated Ternary Complexes for Predicting Protein Degradation

Michael Drummond, PhD, Scientific Applications Manager, Chemical Computing Group

Successful development of Proteolysis-Targeting Chimeras (PROTACs) hinges upon the ability to rationally modify and design new PROTACs. We have recently developed a suite of computational tools for generating ensembles of PROTAC-mediated ternary complexes. Furthermore, we propose metrics based on available experimental knowledge to identify the structures within the larger ensemble that are likely to degrade. We demonstrate the utility of our methods in a number of scenarios, including across different targets and PROTAC molecules.

12:25 pm Session Break

12:35 Luncheon Presentation (Sponsorship Opportunity Available) or Enjoy Lunch on Your Own

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

NEW APPROACHES & APPLICATIONS FOR PROTEIN DEGRADATION

2:05 Chairperson's Remarks

Nello Mainolfi, PhD, Founder and CSO, Kymera Therapeutics, Inc.

2:10 KEYNOTE PRESENTATION AND DISCUSSION: Targeting Kinases for Degradation- Challenges and Opportunities

Nathanael S. Gray, PhD, Professor of Biological Chemistry and Molecular Pharmacology, Dana-Farber Cancer Institute

Heterobifunctional molecules that recruit E3 ubiquitin ligases, such as cereblon, for targeted protein degradation represent an emerging

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PROTACs and Targeted Protein Degradation

Pursuing Undruggable Protein Targets for Drug Discovery and Therapeutics

pharmacological strategy. A major unanswered question is how generally applicable this strategy is to all protein targets. In this talk I will discuss our efforts to develop chemoproteomic strategies to identify degradable kinases. Methods to characterize small molecule kinase degraders will also be discussed.

3:10 Novel Strategies for Oncoprotein Degradation

Willem den Besten, PhD, Senior Scientific Researcher, Genentech

Targeted protein degradation has the potential to open the door to therapeutic targets previously deemed undruggable. In this talk, I will present the characterization of two ligase ligands and show how target degradation coupled with modulation of ligase biology leads to increased cellular efficacy. I will also share results on a new method for inducing the degradation of an ubiquitin ligase.

3:40 E3 Ubiquitin Ligases for PROTACs Discovery

Matthieu Schapira, PhD, Principal Investigator, Structural Genomics Consortium and Associate Professor, Pharmacology & Toxicology, University of Toronto

To be active, a PROTAC must induce the formation of a productive complex between a target of interest and a structurally and functionally compatible E3 ubiquitin ligase. Considering that less than ten E3 ligases out of over 600 in the human proteome are exploited by current PROTACs, extending the repertoire of ligands to E3 ligases with a variety of structural properties as well as diverse temporal and spatial expression profiles should considerably expand potential applications of PROTACs for chemical biology, and broaden the horizon for future drug discovery efforts. I will review the classification, ubiquitin-proteasome system association, tissue expression profile and druggability of human E3 ligases.

4:10 Close of Conference

Please click [here](#) to return to the agenda for Emerging Ubiquitin and Autophagy Targets

INTERACTIVE BREAKOUT DISCUSSION GROUPS

Join a breakout discussion group. These are informal, moderated discussions with brainstorming and interactive problem solving, allowing participants from diverse backgrounds to exchange ideas and experiences and develop future collaborations around a focused topic. Details on the topics and moderators are available on the conference website.



Targeting NASH

Drug Development for Inflammation and Fibrosis of the Fatty Liver

Non-alcoholic steatohepatitis (NASH) is a disease whose incidence is rising and is related to an accumulation of fat in the liver that can lead to its dysfunction due to excessive inflammation and fibrosis. No medical treatments yet exist for NASH but it's a hopeful time for the field because several drug candidates are in Phase II and III clinical trials. New NASH drug targets are also being revealed due to progress in the fields of NASH contributors: metabolic dysfunction, inflammation and fibrosis. Significant challenges remain, however, such as the need for non-invasive biomarkers and better models for the disease. At Cambridge Healthtech Institute's Targeting NASH conference, join academic and industry investigators to learn and discuss with one another drug development progress, challenges and solutions in the arena of treating fatty liver disease.

RECOMMENDED PREMIUM PACKAGE:

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- September 16 Pre-Conference Short Course: **SC1: Immunology Basics: Focusing on Autoimmunity and Cancer**
- September 17-18 Conference: **Targeting NASH**
- September 18 Dinner Short Course: **SC9: Targeted Protein Degradation Using PROTACs, Molecular Glues and More**
- September 18-19 Conference: **Targeting Fibrosis**

MONDAY, SEPTEMBER 16

1:00 pm Pre-Conference Short Course Registration

Click [here](#) for details on short courses offered.

TUESDAY, SEPTEMBER 17

7:00 am Registration Open and Morning Coffee

NASH DRUG CANDIDATES

8:00 Organizer's Welcome Remarks

8:05 Chairperson's Opening Remarks

Claus Kremsler, PhD, CEO, Phenex

8:10 NEW: FEATURED PRESENTATION: NASH Overview: Drug Development Landscape and Key Questions

H. James Harwood Jr., PhD, Founder and CEO, Delphi BioMedical Consultants, LLC

This presentation will begin with a quick medical explanation of NASH (what it is, symptoms, how it is diagnosed and currently treated) but will focus on reviewing drug development landscape and include a brief discussion of major issues facing the field to give context to presentations appearing later in the program.

8:40 FEATURED PRESENTATION: Thyroid Hormone Receptor Agonists

Rebecca Taub, MD, CMO & President, R&D, Madrigal Pharmaceuticals

I will present data from clinical studies of resmetrom (MGL-3196). MGL-3196 is an orally administered, small-molecule, liver-directed compound that is currently in Phase III development for NASH. The data show highly significant reduction of liver fat and biomarkers of inflammation and fibrosis and resolution of NASH on liver biopsy in a 36-week serial liver biopsy study.

9:10 Targeting GLP-1 for NASH

Karin Conde-Knape, PhD, Corporate Vice President, Cardiovascular and Liver Disease Research, Novo Nordisk

GLP1 receptor agonists have been successfully positioned for the treatment of diabetes and obesity. It has been documented that weight loss either by dietary or surgical intervention leads to improvement in NASH and fibrosis. Initial clinical data suggests a beneficial effect of GLP1 receptor agonists in NASH clinical trials. An overview of GLP1 receptor agonism in the treatment of NASH and future directions will be provided.

9:40 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

NASH THERAPEUTIC COMBINATIONS

10:25 Combinations with ACC Inhibitor for Treating NASH

Archana Vijayakumar, PhD, Research Scientist, Fibrosis, Gilead

Firsocostat (FIR), a liver-targeted acetyl-CoA carboxylase inhibitor (ACCI), improves hepatic steatosis and liver biochemistry in NASH patients, but may increase plasma TGs in patients with pre-existing hypertriglyceridemia. This is likely mediated by repression of PPAR α activity. In diet-induced obese mice, co-administration of fenofibrate, a PPAR α agonist, with a liver-targeted FIR analogue ACCi completely normalized elevations in plasma TGs, and improved liver metabolism. The data suggest that ACCi/fenofibrate combination may improve NASH efficacy more than either monotherapy.

10:55 CC-Chemokine Receptor Antagonism as a Therapeutic Target in NASH

Star Seyedkazemi, PharmD, Associate Vice President, Clinical Development, Liver Therapeutic Area, Allergan

11:25 Combination Therapy for NASH

Marcos Pedrosa, MD, MPH, Global Program Clinical Head, Therapeutic Area Hepatology and Transplantation, Novartis Pharma AG

11:55 Accelerating NASH in an Improved Translational Model: MS-NASH Mouse on Western Diet and CCl₄

Guodong Zhang, PhD, Director, Cardiovascular and Metabolic Disease, Crown Bioscience

Enhanced models are needed to improve NASH drug development, combining the severe pathology and dysmetabolism seen clinically. Discover the MS-NASH mouse on Western diet, fructose, and CCl₄, a new preclinical NASH model combining both severe fibrosis and dysmetabolism in an accelerated timeframe. Explore model characterization and outcomes following OCA treatment.

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12:10 pm Population-scale Human Genetics and Genomics for NASH Drug Target & Biomarker Discovery

Richard Williams, MBBS, PhD, Global Head, Medicine, WuXi NextCODE

New drug targets & biomarkers are desperately needed for effective NASH therapy, monitoring & prevention. In our global NASH discovery programs, we will (1) use whole genome sequencing (WGS) to compare thousands of patients with high fibrosis NASH, Low or No fibrosis NASH & NAFL, and population controls, and (2) interrogate hundreds of fresh liver biopsies from NASH & NAFL patients and control individuals with 'bulk' multi-omic genomic analysis (WGS, RNA-Seq, DNA methylation), single cell RNA-seq and fully-integrated AI to reveal novel disease biology, drug targets and biomarkers.

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12:25 pm Session Break

12:35 Luncheon Presentation (Sponsorship Opportunity Available) or Enjoy Lunch on Your Own



Targeting NASH

Drug Development for Inflammation and Fibrosis of the Fatty Liver

1:15 Refreshment Break in the Exhibit Hall with Poster Viewing

NASH DRUG DEVELOPMENT CHALLENGES

1:50 Chairperson's Remarks

Kendra K. Bence, PhD, Senior Director, Metabolism, Internal Medicine Research Unit (IMRU), Pfizer, Inc.

1:55 Are Circulating Fibrosis Biomarkers Useful in NASH Drug Development?

Saurabh Gupta, PhD, Director, Translational Medicine and Early Clinical, Takeda Pharmaceuticals International Co.

Clinical Diagnosis of NASH and evaluation of anti-fibrotic activity in clinical trials heavily relies on the histological readouts based on liver biopsy, a highly invasive, variable and a non-representative technique. We will summarize soluble biomarkers which have shown most promising results in terms of fibrosis and NASH staging, and measuring the anti-fibrotic activity in clinical trials.

2:25 Federal Landscape for NASH Patients and Products

Barrett Thornhill, JD, Executive Director, NASH Alliance

Washington, DC has become the confluence of products, policy, pricing and access, but NAFLD-NASH is a virtual unknown among federal policymakers. The now-silent public health crisis will grow dramatically in coming years, and the NASH community of clinicians, innovators and patients is developing the public health infrastructure to better understand NASH implications and support product commercialization. This session will provide an overview of these efforts and explore how federal programs can be a 'pull incentive' that bolsters product development.

2:55 Precision Metabolomics: Understanding the Complexity of NAFLD/NASH

Kari Wong, Senior Study Director, Metabolon, Inc.

Disease drivers including genetics, environmental cues and microbiota drive the development of nonalcoholic-steatohepatitis(NASH). The constellation of factors inciting NASH has spawned a remarkable array of targets. A tool for augmenting the challenges of R&D programs is Metabolon's Metabolomics platform. By identifying 1000+ metabolites in a single sample across pathways that underly NASH pathogenesis, key insights of target/molecule combinations can be illuminated with this platform. This approach can be applied at any stage of drug development.

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3:25 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

4:05 Drug Development for NASH Cirrhosis

Peter Traber, MD, Partner, Alacrita Consulting; Adjunct Professor of Medicine, University of Pennsylvania School of Medicine

NASH is a chronic, slowly progressive inflammatory and fibrotic disease of the liver which progresses in some individuals to cirrhosis with its attendant complications, including death and liver transplant. In this presentation, the differences in the pathophysiology and impact on patients between precirrhotic and cirrhotic NASH will be reviewed. Additionally, acceptable and potential regulatory endpoints for clinical trials will be reviewed and put in the context of current ongoing development programs. The publicly disclosed information on established clinical trial programs in cirrhotic NASH will be reviewed and compared, and thoughts about future clinical development for NASH cirrhosis will be discussed.

4:35 NEW: Selected Poster Presentation(s): A Translational Mouse Model for NASH and Advanced Fibrosis in Association with Atherosclerosis

Robert Kleemann, PhD, Principal Scientist TNO Metabolic Health Research & Associate Professor, University of Leiden Medical Center

5:05 Interactive Breakout Discussion Groups

Join a breakout discussion group. These are informal, moderated discussions with brainstorming and interactive problem solving, allowing participants from diverse backgrounds to exchange ideas and experiences and develop future collaborations around a focused topic. Visit the conference website for discussion topics and moderators.

6:05 Welcome Reception in the Exhibit Hall with Poster Viewing (Sponsorship Opportunity Available)

7:10 Close of Day

WEDNESDAY, SEPTEMBER 18

7:30 am Registration Open and Morning Coffee

NEW DRUG TARGETS OR EARLIER STAGE COMPOUNDS FOR FATTY LIVER DISEASE

8:00 Chairperson's Remarks

Weilin Xie, PhD, Senior Principal Scientist, Biotherapeutics, Celgene

8:05 Targeting Integrin $\alpha V\beta 1$ for the Treatment of Liver Fibrosis Associated with NASH

Eric Lefebvre, PhD, CMO, Pliant Therapeutics

Fibrosis is a common pathway for progression of many debilitating diseases associated with loss of organ function. Integrins play a key role in regulating TGF- β activation and cell-matrix interactions, and thus represent attractive antifibrotic targets. We evaluated small molecule integrin inhibitors with different selectivity profiles in lung, liver and kidney models of injury and fibrosis, in tissue slices from patients with lung and liver fibrosis, as well as assessed non-invasive *in vivo* biomarkers of target engagement.

8:35 Targeting Fructose Metabolism: Update on KHK Inhibitor for NASH

Kendra K. Bence, PhD, Senior Director, Metabolism, Internal Medicine Research Unit (IMRU), Pfizer, Inc.

Excessive fructose intake leads to increased energy storage in the form of fat as well as accumulation of pro-inflammatory metabolites, both important components in the development of NAFLD and NASH. To understand the specific role of fructose in T2DM and NAFLD/NASH, we designed and tested a potent, novel, orally-bioavailable inhibitor of ketohexokinase (KHK), the primary enzyme which catalyzes the conversion of fructose to fructose-1-phosphate (F1P) in the first step of fructose metabolism.

9:05 Population-scale Human Genetics and Genomics for NASH Drug Target & Biomarker Discovery

Richard Williams, MBBS, PhD, Global Head, Medicine, WuXi NextCODE
New drug targets & biomarkers are desperately needed for effective NASH therapy, monitoring & prevention.

In our global NASH discovery programs, we are (1) using whole genome sequencing (WGS) to compare thousands of patients with high fibrosis NASH, Low or No fibrosis NASH & NAFL, and population controls, and (2) interrogating hundreds of fresh liver biopsies from NASH & NAFL patients and control individuals with 'bulk' multi-omic genomic analysis (WGS, RNA-Seq, DNA methylation), single cell RNA-seq and fully-integrated AI to reveal novel disease biology, drug targets and biomarkers.

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9:35 Coffee Break in the Exhibit Hall with Poster Viewing

10:20 Liver X Receptor (LXR) Agonists PX665 for NASH

Claus Kremoser, PhD, CEO, Phenex



Targeting NASH

Drug Development for Inflammation and Fibrosis of the Fatty Liver

The liver X receptor is a nuclear hormone receptor and is therefore similar to other promising NASH targets such as PPARs and FXR. LXRs regulate cholesterol, fatty acid and glucose levels in the cell. We present our results on an LXR inverse agonist, PX665, which combines antisteatotic, weight lowering, antifibrotic and insulin sensitizing properties in one approach to combat NASH.

10:50 An Antisense DGAT Inhibitor for NASH

Erin Morgan, Executive Director, Clinical Development, Ionis Pharmaceuticals
 DGAT2 catalyzes the terminal step in the synthesis of triacylglycerols from *de novo* synthesized fatty acids and newly formed diglycerides. In pre-clinical models of NAFLD, we previously reported that specific inhibition of DGAT2 caused a marked improvement in hepatic steatosis. The talk will discuss results with a Novel antisense inhibitor of diacylglycerol acyltransferase 2 (IONIS-DGAT2RX) administered in NAFLD patients with type 2 diabetes. Results from the international randomized placebo-controlled Phase 2 trial demonstrated that IONIS DGAT2 RX significantly improved hepatic steatosis without causing hypertriglyceridemia or affecting hepatic function in type-2 diabetes mellitus patients with steatosis, supporting further development of IONIS- DGAT2 RX in NASH patients.

11:20 Enjoy Lunch on Your Own

11:20 Conference Registration for Programs 1B-7B

PLENARY KEYNOTE PROGRAM

Click [here](#) for full abstracts.

12:20 pm Event Chairperson's Opening Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target 2019, Cambridge Healthtech Institute

12:30 Plenary Keynote Introduction

Anjan Chakrabarti, Vice President, Discovery Chemistry, Syngene International Ltd

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Syngene



12:40 Base Editing: Chemistry on a Target Nucleotide in the Genome of Living Cells

David R. Liu, PhD, Howard Hughes Medical Institute Investigator, Professor of Chemistry & Chemical Biology, Harvard University



1:20 PROTACs: Past, Present, and Future

Craig M. Crews, PhD, Professor, Chemistry; Pharmacology; Molecular, Cellular & Developmental Biology; Yale University

2:00 Close of Plenary Keynote Program

2:00 Dessert Break in the Exhibit Hall with Poster Viewing

2:45 Close of Targeting NASH Conference

Please click [here](#) to continue to the agenda for Targeting Fibrosis





Inaugural | September 18-19

Targeting Fibrosis

Developing Medical Therapies for Fibrotic Diseases

NEW

The incidence of fibrosis, a process that under conditions of persistent injury or inflammation contributes to organ damage, has been steadily increasing over the past decade. Activity in the drug development arena for fibrosis has also grown. Much of the progress has been spurred by the fields of autoimmunity and inflammation which are revealing common mechanisms for fibrosis across the organs where fibrosis is most frequently observed: lung, liver, heart, kidney and skin. CHI's Inaugural Targeting Fibrosis conference aims to convene the leading fibrosis researchers from academics and industry working across organ types, as well as immunology and inflammation investigators to share progress and shape future directions in this burgeoning field of new drug discovery.

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WEDNESDAY, SEPTEMBER 18

11:20 am Conference Registration Open

PLENARY KEYNOTE PROGRAM

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12:40 Base Editing: Chemistry on a Target Nucleotide in the Genome of Living Cells

David R. Liu, PhD, Howard Hughes Medical Institute Investigator, Professor of Chemistry & Chemical Biology, Harvard University



1:20 PROTACs: Past, Present, and Future

Craig M. Crews, PhD, Professor, Chemistry; Pharmacology; Molecular, Cellular & Developmental Biology; Yale University

2:00 Close of Plenary Keynote Program

2:00 Dessert Break in the Exhibit Hall with Poster Viewing

INTEGRINS AS FIBROSIS TARGETS

2:45 Organizer's Welcome Remarks

2:50 Chairperson's Opening Remarks

Carolyn Cuff, PhD, Senior Director, Translational Immunology, Immunology Discovery, AbbVie Bioresearch Center

2:55 NEW: Cell Therapy for Liver Fibrosis Using Reprogrammed Hepatic Stellate Cells Locked into a Quiescent-like State

Michael Choi, MD, Assistant Professor, Medicine, Harvard Medical School
Hepatic stellate cell (HSC), once activated, plays a central role in promoting progressive liver fibrosis. We identified a key driver to reprogram activated HSC back toward quiescence to generate what we designate as induced

quiescent hepatic stellate cell (iqHSC). iqHSCs had morphologic, transcriptional, and functional phenotype similar to that of truly quiescent HSCs. Finally, performing cell therapy with iqHSCs locked into a quiescent-like state in mouse models of liver injury attenuated hepatic inflammation and fibrosis. Cell therapy using iqHSCs could be a template for treating multiple human liver diseases that lead to fibrosis.

3:25 Targeting Integrins for Fibrotic Diseases

Liangsu Wang, PhD, Vice President, Head of Biology, Morphic Therapeutic

Integrins lie at the heart of many biological processes and are involved in the pathophysiology of a variety of human diseases. This talk will discuss the roles of integrins in fibrotic diseases, highlight some key data on pharmacological effects of Morpnic small molecule inhibitors against selected integrin targets, and share our insights of molecular modes of action of different inhibitors and the implications of integrin conformations in disease microenvironment.

3:55 Role of Integrin-alpha V in Fibrosis and Inflammation

Kevin Hart, PhD, Principal Scientist, Inflammation, Pfizer

Since some integrins can serve as master regulators of fibrosis, we investigated if integrin-alpha V is critical during polarized inflammatory responses during tissue damage disease models. While data confirmed a role for integrin-alpha V in type 17-associated fibrosis, integrin-alpha V was not critical to the development of type 2-driven fibrosis. However, our studies reveal a novel mechanism through which fibroblasts, via integrin-alpha V expression, are capable of regulating immune polarization.

4:25 Refreshment Break in the Exhibit Hall with Poster Viewing

5:00 Targeting Integrins for Fibrosis

Ji Zhang, PhD, Scientist, Cardiorenal Metabolic & Ophthalmologic Drug Discovery, Merck Research Labs

Fibrosis is an evolutionarily conserved mechanism developed by an organism to survive chronic injury. Excessive fibrosis, however, leads to disruption of organ function and is a common feature of many chronic diseases. We are developing new medicines for multiple indications and this presentation will describe some of our efforts to target integrins for fibrosis.

5:30 IDL-2965: A Selective, Highly Potent, Clinical-Stage, Oral Integrin Antagonist for Treatment of Chronic Fibrosis

Karl Kossen, PhD, Senior Vice President, Translational Science, Indalo Therapeutics

IDL-2965 is an oral small-molecule integrin antagonist that potently inhibits $\alpha v \beta 1$, $\alpha v \beta 3$, and $\alpha v \beta 6$. These integrins play central roles in TGF- β activation and the ability of stiff extracellular matrix to promote fibroblast activation and survival. Once-daily, oral, therapeutic dosing reduces fibrosis in multiple animal models across organ systems with minimal effective doses ranging from 0.4 to 3 mg/kg. 28-day GLP safety studies suggest a large therapeutic index. IDL-2965 entered clinical studies in April 2019.

6:00 Established and Emerging Integrin Targets and Treatments for Fibrosis

Scott Turner, PhD, Vice President, Translational Sciences, Pliant Therapeutics

Fibrosis is a common pathway for progression of many debilitating diseases associated with loss of organ function. Integrins play a key role in regulating TGF- β activation and cell-matrix interactions, and thus represent attractive antifibrotic targets. We evaluated small molecule integrin inhibitors with different selectivity profiles in lung, liver and kidney models of injury and fibrosis, in tissue slices from patients with lung and liver fibrosis, as well as assessed non-invasive *in vivo* biomarkers of target engagement.

6:30 Dinner Short Course Registration

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9:30 Close of Day





THURSDAY, SEPTEMBER 19

7:00 am Registration Open

7:30 Interactive Breakfast Breakout Discussion Groups

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8:30 Transition to Sessions

CHALLENGES IN ANTI-FIBROTIC DRUG DEVELOPMENT

8:40 Chairperson's Remarks

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

8:45 FEATURED PRESENTATION: Cell Senescence and Senolytic Strategies in IPF

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

Cellular senescence is a state of permanent growth arrest combined with stereotyped phenotypic changes and it has an important role in maintaining physiological homeostasis. While cellular senescence may be a protective mechanism in modulating proliferative capacity, the accumulation of senescent fibroblasts and epithelial cells is now recognized as a key pathogenic mechanism in idiopathic fibrosis (IPF), a form of lung fibrosis. This presentation will cover therapeutic interventions that target and reduce the burden of senescent cells, which are promising for modulating the progression of IPF and other age-related lung disease.

9:15 Utility and Futility: Cell Co-Cultures and Ex Vivo Tissue Slices as Fibrosis Models

Glenda Trujillo, PhD, Principal Scientist, CV and Fibrosis Drug Discovery Disease Sciences and Biology, R&D, Bristol-Myers Squibb

This presentation will discuss the pros and cons of using ex-vivo precision-cut tissues and cell co-cultures for anti-fibrotic compound testing and fibrosis biomarker identification.

9:45 Developing Translational Tools for the Development of Anti-Fibrotic Therapies

Melanie Ruzek, PhD, Principal Scientist, Translational Immunology, AbbVie
Assessment of anti-fibrotic drug activities and/or fibrosis endpoints within target tissues can be difficult due to accessibility or limited frequency of collections. Thus, novel methodologies are needed for non-invasive or peripheral biomarkers that will reflect tissue fibrosis and local anti-fibrotic drug activities. Case studies of some of these approaches will be discussed.

10:15 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

EMERGING FIBROSIS TARGETS (NON-INTEGRINS)

10:55 Targeting ROS-Generating NADPH Oxidases in Aging and Fibrosis

Victor J. Thannickal, MD, Professor & Director, Division of Pulmonary, Allergy and Critical Care Medicine, University of Alabama at Birmingham

Fibrosis may be viewed as a physiological, evolutionarily-conserved response to tissue injury, even at the cost of a loss in organ structure/function. This "trade-off" may result in progressive/pathological fibrosis when certain genes associated with tissue repair manifest antagonistically pleiotropic effects with aging. In this seminar, we provide evidence for the reactive oxygen species (ROS)-generating enzyme, NADPH oxidase 4 (Nox4), in age-related lung fibrosis and pre-clinical studies to support its therapeutic targeting.

11:25 CXCR4: A Novel i-body for the Treatment of Fibrosis

Mick Foley, CSO, AdAlta Limited

AdAlta has used its unique human single domain protein platform to identify a novel i-body, AD-214, that specifically antagonizes the GPCR CXCR4 and shows both anti-inflammatory and anti-fibrotic in several animal models of fibrosis.

11:55 Enjoy Lunch on Your Own

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

EMERGING FIBROSIS TARGETS (NON-INTEGRINS)

2:05 Chairperson's Remarks

Brian Murphy, PhD, Senior Principal Scientist, CV and Fibrosis Drug Discovery, Disease Sciences and Biologics, R&D, Bristol-Myers Squibb

2:10 NEW: Breakout Discussion Report-Back

Moderator: Carolyn Cuff, PhD, Senior Director, Translational Immunology, Immunology Discovery, AbbVie Bioresearch Center

2:40 Lysyl Oxidase and Lysyl Oxidase-Like Inhibitors for the Direct Treatment of Fibrosis

Jonathan Foot, PhD, Senior Research Scientist, Drug Discovery, Pharmaxis Ltd.

The lysyl oxidase (LOX/LOXL1-4) family are proteins involved in the cross-linking of elastin and collagen fibrils in the extracellular matrix. Up-regulation of one or more of the LOX family can lead to aberrant cross-linking, excessive local collagen deposition and propagation of pro-fibrotic signaling. This can lead to tissue scarring, fibrosis and ultimately organ failure. We will present strategies to directly target lysyl oxidases using small molecule inhibitors, and their effectiveness in treating fibrosis.

3:10 Targeting ROCK in Fibrotic Disease

Masha Poyurovsky, PhD, Vice President, Discovery Biology, Kadmon Corporation, LLC

Rho-associated coiled-coil kinase (ROCK) is central to the control of cell movement and shape. This presentation will cover the role of ROCK in the regulation of the bio-mechanical and biochemical signaling pathways in fibrotic disease. We discuss re-sults of Kadmon's ROCK inhibitor discovery program which integrated lessons from earlier ROCK inhibitors, SBDD and medicinal chemistry. Our compounds are currently progressing toward early stage clinical development and Phase II clinical trials for IPF.

3:40 Close of Conference

Please click [here](#) to return to the agenda for Targeting NASH





Inaugural | September 17-18

NEW

Immuno-Oncology: Emerging Targets and Therapeutics

New Ways to Refocus the Immune System to Attack Cancer

The paradigm of immuno-oncology: figuring out and then circumventing how cancer cells evade the immune system has been validated by a few high-impact therapeutic successes in the past few years and has thus spurred a flurry of more drug discovery and development in the field. However, much of the current pharmaceutical activity is focused on a few cell surface drug targets and their inhibition by biologics-based therapies. CHI's Inaugural Immuno-Oncology: Emerging Targets and Therapeutics conference will cover newer cell surface targets in the IO field that are being investigated for modulation by biologics as well as by other modalities, especially small molecules that have the potential to be oral-based medicines. We will also cover drug targets that are intracellular, thus only accessible to small molecules or newer, non-biologic modalities. Please join us to stay abreast of this rapidly progressing field.

RECOMMENDED PREMIUM PACKAGE:

Choose 2 Short Courses and 2 Conferences/Training Seminars

- September 16 Pre-Conference Short Course: **SC1: Immunology Basics: Focusing on Autoimmunity and Cancer**
- September 17-18 Conference: **Immuno-Oncology: Emerging Targets and Therapeutics**
- September 18 Dinner Short Course: **SC8: GPCR Structure-Based Drug Discovery**
- September 18-19 Conference: **Targeting Fibrosis**

MONDAY, SEPTEMBER 16

1:00 pm Pre-Conference Short Course Registration

Click [here](#) for details on short courses offered.

TUESDAY, SEPTEMBER 17

7:00 am Registration Open and Morning Coffee

RE-ACTIVATING THE INNATE IMMUNE SYSTEM AGAINST CANCER

8:00 Organizer's Welcome Remarks

8:05 Chairperson's Opening Remarks

Charles A. Lesburg, PhD, Senior Principal Scientist, Computational and Structural Chemistry, Merck & Co., Inc

8:10 Discovery of STING Agonist with Systemic Anti-Tumor Response

Scott Pesiridis, PhD, Associate Fellow, Scientific Leader - Discovery Biology, GSK

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

8:40 Characterization of Novel STING Ligands

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

Modulation of the innate immune receptor STING is of pharmacological interest for both oncology and autoimmune indications. Binding of cyclic dinucleotide 2'3'-cGAMP to dimeric STING stabilizes a 'lid-closed' protein conformation, ultimately inducing interferon production. Biophysical characterization of different classes of STING ligands using surface plasmon

resonance (SPR) has revealed significant differences in binding kinetics, stoichiometry and mode of action. The results of complimentary techniques further support these observed mechanistic differences.

9:10 Potent STING and RIG-1 Agonists for Immuno-Therapy of Cancer

Radhakrishnan P. Iyer, PhD, CSO, Spring Bank Pharmaceuticals

The induction of innate and adaptive immunity via activation of Stimulator of Interferon Genes (STING) signaling is a potentially transformative immuno-therapeutic strategy in cancer. Using structure-based drug design and focused library synthesis, we have discovered novel cyclic dinucleotides (CDNs) that self-assemble into cell-permeable nanostructures for uptake by immune cells. The lead CDNs administered by i.v., i.p., and i.t. routes in subcutaneous and orthotopic syngeneic tumor models show potent STING-mediated induction of Type I IFNs and cytokines resulting in profound and durable anti-tumor activity, abscopal effects and induction of immune memory. The lead CDNs have been formulated into nanospheres for controlled and sustained delivery and have also been conjugated with antibodies to enable targeted delivery to the tumor site.

9:40 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

10:25 Using Synthetic Biology to Target Innate Immunity in the Tumor Microenvironment

Daniel Leventhal, PhD, Lead Biologist, Immuno-Oncology, Synlogic, Inc.

STING plays an essential role in initiating anti-tumor immunity through activation of antigen presenting cells (APCs), production of type I interferon and T cell priming. Bacteria provide an ideal mechanism for STING activation as they can be deployed within the tumor microenvironment, are engulfed by APCs and activate parallel pathways of innate immunity. We have generated an engineered bacterial strain, SYN1891, that is capable of efficient activation of innate immunity through engagement of TLRs and activation of STING.

10:55 Using the Gut Microbiome to Re-Direct Innate Immunity for Enhancing Responses to Engineered T-Cell Therapy

Muhammad Bilal Abid, MD, Clinician-Scientist, Division of Hematology/Oncology & Infectious Diseases, Medical College of Wisconsin

Despite impressive outcomes in select patients, there remains significant heterogeneity in clinical responses to both immunotherapy and CAR T-cells. The diversity and composition of the gut microbiome influences response to immunotherapy, according to recent evidence. The role of the gut microbiome in ACT or CAR T-cell setting have not been explored. We hypothesize that the gut microbiome modulation carries the potential for enhancing CAR T-cell responses.

11:25 RNAi Therapy for Activation of the Innate Immune System to Remodel the Tumor Microenvironment

Shanthi Ganesh, PhD, Associate Director, Oncology, Dicerna Pharmaceuticals, Inc

Recent research implicates the role of oncogenic pathways in mediating resistance to cancer immunotherapy. In preclinical models, systemic administration of RNAi-based experimental drugs targeting the un-druggable β -catenin or KRAS formulated in a tumor-selective nanoparticle dramatically increased T-cell infiltration and responses to immunotherapy agents. In this presentation, we will explore translational strategies for overcoming resistance in patient populations by synergistically targeting oncogenic pathways and other suppressive pathways using RNAi drugs and small molecule inhibitors.

11:55 Fragment Based Drug Discovery for Human STING Protein

Ismail Moarefi, CSO, Crelux GmbH - a WuXi AppTec company

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Inaugural | September 17-18

NEW

Immuno-Oncology: Emerging Targets and Therapeutics

New Ways to Refocus the Immune System to Attack Cancer

The cyclic GMP-AMP synthase (cGAS) –stimulator of interferon genes (STING) pathway stimulates innate immunity by triggering the production of interferons and inflammatory cytokines. Here we describe the production of the two most-prominent human STING isoforms & assay optimization for surface plasmon resonance (SPR) and microscale thermophoresis (MST) based fragment-screening.

12:10 pm Late Breaking Presentation: EOS100850, A Best-in-Class Non Brain Penetrant A2aR elective antagonist that maintains potency in high adenosine tumor microenvironment

Gregory Driessens, PhD, Project Leader, *in vivo* Pharmacology, iTeos Therapeutics

The A2a receptor is the main adenosine receptor expressed on immune cells. Its activation by adenosine, present in high concentrations in the tumor microenvironment, induces potent local immunosuppression and protects tumor cells against immune attack. This presentation will highlight the development of the clinical compound EOS100850, a highly selective, non-brain penetrant best-in-class A2AR antagonist which is able to maintain strong potency and restore immune cells function within an elevated adenosine environment found in some tumors.

12:35 Enjoy Lunch on Your Own

1:15 Refreshment Break in the Exhibit Hall with Poster Viewing

IMMUNO-METABOLISM AND REMODELING THE TUMOR MICROENVIRONMENT (TME)

1:50 Chairperson's Remarks

Scott Pesiridis, PhD, Associate Fellow, Scientific Leader - Discovery Biology, GSK

1:55 Antagonists of the Adenosine 2a Receptor (A2AR) to Reverse Tumor Suppression in the TME

Alwin Schuller, PhD, Senior Principal Scientist/Team Lead, Oncology, IMED Biotech Unit, Astra Zeneca

Adenosine, signaling through the high affinity A2AR receptor, contributes to an immune suppressed tumor micro environment by inhibiting multiple cell types involved in both innate and adaptive immunity. AZD4635 (HTL-1071) is a potent oral A2AR antagonist in clinical development in combination with durvalumab (anti-PDL1). This presentation will highlight our current pre-clinical understanding of the mechanism of action of AZD4635, including activation of various immune cell types, and anti-tumor activity in different syngeneic tumor models.

2:25 Targeting the Adenosine Immunosuppressive Pathway

Daniela Cipolletta, PhD, Investigator III, Exploratory ImmunoOncology, Novartis

2:55 Arrayed CRISPR Screening to Enable Immuno-Oncology

Abhishek Saharia, Vice President, Commercial Development, Synthego INC

The ability to conduct loss-of-function screens effectively in primary T Cells or primary dendritic cells, as well as cancer cell lines, can enable novel target discovery in immuno-oncology. Here, we discuss a platform for arrayed CRISPR screening, which drives high-efficiency protein knockout in a variety of primary cell types and numerous cancer cell lines, enabling high confidence screening using a broad number of functionally relevant assays.

3:25 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

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4:05 A Dual CD73-A2AR Antagonist to Reduce Adenosine in the TME

Susanta Samajdar, PhD, Senior Vice President and Head of Discovery, Aurigene
Adenosine generated within the tumor by CD73 thwarts the anti-tumor immune response by signaling through receptors such as A2AR on immune cells. Interestingly, the co-blockade of CD73 and A2AR results in a more pronounced anti-tumor activity than blockade of either, likely due to production of adenosine by alternate routes, increased CD73 expression upon A2AR inhibition and compensatory activity of other adenosine receptors. We will discuss our success in discovering inhibitors that dually target CD73 and A2AR.

4:35 Discovery of Small Molecule Aryl Hydrocarbon Receptor (AhR) Antagonists for Cancer Immunotherapy

Thomas Hoffman, PhD, CFO, Phenex Pharmaceuticals

Activation and accumulation of the nuclear aryl hydrocarbon receptor (AhR) protein is frequently seen in different tumor types and has been linked to immunosuppression, resulting in a diminished anti-tumor immune response. Targeting of AhR with an antagonist may therefore provide a novel immunotherapeutic approach for enhancing anti-tumoral immune responses. We identified small molecule AhR antagonists to block activated downstream signaling of AhR. The lead molecules show high potency, selectivity, favorable ADME/PK and *in vivo* efficacy in different preclinical models.

5:05 Interactive Breakout Discussion Groups

Join a breakout discussion group. These are informal, moderated discussions with brainstorming and interactive problem solving, allowing participants from diverse backgrounds to exchange ideas and experiences and develop future collaborations around a focused topic. Visit the conference website for discussion topics and moderators.

6:05 Welcome Reception in the Exhibit Hall with Poster Viewing (Sponsorship Opportunity Available)

7:10 Close of Day

WEDNESDAY, SEPTEMBER 18

7:30 am Registration Open and Morning Coffee

NEW INHIBITORS OF CHECKPOINT BLOCKADE

8:00 Chairperson's Remarks

Alwin Schuller, PhD, Senior Principal Scientist/Team Lead, Oncology, IMED Biotech Unit, Astra Zeneca

8:05 Discovery of Versatile Short Linear Peptide-based Checkpoint Inhibitors

Vinayaka Kotraiah, PhD, Preclinical Discovery Lead, Leidos – Explorations in Global Health (ExGloH)

Explorations in Global Health (ExGloH) is a division of Leidos Health engaged in identifying novel peptide scaffolds (microtides) with immune modulating properties. By screening diverse peptide libraries (e.g. microbiome) and using computational chemistry, we have identified linear peptides that bind and inhibit PD1, CTLA4 and LAG3. In mouse oncology and infectious disease models, the lead peptide LD01 with dual PD-1/CTLA4 antagonist expands vaccine-induced antigen-specific T cells, enhances anti-tumor activity and therapeutically rescues immune dysregulation. ExGloH seeks to out-license the use of microtides and establish new discovery partnerships for its platform.

8:35 EOS884448, a Novel a-TIGIT Antagonist Antibody with Dual MOA: Restoring T Cell Effector Functions and Depleting Tregs





Inaugural | September 17-18

NEW

Immuno-Oncology: Emerging Targets and Therapeutics

New Ways to Refocus the Immune System to Attack Cancer

Gregory Driessens, PhD, Project Leader, in vivo Pharmacology, iTeos Therapeutics

TIGIT is a co-inhibitory receptor expressed by lymphoid populations. α -TIGIT Abs have the potential to restore effector functions of T and NK cells by blocking TIGIT-ligand interaction. Due to elevated TIGIT expression on Treg, ADCC-enabled α -TIGIT Abs have also the potential of direct Treg depletion. This presentation will focus on the preclinical development of EOS884448 a novel α -TIGIT Ab with potent antitumor activity through several mechanisms of action and strong therapeutic potential in the clinic.

9:05 Robust and Reproducible Target Biology-Based Bioassays for Characterization and Potency Measurement of Biologics Targeting Checkpoint Modulators

Alpana Prasad, PhD, Product Manager, Marketing, Eurofins Discovery

A quantitative and robust bioassay that is reflective of the MOA of the drug is a critical component of any development program. PathHunter® cell-based assay platform offers ready to use bioassays for potency determination & stability testing of biological drugs. These quantitative and robust assays rely on the native biology of the relevant receptor, allowing developers to choose a readout reflective of the MOA of their drug. Importantly, since these are homogeneous assays that employ thaw-and-use cryopreserved cells, they not only provide convenience while minimizing assay variability, they are also highly scalable and suitable for automation. We will share case studies from our expanding portfolio of qualified bioassays for several immune-oncology targets.

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9:35 Coffee Break in the Exhibit Hall with Poster Viewing

10:20 NEW: Late Breaking Presentation: Small-Molecule TEAD-Yap Antagonists

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

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

10:50 NEW: CA-170, a First-in-Class, Orally Available, Small Molecule Immune Checkpoint Inhibitor Dually Targeting VISTA and PDL1

Raul Soikes, PhD, Senior Director & Global Program Leader, Curis

11:20 Enjoy Lunch on Your Own

11:20 Conference Registration for Programs 1B-7B

PLENARY KEYNOTE PROGRAM

Click [here](#) for full abstracts.

12:20 pm Event Chairperson's Opening Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target 2019, Cambridge Healthtech Institute

12:30 Plenary Keynote Introduction

Anjan Chakrabarti, Vice President, Discovery Chemistry, Syngene International Ltd

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12:40 Base Editing: Chemistry on a Target Nucleotide in the Genome of Living Cells

David R. Liu, PhD, Howard Hughes Medical Institute Investigator, Professor of Chemistry & Chemical Biology, Harvard University



1:20 PROTACs: Past, Present, and Future

Craig M. Crews, PhD, Professor, Chemistry; Pharmacology; Molecular, Cellular & Developmental Biology; Yale University

2:00 Close of Plenary Keynote Program

2:00 Dessert Break in the Exhibit Hall with Poster Viewing

2:45 Close of Immuno-Oncology: Emerging Targets and Therapeutics Conference



GPCR-Based Drug Discovery

Modulating G Protein-Coupled Receptors for New Therapeutic Options

G-protein coupled receptors (GPCRs) play roles in many physiological processes and have therefore been the target of medical therapeutics for decades. Their complexities in signaling, however, are still being unraveled and starting to be exploited for more targeted therapies. Progress in biophysical techniques and cryo-electron microscopy have also aided targeted drug discovery against GPCRs. At CHI's well-established GPCR-Based Drug Discovery conference, join colleagues and experts in the GPCR field who hail from both academics and industry to review advances in the field and discuss cutting edge topics impacting drug development against this very medically relevant class of drug targets.

RECOMMENDED PREMIUM PACKAGE:

Choose 2 Short Courses and 2 Conferences/Training Seminars

- September 16 Pre-Conference Short Course: **SC1: Immunology Basics: Focusing on Autoimmunity and Cancer**
- September 17-18 Training Seminar: **TS1: Targeting GPCRs for Drug Discovery**
- September 18 Dinner Short Course: **SC8: GPCR Structure-Based Drug Discovery**
- September 18-19 Conference: **GPCR-Based Drug Discovery**

WEDNESDAY, SEPTEMBER 18

10:50 - 11:50 BRIDGING LUNCHEON PANEL DISCUSSION: GPCRs: Leveraging Years of Data for Transformative Drug Discovery

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This 1-hour panel moderated by *Michel Bouvier, PhD, Principal Investigator & CEO, Institute for Research in Immunology and Cancer (IRIC) and Professor, Department of Biochemistry and Molecular Medicine, Faculty of Medicine, Université de Montréal* will feature two talks related to new horizons in GPCR drug discovery. The talks will be followed by a question and answer session.

- GPCR Mutations: Towards a More Personalized Drug Discovery**
Olivier Lichtarge, MD, PhD, Molecular and Human Genetics, Computational and Integrative Biomedical Research Center
- Virtual Screening: A Post-Structural Era**
John Irwin, PhD, Adjunct Professor, Department of Pharmaceutical Chemistry, University of California, San Francisco

11:20 Conference Registration Open

11:50 Session Break

PLENARY KEYNOTE PROGRAM

Click [here](#) for full abstracts.

12:20 pm Event Chairperson's Opening Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target 2019, Cambridge Healthtech Institute

12:30 Plenary Keynote Introduction

Anjan Chakrabarti, Vice President, Discovery Chemistry, Syngene International Ltd

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Syngene

12:40 Base Editing: Chemistry on a Target Nucleotide in the Genome of Living Cells

David R. Liu, PhD, Howard Hughes Medical Institute Investigator, Professor of Chemistry & Chemical Biology, Harvard University

1:20 PROTACs: Past, Present, and Future

Craig M. Crews, PhD, Professor, Chemistry; Pharmacology; Molecular, Cellular & Developmental Biology; Yale University

2:00 Close of Plenary Keynote Program

2:00 Dessert Break in the Exhibit Hall with Poster Viewing

GPCRs IN DISEASE

2:45 Organizer's Welcome Remarks

2:50 Chairperson's Opening Remarks

Ajay Yekkirala, Co-Founder and CSO, Blue Therapeutics

2:55 Design and Preclinical Profile of a GPR40 Superagonist

Mark R. Player, MD, PhD, Senior Scientific Director & Fellow, Discovery Chemistry, Janssen Pharmaceutical Research & Development

Full agonists of GPR40 exhibit superior glucose lowering to partial agonists in pre-clinical species due to increased insulin and GLP-1 secretion, the latter also promoting weight loss. We have identified a GPR40 superagonist which displayed excellent *in vitro* potency and superior efficacy in the Gas-mediated signaling pathway. Design and preclinical efficacy (human islets, oGTT and weight loss in DIO mice) and safety data (DILI-derisking, pancreatic insulin/proinsulin after compound rechallenge in Wistar rats) will be presented.

3:25 GLP1-R Agonist

David A. Griffith, PhD, Research Fellow, Medicinal Chemistry, Pfizer Global R&D

Glucagon-like peptide-1 receptor (GLP-1R) agonists comprise a growing class of agents that deliver unprecedented efficacy in diabetes. We will report on a program to identify an oral, small molecule GLP-1 receptor agonist for the treatment of diabetes. An innovative hit identification strategy provided weak leads that were progressed through structure-activity exploration to achieve drug-like potency and ADME attributes. This presentation will disclose the discovery of the oral small molecule GLP-1R agonist PF-06882961, including emerging human pharmacokinetic data.

3:55 Enabling Drug Discovery with Multispan

Lisa Minor, Scientific Consultant, Multispan, Inc.

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The path to successful drug discovery requires 1) a validated target, 2) assays accurately measuring the specific target, and 3) assays run reproducibly and robustly. This presentation will demonstrate how Multispan can uniquely empower your drug discovery efforts. We provide fully validated cells expressing your target along with a battery of well characterized MultiScreen™ assays for conducting your primary and secondary screens in our Bay Area laboratory. Our vast attention to detail and cellular pharmacology helps to ensure your project's success and shorten your timeline.

4:25 Refreshment Break in the Exhibit Hall with Poster Viewing

5:00 Signaling Bias of a Novel LPAR1 "Antagonist" Lead Molecule and Implications for Drug Discovery

Marie-Laure Rives, PhD, Senior Scientist, Molecular and Cellular Pharmacology, Lead Discovery, Janssen Research & Development

Lysophosphatidic acid (LPA) is a bioactive lipid and pro-fibrotic agent acting through LPA receptors: LPAR1 - 6. A wealth of preclinical data has revealed the relevance of LPAR1 in the development of kidney fibrosis. We have identified a new LPAR1 allosteric antagonist that shows promising selectivity. However, this compound and its analogs show intriguing signaling bias properties whose physiological consequences are still unknown and under investigation.

5:30 GPR84: Can Context-Dependent Signaling Inform Therapeutic Direction?

Carleton Sage, PhD, Vice President, Computational Sciences, Beacon Discovery

GPR84 is an inflammation-related orphan G Protein-Coupled GPCR. Expression analysis suggests that modulation of GPR84 could be valuable



GPCR-Based Drug Discovery

Modulating G Protein-Coupled Receptors for New Therapeutic Options

for inflammation related diseases such as Crohn's disease, IBD, or idiopathic pulmonary fibrosis, but thus far agonists have proven unsuccessful in clinical trials. New observations of signaling in immune cells suggest an explanation and a path forward.

6:00 Drug-Target Binding Kinetics – Implications for Insurmountable Antagonism at GPCRs

Laura H. Heitman, PhD, Associate Professor for Molecular Pharmacology, Leiden Academic Centre for Drug Research (LACDR), Leiden University

6:30 Dinner Short Course Registration

Click [here](#) for details on short courses offered.

9:30 Close of Day

THURSDAY, SEPTEMBER 19

7:00 am Registration Open

7:30 Interactive Breakfast Breakout Discussion Groups

Grab a cup of coffee and join a breakout discussion group. These are informal, moderated discussions with brainstorming and interactive problem solving, allowing participants from diverse backgrounds to exchange ideas and experiences and develop future collaborations around a focused topic. Visit the conference website for discussion topics and moderators.

8:30 Transition to Sessions

BIASED AGONISTS AND ALLOSTERISM

8:40 Chairperson's Remarks

Huixian Wu, PhD, Principal Scientist, Structural and Molecular Sciences, Discovery Sciences, Pfizer, Inc.

8:45 FEATURED PRESENTATION: Bias and Beyond: Challenges and Opportunities in GPCR Drug Development

Michael Fossler, PharmD, PhD, FCP, Vice President, Clinical Operations and Quantitative Sciences, Trevena, Inc.

Oliceridine is a novel investigational G protein-biased ligand at the μ -opioid receptor developed for the management of moderate to severe acute pain. Oliceridine produced differentiated pharmacology in preclinical studies compared to unbiased ligands and maintained a similar profile in the clinic—rapid analgesia with a favorable safety profile with regard to respiratory and gastrointestinal adverse effects compared to morphine. The totality of the data indicate that ligand bias is an important concept in designing new drugs.

9:15 De novo Design of G α Mimetics: Generalizable Tools for Allosteric Control of G Protein-Coupled Receptors

Christopher D. Bahl, PhD, Head of Protein Design, Institute for Protein Innovation

Generalizable tools to stabilize the active conformational state of GPCRs will facilitate protein purification and structure determination, as well as accelerate the engineering of molecules which act as agonists or antagonists. Using *de novo* protein design, we have developed novel G α mimetic proteins that are thermostable, selectively bind to the active state of GPCRs, and can bind to a wide range of different GPCRs.

9:45 Structure-Based Conversion of the Subtype Selectivity of the Muscarinic Toxin

Shoji Maeda, PhD, Senior Postdoctoral Fellow, Kobilka Lab, Department of Molecular and Cellular Physiology, Stanford University

Muscarinic toxin 7 (MT7) is a natural protein toxin produced by green mamba snakes that exclusively binds to muscarinic acetylcholine receptor 1 (M1R) and modulates its function. To understand the molecular mechanism of this strict subtype selectivity and allosteric mechanism, we solved the crystal structure of M1R-MT7 complex. Furthermore, we converted the selectivity of MT7 towards M2R by *in vitro* engineering. This study suggests the possibility of the three-finger fold as a promising scaffold to target GPCRs.

10:15 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

NON-CLASSICAL SIGNALING

10:55 Understanding the Consequences of GPCR Dimerization

Terry Hébert, PhD, Professor, Department of Pharmacology and Therapeutics, McGill University

How GPCRs interact with one another remains an area of active investigation. Well-characterized dimers of class C GPCRs such as GABA-B and glutamate receptors are well accepted, but whether this is a general feature of GPCRs is still debated. GPCR oligomers are better imagined as parts of larger metastable signaling complexes. The nature of functional oligomeric entities, stability, kinetic features and structural and functional asymmetries of such metastable entities have implications for drug discovery.

11:25 NEW: Late Breaking Presentation

11:55 Using Smart Drug Discovery Software to Enhance Collaboration and Manage Disperse Assay Data

Robert Thorn, PhD, Customer Engagement Scientist, Collaborative Drug Discovery, Inc.

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 Complexity Simplified

12:10 pm Machine-Learning & AI-Based Approaches for GPCR Bioactive Ligand Discovery

Sebastian Raschka, PhD, Assistant Professor, Department of Statistics, University of Wisconsin at Madison

This talk will provide an overview of the latest advances for automating the discovery of bioactive ligands using machine learning. Applications include the discovery of a potent GPCR pheromone inhibitor as well as models predicting active and inactive GPCR states by combining machine learning and structural rigidity analysis. Lastly, the talk will conclude with the recent developments in deep learning that are aimed at replacing the need for hand-engineering molecular representations by automatic representation learning.

12:40 Session Break

12:45 Luncheon Presentation: Integrating Experimental and Computational Pharmacology for Intelligent GPCR Drug Candidate Selection

Martin Ostermaier, PhD, CEO, InterAx Biotech AG

InterAx built a computational tool to integrate theoretical knowledge with experimental data of GPCR-mediated trafficking events. As a result, deeper mechanistic insights into the dynamic cellular system are achievable. Such mathematical models allow to predict experimental outcomes and deliver novel insights into drug actions on GPCRs. As an example, our predictive model allowed us to discriminate 17 marketed asthma drugs for their duration of action. This technology is currently applicable to discovery programs on GPCRs.

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14th Annual | September 18-19

GPCR-Based Drug Discovery

Modulating G Protein-Coupled Receptors for New Therapeutic Options

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

3:55 Close of Conference

MEDICINAL CHEMISTRY AND BIOPHYSICAL APPROACHES FOR GPCRS

2:05 Chairperson's Remarks

Mark R. Player, MD, PhD, Senior Scientific Director & Fellow, Discovery Chemistry, Janssen Pharmaceutical Research & Development

2:10 Lessons Learned from Various GPCR Lead Optimization Projects

Chi Sum, PhD, Senior Research Investigator, Lead Discovery and Optimization, Bristol Myers Squibb & Co.

The recent new concepts of GPCR function, including signaling bias, allosteric, kinetics, and receptor trafficking, have provided an important frame of reference for GPCR Drug Discovery. Recognizing these pharmacological properties has become fundamental for a successful campaign. Here, we present some case studies on how these principles operate directly or indirectly to influence lead optimization effort.

2:40 First Orally Bioavailable Antagonist of the Neuropeptide Y Receptor 2 (NPY2R)

Pierre Wasnaire, PhD, Senior Scientist, Pharmaceuticals R&D, Bayer AG

Autonomic imbalance with increased sympathetic activity and withdrawal of vagal activity is associated with increased mortality both after myocardial infarction (MI) and in heart failure (HF). Neuropeptide Y (NPY) is suggested to be a key link between enhanced sympathetic and decreased vagal activity in autonomic imbalance in HF. NPY receptor 2 (NPY2R) antagonism seems attractive for the treatment of autonomic imbalance by restoring vagal activity in HF patients and patients post-MI. After high-throughput screening and medicinal chemistry optimization we found new, potent and selective NPY2R antagonist, showing suitable DMPK and safety profiles.

3:10 Structural Insights into GPCR Recognition by Arrestin

John Janetzko, PhD, Damon Runyon Postdoctoral Fellow, Kobilka Lab, Department of Molecular and Cellular Pharmacology, Stanford University

While there is a wealth of structural information pertaining to the basis of G protein-receptor interactions, there exists no structure of a non-rhodopsin GPCR in complex with arrestin. Using cryo-electron microscopy we obtained a structure of the neurotensin type I receptor (NTSR1) in complex with arrestin 2. This structure reveals how the receptor is engaged by arrestin, how phosphorylation of the receptor might regulate arrestin recruitment and activation and how the plasticity of the interactions formed between the two enable arrestin to recognize a large set of diverse GPCRs.

3:40 Surface Plasmon Resonance Microscopy for GPCRS

Shijie Wu, PhD, Application Scientist, Biosensing Instrument

One of the most recent significant biophysical advances to study GPCR binding properties is Surface Plasmon Resonance Microscopy (SPRM), a powerful technique that simultaneously visualizes cellular structures and measures molecular binding interactions of membrane proteins label-free, *in vitro* and in real time. With this award-winning biosensor technique, the measurement of phenotypical changes of the cell via bright field and binding affinity and kinetics of GPCR targets via SPR can be done. In this presentation, we will review the principles behind SPRM and show application examples of binding affinity and kinetics of multiple whole cells as well as localized responses on a single cell.

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Antibodies Against Membrane Protein Targets Part 1

Antigen and Antibody Generation

Membrane-bound proteins are attractive drug targets for antibodies and other protein scaffolds, but for the field to advance, fundamental challenges in optimizing antigen quality and presentation, discovery methodologies, protein engineering and target identification must be resolved. This two-part meeting provides a forum in which discovery biologists and protein engineers can come together to discuss next-generation strategies and technologies that will allow antibody-based therapeutics directed against GPCR and ion channel targets to advance into the clinic and beyond. **Part 1, Antigen and Antibody Generation**, will focus on best practices for antigen preparation, new approaches to antibody generation and the important role of structural modeling and analysis – and track early stage, preclinical and clinical progress in this space.

RECOMMENDED PREMIUM PACKAGE:

Choose 2 Short Courses and 2 Conferences/Training Seminars

- September 16 Pre-Conference Short Course: **SC2: Targeting of Ion Channels with Monoclonal Antibodies**
- September 17-18 Conference: **Antibodies Against Membrane Protein Targets – Part 1**
- September 18 Dinner Short Course: **SC8: GPCR Structure-Based Drug Discovery**
- September 18-19 Conference: **Antibodies Against Membrane Protein Targets – Part 2**

MONDAY, SEPTEMBER 16

1:00 pm Pre-Conference Short Course Registration

Click [here](#) for details on short courses offered.

TUESDAY, SEPTEMBER 17

7:00 am Registration Open and Morning Coffee

INNOVATION IN TARGETING MEMBRANE PROTEINS

8:00 Organizer's Welcome Remarks

8:05 Chairperson's Opening Remarks

Catherine Hutchings, PhD, Independent Consultant, United Kingdom

8:10 Novel Biologies and Modalities for Targeting Membrane Proteins

Zhiqiang An, PhD, Professor, Chemistry; Director, Texas Therapeutics Institute, University of Texas Health Science Center at Houston

Rapid progress in the discovery of membrane proteins' role in disease development provides a rich pool of targets for biologics-based drug modalities. Challenges in the development of these drugs include delivery across the BBB, targeting multiple targets simultaneously, and specific delivery of cytotoxic drugs inside a cell and to the disease microenvironment. This presentation will provide an overview of opportunities and challenges in developing novel biologics targeting membrane proteins.

8:40 Clinical and Preclinical Progress in Targeting Membrane Proteins: What Is Working (and Not)?

Catherine Hutchings, PhD, Independent Consultant, United Kingdom

G protein-coupled receptors (GPCRs), ion channels and transporters represent some of the most important drug target classes across a wide range of diseases. An update on the clinical and preclinical progress made by antibody-based therapeutics directed to these target classes will be presented along with examples of success and failure encountered in the R&D pipeline.

9:10 KEYNOTE PRESENTATION: GPCRomics: "New" GPCRs That Expand Their Utility as Drug Targets

Paul A. Insel, MD, Distinguished Professor, Pharmacology and Medicine, University of California, San Diego

G protein-coupled receptors (GPCRs) are the largest family of cell surface receptor proteins and the most frequent targets (~35%) of approved drugs. However, only ~15% of the ~800 human GPCRs are currently targeted. This talk will discuss how GPCRomics – approaches to identify and quantify endogenously expressed GPCRs in healthy and diseased cells and tissues – can reveal "new" GPCRs as targets for new therapeutics and the repurposing of approved drugs.

9:40 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

ANTIGEN GENERATION AND OPTIMIZATION

10:25 Functional Validation and High-Throughput Screening of Purified Ion Channel Proteins Using Reconstituted Proteoliposomes

Zhenwei Su, PhD, Senior Scientist, Biomedicine Design, Pfizer, Inc.

Maintaining native conformations and biological functions of purified membrane proteins greatly facilitates drug discovery. This presentation focuses on the use of reconstituted proteoliposomes as a powerful tool to validate functionality of purified ion channel proteins. Validated proteins serve as valuable resources for immunizations and assay developments. The proteoliposome system also offers a screening method for the hit identification.

10:55 Large Asymmetric Nanodiscs and Their Applications in Drug Discovery

Mahmoud Nasr, PhD, Instructor, Medicine, Brigham and Women's Hospital

Lipids are asymmetrically distributed between the two leaflets of many biological membranes. Also, membrane proteins may assemble in functional clusters in the plane of the membrane. We have developed large nanodiscs up to 90 nm in diameter that are suitable for reconstructing this asymmetry and can be used to study membrane protein complexes and virus entry. The methods for making these nanodiscs as well as their application in drug discovery will be presented.

11:25 Overcoming Production Challenges for Membrane Proteins in Antibody Discovery

Leyu Wang, PhD, Senior Scientist and Project Leader, Protein Sciences, AbbVie

Antibodies against membrane proteins are highly attractive as therapeutics. The success to discover the therapeutic antibodies is critically depending on the quality of membrane protein itself. Due to the complex nature of membrane proteins, there is no single method to address the membrane protein production challenges. Practical solution is to develop "fit-for-purpose" membrane production for immunization, display, screening and characterization that will be discussed in this presentation.

11:55 Discovery and Development of Antibodies Against Ion Channel Targets

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Ted Clark, Founder & CSO, TetraGenetics, Inc.

Identifying antibodies that block ion channels is a challenging endeavor exacerbated by difficulties in producing recombinant protein in amounts that support drug discovery programs. We have developed a general strategy to address this challenge by combining high-level expression of recombinant VGICs with immunization of diverse species and unique screening tools.



Antibodies Against Membrane Protein Targets Part 1

Antigen and Antibody Generation

12:10 pm NGS-Guided Discovery of Fully-Human Antagonist Antibodies against the Class A GPCR CXCR5

Valerie Chiou, Scientist, Distributed Bio

Due to their challenging structure within the membrane, generating functionally active antibodies against GPCRs remains an engineering challenge. We established a new cell-based panning method using our fully human computationally optimized phage display library, establishing a general method for generating fully human and functional anti-GPCR therapeutic antibodies.

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affinities and good stabilities which are compatible with different antibody designs including bispecifics.

3:25 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

4:05 Single-Domain Antibody Fragments as Tools to Interrogate GPCR Structure and Function

Andrew C. Kruse, PhD, Associate Professor, Biological Chemistry and Molecular Pharmacology, Harvard Medical School

Camelid VHH antibody fragments have become versatile tools to study G protein-coupled receptor (GPCR) structure and signaling. Using a fully synthetic VHH fragment library displayed on yeast we developed high-affinity binders to the angiotensin II type 1 receptor and used these to shed light on its activation mechanism and regulation by peptide agonists. These approaches are highly general to GPCR modulator discovery and provide a tool to accelerate GPCR research.

12:25 Session Break

12:35 Luncheon Presentation: Specificity Profiling and High-Resolution Epitope Mapping of Challenging MAbs

Benjamin Doranz, PhD, MBA, President and CEO, Integral Molecular

Specificity testing across the proteome de-risks lead selection. We have tested hundreds of mAbs for specificity and off-target binding using our Membrane Proteome Array (MPA) platform. This platform contains 5,300 human membrane proteins, each expressed in live cells in their native conformation. Conformational epitopes generate novel IP and mechanistic insights. We have mapped >1,000 such epitopes with a success rate >95% using our high-resolution Shotgun Mutagenesis Epitope Mapping platform.

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4:35 Modulating Effector Functions of Membrane Protein-Specific Heavy-Chain Antibodies through Hinge Engineering

Jamshid Tanha, PhD, Research Officer, National Research Council, Canada

The effector functions of membrane protein-specific conventional and heavy-chain antibodies are known to be affected by Fc modification, i.e., glycan or protein engineering. Data on a series of hinge-engineered heavy-chain antibodies (HCAs) are presented and demonstrate that the effector functions of HCAs can also be modulated simply by varying the length of the Ab hinge; this strategy may be useful to consider when engineering therapeutic heavy chain antibodies for optimal effector functions.

1:15 Refreshment Break in the Exhibit Hall with Poster Viewing

STRATEGIES FOR GENERATING ANTIBODIES AGAINST MEMBRANE PROTEINS

1:50 Chairperson's Remarks

Rajesh Vij, Senior Scientific Researcher, Antibody Engineering, Genentech

1:55 Antibody Discovery and Characterization in Absence of a Soluble Recombinant Target Antigen

Nikša Kastrapeli, PhD, Director, Lead Identification, Biotherapeutics Molecule Discovery, Boehringer Ingelheim

Well-behaved, extensively characterized targets and their associated mechanisms are increasingly saturated with therapeutic options. The path to innovation often leads to exploring novel target antigens with difficult expression profiles and poorly understood pathways. Therapeutic antibody generation relies on high-quality antigens that are functionally and structurally relevant to their natural forms. Here we will review options to generate and characterize antibodies without the luxury of using a suitable soluble antigen protein.

2:25 New Tools to Characterize Antibodies against Membrane Proteins

Rajesh Vij, Senior Scientific Researcher, Antibody Engineering, Genentech

Characterization of antibody-antigen interactions is an essential part of antibody development. This step becomes a larger bottleneck when targeting complex membrane proteins, due to limitations with existing assays. We will discuss a novel high-throughput cell-based assay that can measure cell-based affinities and receptor expression levels and demonstrate how this workflow can support lead antibody selection.

2:55 High Quality Antibodies for Therapeutic Applications

Vera Molkenthin, PhD, Chief Scientist, AbCheck

AbCheck discovers and optimizes human antibodies for therapeutic applications leveraging several proprietary platforms including *in vitro* and *in vivo* technologies. AbCheck delivers high quality leads with subnanomolar

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AB CHECK

5:05 Interactive Breakout Discussion Groups

Join a breakout discussion group. These are informal, moderated discussions with brainstorming and interactive problem solving, allowing participants from diverse backgrounds to exchange ideas and experiences and develop future collaborations around a focused topic. Visit the conference website for discussion topics and moderators.

6:05 Welcome Reception in the Exhibit Hall with Poster Viewing (Sponsorship Opportunity Available)

7:10 Close of Day

WEDNESDAY, SEPTEMBER 18

7:30 am Registration Open and Morning Coffee

STRUCTURAL BIOLOGY

8:00 Chairperson's Remarks

Friedrich Koch-Nolte, PhD, Professor, Laboratory of Molecular Immunology, University Medical Center Hamburg-Eppendorf, Germany

8:05 Applications of Cryo-EM for Discovery and Development of Antibodies against Membrane Protein Targets

Xinchao Yu, PhD, Senior Scientist, Cryo-EM, Amgen

Antibodies have shown great potential to facilitate cryo-EM structure determination of small membrane protein targets. Here we present the discovery and characterization of antibodies against an ABC transporter involved in cholesterol transport. We solved the 3.3 Å resolution cryo-EM structure of the transporter with the help of 2 Fabs. The cryo-EM structure provides structural insight into substrate engagement to the transporter.



Antibodies Against Membrane Protein Targets Part 1

Antigen and Antibody Generation

8:35 How Native-MS Can Complement X-Ray and CryoEM Studies in Understanding the Interactions of Membrane Proteins with Lipids and Proteins

Arthur Laganowsky, PhD, Assistant Professor, Chemistry, Texas A&M University

Native ion mobility mass spectrometry (IM-MS) is an emerging biophysical technique to probe membrane protein complexes and their interactions with lipids and other molecules. I will describe how native IM-MS can be used to determine thermodynamics of individual ligand binding events to proteins. We also have developed native IM-MS approaches to unravel how individual lipid-binding events to membrane proteins can allosterically modulate their interactions with proteins and lipids.

9:05 Efficient Discovery of Single Domain Antibodies to Membrane Proteins Using a Synthetic Library

Guy Hermans, PhD, CSO, Isogenica Ltd

Isogenica's IImadA™ library is a highly diverse, fully synthetic single domain VHH library. We will illustrate some of the unique benefits of VHH technology over conventional antibodies and demonstrate how the unbiased diversity and lack of tolerance enables rapid and resource efficient isolation of VHH to membrane proteins. Examples will include the use of the library in 'whole cell' panning projects, as well as in selections using purified membrane proteins complexes.

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9:35 Coffee Break in the Exhibit Hall with Poster Viewing

PANEL DISCUSSION

10:20 Membrane Protein Tools and Technologies – What Is Working and What Isn't?

Moderator: Kevin Heyries, PhD, Co-Founder, AbCellera, Canada

Panelists: John Blankenship, PhD, Senior Investigator and Group Leader, Antibody Discovery, Novartis

Brian Booth, PhD, Senior Scientist, Drug Discovery, Visterra

Benjamin Doranz, PhD, MBA, President and CEO, Integral Molecular

Heike Wulff, PhD, Associate Professor, Pharmacology, School of Medicine, University of California, Davis

The challenging nature of membrane proteins has often dictated that researchers employ a toolbox approach to this work, cycling through a wide range of methods and technologies to find the best fit for a specific project. Join this panel – shared between the Antibodies Against Membrane Targets and Antibody Forum audiences – for an interactive discussion of experiences with different discovery tools used in this space. You'll hear perspectives from both panelists and other audience members and have the opportunity to share your own questions and best practices.

11:20 Enjoy Lunch on Your Own

11:20 Conference Registration for Programs 1B-7B

PLenary KEYNOTE PROGRAM

Click [here](#) for full abstracts.

12:20 pm Event Chairperson's Opening Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target 2019, Cambridge Healthtech Institute

12:30 Plenary Keynote Introduction

Anjan Chakrabarti, Vice President, Discovery Chemistry, Syngene International Ltd

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12:40 Base Editing: Chemistry on a Target Nucleotide in the Genome of Living Cells

David R. Liu, PhD, Howard Hughes Medical Institute Investigator, Professor of Chemistry & Chemical Biology, Harvard University



1:20 PROTACs: Past, Present, and Future

Craig M. Crews, PhD, Professor, Chemistry; Pharmacology; Molecular, Cellular & Developmental Biology; Yale University

2:00 Close of Plenary Keynote Program

2:00 Dessert Break in the Exhibit Hall with Poster Viewing

2:45 Close of Antibodies Against Membrane Protein Targets – Part 1 Conference

Please click [here](#) to continue to the agenda for Antibodies Against Membrane Protein Targets – Part 2



Antibodies Against Membrane Protein Targets Part 2

Discovery, Characterization and GPCR/Ion Channel Updates

Membrane-bound proteins are attractive drug targets for antibodies and other protein scaffolds, but for the field to advance, fundamental challenges in optimizing antigen quality and presentation, discovery methodologies, protein engineering and target identification must be resolved. This two-part meeting provides a forum in which discovery biologists and protein engineers can come together to discuss next-generation strategies and technologies that will allow antibody-based therapeutics directed against GPCR and ion channel targets to advance into the clinic and beyond. **Part 2, Discovery, Characterization and GPCR/Ion Channel Updates**, explores developments at the discovery and screening stages and offers focused sessions on each of these target classes.

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WEDNESDAY, SEPTEMBER 18

11:20 am Conference Registration Open

PLENARY KEYNOTE PROGRAM

Click [here](#) for full abstracts.

12:20 pm Event Chairperson's Opening Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target 2019, Cambridge Healthtech Institute

12:30 Plenary Keynote Introduction

Anjan Chakrabarti, Vice President, Discovery Chemistry, Syngene International Ltd

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12:40 Base Editing: Chemistry on a Target Nucleotide in the Genome of Living Cells

David R. Liu, PhD, Howard Hughes Medical Institute Investigator, Professor of Chemistry & Chemical Biology, Harvard University



1:20 PROTACs: Past, Present, and Future

Craig M. Crews, PhD, Professor, Chemistry; Pharmacology; Molecular, Cellular & Developmental Biology; Yale University

2:00 Close of Plenary Keynote Program

2:00 Dessert Break in the Exhibit Hall with Poster Viewing

DISCOVERY STRATEGIES

2:45 Organizer's Welcome Remarks

2:50 Chairperson's Opening Remarks

Brian Booth, PhD, Senior Scientist, Drug Discovery, Visterra

2:55 Therapeutic Antibody Affinity Maturation by Cell Surface Display: Closing the Gap

Agnieszka Kielczewska, Senior Scientist, Antibody Discovery, Amgen, Canada

AMGN12 antibody, derived from an *in vivo* immunization of the XenoMouse®, demonstrated single digit pM affinity to the human orthologue of the target protein, but a 200-fold weaker binding to the cyno orthologue. We applied a novel affinity maturation approach, based on combining non-hypothesis driven CDR-engineering with cell surface display, to "close" the affinity gap without compromising binding affinity to the human target. This led to identification of variants with affinity improvements and potency improvement in bioassays.

3:25 Lead Antibody Identification against Membrane Protein Targets Using Rabbit Single B Cell Cloning Technology

Noriyuki Takahashi, Unit Leader, Lead Identification Unit, Chugai Pharmabody Research, Singapore

Membrane proteins are attractive targets for drug discovery but antibody identification against membrane targets are challenging. Rabbit single B cell cloning technology is an immunization based powerful high throughput platform to identify lead antibodies. Our antibody identification strategy against membrane protein targets will be introduced.

3:55 Uncovering Novel Receptor Targets and Assessing Target Specificity Against Human Membrane and Secreted Proteins

Alex Kelly, US Business Development Manager, Retrogenix Limited

Cell microarray screening of plasma membrane and tethered secreted proteins that are expressed in human cells enables rapid discovery of primary receptors as well as potential off-targets for a variety of biologics including: peptides, antibodies, proteins, CAR T and other cell therapies. Case studies will demonstrate the utility of the technology in identifying novel, druggable targets as well as in specificity screening to aid safety assessment and provide key data to support IND submissions.

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4:25 Refreshment Break in the Exhibit Hall with Poster Viewing

THERAPEUTIC DEVELOPMENT FOR GPCRS

5:00 Discovery and Optimization of Antibodies Targeting Ion Channels and G Protein-Coupled Receptors

Trevor Wilkinson, PhD, Associate Director, Antibody Discovery and Protein Engineering, AstraZeneca BioPharmaceuticals Unit, United Kingdom

Multi-spanning membrane proteins such as GPCRs and ion channels are important drug target classes and are implicated in a broad range of diseases. There is significant interest in developing monoclonal antibodies directed against these target classes which exploit the unique properties of these therapeutics. This presentation will use case studies to address the challenges of isolating and optimizing antibodies against complex membrane proteins which have desired functional properties.

5:30 Development of Therapeutic Antibodies Targeting C5aR1

Brian Booth, PhD, Senior Scientist, Drug Discovery, Visterra

The potent anaphylatoxin, C5a, promotes chemotaxis and activation of neutrophils, a key driver in inflammatory diseases such as ANCA-vasculitis. Blockade of the C5a-C5aR1 axis mitigates disease symptoms of ANCA-vasculitis animal models and in humans. An antibody targeting C5aR1 can provide improved specificity and pharmacokinetic properties and would be an ideal treatment modality for diseases involving complement pathway dysregulation. We detail the discovery of antibodies that antagonize the C5a receptor (C5aR1).



Antibodies Against Membrane Protein Targets Part 2

Discovery, Characterization and GPCR/Ion Channel Updates

6:00 Discovery and Optimization of Fully Human CCR8 Antibodies with CCL1 Antagonistic Function using a Whole Cell Selection Platform

Robert Pejchal, Ph.D. Director, Antibody Discovery Adimab LLC

Whole cell selections extend discovery of IgGs to integral membrane proteins, such as GPCRs. A case study from initial binder identification to functional characterization of affinity-optimized antagonist leads against a C-C chemokine receptor 8 (CCR8) will be presented, along with takeaways for leveraging multiple cell lines to affect the largest clonal frequency changes in NGS-based enrichment analysis of highly-diverse library selection outputs.

6:30 Dinner Short Course Registration

Click [here](#) for details on short courses offered.

9:30 Close of Day

THURSDAY, SEPTEMBER 19

7:00 am Registration Open

7:30 Interactive Breakfast Breakout Discussion Groups

Grab a cup of coffee and join a breakout discussion group. These are informal, moderated discussions with brainstorming and interactive problem solving, allowing participants from diverse backgrounds to exchange ideas and experiences and develop future collaborations around a focused topic. Visit the conference website for discussion topics and moderators.

8:30 Transition to Sessions

THERAPEUTIC DEVELOPMENT FOR ION CHANNELS

8:40 Chairperson's Remarks

Jen Pan, PhD, Director, Translational Neurobiology, Stanley Center at the Broad Institute

8:45 Targeting Kv1.3 with Biologics: Venom Peptides, Antibodies and Things in Between

Heike Wulff, PhD, Associate Professor, Pharmacology, School of Medicine, University of California, Davis

The voltage-gated potassium channel Kv1.3 is expressed in T cells, B cells, microglia and macrophages and has long been pursued as a target for T-cell mediate autoimmune diseases. It has more recently also emerged as an attractive target for reducing neuroinflammation associated with stroke, Alzheimer's and Parkinson's disease. This talk will discuss targeting of Kv1.3 with venom peptides or conventional monoclonal antibodies and compare these approaches to so called "knotbodies".

9:15 Controlling Membrane Proteins with Photopharmacology

Dirk Trauner, PhD, Professor, Chemistry, New York University

Photopharmacology endeavors to control biological function with synthetic photoswitches that interact in various ways with their biological targets. I will discuss the advantages and disadvantages of photopharmacology and its potential applications in biology and medicine, in particular with respect to controlling cell proliferation, cell migration, and targeted protein degradation. I will also touch on the use of biological binders (nanobodies, etc.) for targeting GPCRs and ion channels with photopharmacology.

9:45 Modulating the Function of the P2X7 Ion Channel with Antibodies and Nanobodies

Friedrich Koch-Nolte, PhD, Professor, Laboratory of Molecular Immunology, University Medical Center Hamburg-Eppendorf, Germany

The P2X7 ion channel is expressed by immune cells as a sensor for nucleotides released from stressed cells. Blockade of P2X7 ameliorates disease in animal models of sterile inflammation. We have generated antibodies and nanobodies that antagonize or potentiate nucleotide-mediated gating of P2X7 with high specificity and efficacy. We can engineer these biologics to target specific immune cell subsets and to tune the duration of P2X7 antagonism *in vivo*.

10:15 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

10:55 High Throughput, High Resolution Electrophysiology in the Era of Genetic Variations

Jen Pan, PhD, Director, Translational Neurobiology, Stanley Center at the Broad Institute

Whole-exome sequencing has rapidly expanded the genetic variation that are identified in control subjects and in disorders. Here we propose a framework and workflow to dissect the impact of human genetic variations on ion channels in health and in sickness, and present two examples of data-driven approach to investigate the impact of human genetics on risk genes using high throughput and high-resolution electrophysiology.

11:25 Targeting KCa1.1 Channels for the Treatment of Rheumatoid Arthritis

Christine Beeton, PhD, Associate Professor, Molecular Physiology and Biophysics, Baylor College of Medicine

Fibroblast-like synoviocytes (FLS) upregulate KCa1.1 (BK) channels and become highly invasive and erosive during rheumatoid arthritis (RA). Blocking KCa1.1 inhibits their invasiveness and attenuates disease severity in animal models of RA. Combining blockers of KCa1.1 to target FLS and of Kv1.3 channels to target effector-memory T lymphocytes is synergistic in animal models of RA.

11:55 GPCR Focused Antibody Libraries Modeled on Natural Binding Motifs and Patented GPCR Antibodies

Sponsored by



Qiang Liu, PhD, Director, Antibody Engineering, Biopharma, Twist Bioscience

To enable the discovery of functional GPCR antibodies, we grafted a large number of GPCR-binding motifs into a focused antibody library. By incorporating these motifs into the antibody heavy chain CDR3, we developed our first generation GPCR library. Another approach mined the patented GPCR antibody sequences and used the sequence information to guide the design of another synthetic library. We demonstrate the utility of both libraries to discover potent functional antibodies against multiple GPCR targets.

12:25 pm Session Break

12:35 Luncheon Presentation Title to be Announced

Bill Harriman, PhD, MBA, Vice President, Antibody Discovery Services, OmniAb, a Ligand technology

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

SCREENING AND CHARACTERIZATION

2:05 Chairperson's Remarks

Mariana Lemos-Duarte, PhD, Postdoctoral Researcher, Icahn School of Medicine at Mount Sinai

2:10 Massive Antibody Discovery Used to Probe Structure-Function Relationships of an Essential Gram-Negative Bacteria Outer Membrane Protein

Steven Rutherford, PhD, Scientist, Infectious Diseases, Genentech



A diverse library of monoclonal antibodies was used to probe the extracellular loops of an essential *Escherichia coli* outer membrane protein. Epitope binning, mapping, and site-directed mutagenesis suggest that dispensable loops shield functionally important epitopes from antibody interference. Our workflow enables structure-function studies in cellular environments, provides insight into an essential outer membrane protein, and presents a method to assess therapeutic potential of antibody targets.

2:40 Cell-Based Assays to Characterize Ligands for Chemokine Receptor CXCR4

Tom Van Loy, PhD, Senior Postdoctoral Scientist, Rega Institute, K.U. Leuven, Belgium

G protein-coupled receptors (GPCRs) form an important family of membrane proteins and the single largest class of therapeutic targets. In GPCR drug discovery *in vitro* cell-based assays are of key importance to characterize ligands (small molecules, biotherapeutics) that target this receptor class. We will exemplify this by discussing both label-free and label-based methodologies used to profile ligands targeting chemokine receptor CXCR4, as well as several other related GPCRs.

3:10 Generation and Optimization of Antibody-like Modulators of Ion Channels by Fusing Venom Derived Miniproteins into Peripheral CDR Loops

Aneesh Karatt Vellatt, PhD, Group Leader, Iontas Ltd., United Kingdom

Venom derived cysteine-rich miniproteins (knottins) have potential as therapeutic agents to block ion channels involved in cancer, autoimmunity and pain but suffer from manufacturing difficulties, short half-lives and a lack of specificity. Using the KnotBody technology, IONTAS have developed antibody-like inhibitors of multiple ion channels by fusing venom derived knottins into peripheral CDR loops. The "developability" profiles of these KnotBody molecules were further optimized by using the proprietary Mammalian Display technology.

3:40 Development of High Throughput Functional Screening for the Characterization of an Active State-Sensitive Antibody to Protein Kinase C

Mariana Lemos-Duarte, PhD, Postdoctoral Researcher, Icahn School of Medicine at Mount Sinai

We have developed a high-throughput functional screening to explore PKC activation in the context of opioid receptor signaling and desensitization. We generated antibodies to a PKC epitope that is revealed upon activation. This strategy allowed us to obtain rabbit monoclonal antibodies to activated PKC with high affinity and specificity. This talk will highlight a novel antibody-based strategy, with a novel yeast display approach to antibody development, CRISPR-Cas9 to validate it and high content microscopy to explore PKC signaling.

4:10 Close of Conference

Please click [here](#) to return to the agenda for Antibodies Against Membrane Protein Targets – Part 1



Antibody Forum – Part 1

The Discovery Stage

Discovery on Target's Antibody Forum offers R&D research scientists the opportunity to participate in a unique meeting format that encourages discussion and the exchange of best practices on the application of new science and technology for the discovery and development of novel biotherapeutics. The meeting will feature short presentations, panel discussions, facilitated roundtables and an audience layout that allows a sharing of ideas and experiences. **Part 1** will focus on the discovery stage, offering ideas on how to accelerate and optimize these steps, emerging discovery technologies and the integration of artificial intelligence and machine learning.

RECOMMENDED PREMIUM PACKAGE:

Choose 2 Short Courses and 2 Conferences/Training Seminars

- September 16 Pre-Conference Short Course: **SC3: Selection, Screening and Engineering for Affinity Reagents**
- September 17-18 Conference: **Antibody Forum – Part 1**
- September 18 Dinner Short Course: **SC8: GPCR Structure-Based Drug Discovery**
- September 18-19 Conference: **Antibody Forum – Part 2**

MONDAY, SEPTEMBER 16

1:00 pm Pre-Conference Short Course Registration

Click [here](#) for details on short courses offered.

TUESDAY, SEPTEMBER 17

7:00 am Registration Open and Morning Coffee

OPTIMIZING THE DISCOVERY WORKFLOW

8:00 Organizer's Welcome Remarks

8:05 Chairperson's Opening Remarks

Jane Seagal, PhD, Principal Research Scientist, Biologics Generation, AbbVie Bioresearch Center

8:10 KEYNOTE PRESENTATION: Antibody Discovery at the Intersection of Immunology and Oncology

Andrew Nixon, PhD, Vice President, Biotherapeutics Molecule Discovery, Boehringer Ingelheim

8:40 Functional Interrogation of Antibody Repertoire at Single Cell Level

Yuxing Cheng, PhD, Principal Scientist, Antibody Discovery, Pfizer, Inc.

Recent advances in microfluidic technology allow massively parallelized analysis of B cell repertoire at single cell level. Here we are presenting a novel microfluidic platform based on Opto-electroposition technology that enables single cell manipulation in a microfluidic environment with semi-automated workflow and functional interrogation of the antibody repertoire from immunized animals with cell-based binding and functional assays.

9:10 Integrated Antibody Discovery Platforms

Jane Seagal, PhD, Principal Research Scientist, Biologics Generation, AbbVie Bioresearch Center

The constantly growing demand for novel therapeutic biologics drives technology innovation enabling efficient antibody discovery. Optimization and 'digitalization' of antibody discovery workflows is essential for successful identification of antibodies against challenging targets and the sampling diverse antibody repertoires. In this talk, integrated platforms for discovery

of antibodies from yeast display, hybridoma and single B cell technologies are presented highlighting the integration of sequence information, screening data, and informatics for large panels of antibodies.

9:40 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

DISCOVERY WORKFLOW CASE STUDIES

10:25 Integrating Yeast Display with Transgenic Mouse Immunization for Human VH Domain Lead Generation

Irwin Chen, PhD, Principal Scientist, Biologic Discovery, Amgen

Autonomous human VH-only domains (VHOs) promise to simplify the construction of multi-specific molecules and potentially bind epitopes that are difficult to access with conventional antibodies. To discover VHO leads, we employed a workflow combining transgenic Harbour mouse immunization and yeast surface display to isolate binders against diverse targets. I will present on challenges encountered in VHO lead identification and developability assessment, and strategies to overcome some of the obstacles.

10:55 Leveraging Computational Approaches in Antibody Workflows: Discovery, Design and Engineering

Luke Robinson, PhD, Director, Research, Visterra

A variety of computational biology approaches have matured over recent years, positioning them to substantially aid the therapeutic antibody discovery and engineering process. How can we productively leverage these computational approaches, in combination with existing high-throughput experimental techniques, to improve therapeutic antibody discovery and engineering? I will present examples of using computational tools of structural modeling, bioinformatics and machine learning to applications of Fc engineering, antibody-antigen docking and *de novo* antibody design.

11:25 High-Throughput Production of Antibodies Using Yeast and Mammalian Cells

Rebecca Hurley Niles, PhD, Senior Scientist, High Throughput Expression, Adimab

High-throughput, small-scale production of antibodies is an essential part of a discovery workflow. After isolation from a large yeast-based antibody library, Adimab directly expresses large panels of full-length IgGs in 96-well and 24-well format. Protein purification is accomplished in a plate-based format using liquid handling platforms. The same semi-automated process is also compatible with IgGs expressed in mammalian hosts. Process setup, attributes, and output will be reviewed.

11:55 Against Nature: How to Hack Immune Systems to Discover Antibodies that Target Complex Membrane Proteins

Sponsored by



Véronique Lecault, PhD, Co-Founder, AbCellera

Antibodies offer significant selectivity advantages over small molecules to target complex membrane proteins. Yet, few have made it to clinic, primarily due to discovery challenges. Over the years, AbCellera has successfully completed several antibody discovery programs targeting GPCRs and ion channels. We will share lessons and insights that were instrumental to those successes, centred on deep screening and a suite of cutting-edge technologies that includes intelligent antigen formats, strategic immunizations, machine learning, and data visualization.

12:25 pm Session Break

12:35 Luncheon Presentation: Rapid Therapeutic Antibody Discovery in Challenging Projects Using AlivaMab™ Mouse and AlivaMab Discovery Services

Sponsored by



Larry Green, PhD, Founder and CEO, Ablexis / AlivaMab Discovery Services



Antibody Forum – Part 1

The Discovery Stage

AlivaMab Mouse delivers superior molecular diversity and high-affinity, high-potency therapeutic antibody candidates with faster timelines than other platforms on the market. AlivaMab Discovery Services has developed proprietary processes to overcome the challenges of modern antibody drug discovery with industry-leading timelines. We will present case studies in the rapid generation of therapeutic quality antibodies with challenging discovery plans including against several GPCRs.

1:15 Refreshment Break in the Exhibit Hall with Poster Viewing

1:50 Chairperson's Remarks

Andrew Bradbury, PhD, MB BS (MD), CSO, Specifica, Inc.

PANEL DISCUSSION

1:55 Emerging Discovery Technologies

Moderator: Andrew Bradbury, PhD, MB BS (MD), CSO, Specifica, Inc.

Panelists: Irwin Chen, PhD, Principal Scientist, Biologic Discovery, Amgen
Enkelejda Miho, PhD, Professor, Digital Life Sciences, FHNW University of Applied Sciences and Arts Northwestern Switzerland, Switzerland

Andrew Nixon, PhD, Vice President, Biotherapeutics Molecule Discovery, Boehringer Ingelheim

Jane Seagal, PhD, Senior Scientist, Biologics Generation Group, AbbVie Bioresearch Center

Please join us for this informative and useful discussion of new and emerging tools and technologies used to help early stage researchers discover new and novel therapeutic antibodies. Our panel will share updates and best practices on NGS, single b-cell cloning, artificial intelligence, computational modeling and more. Come prepared to share your own experiences and ask questions (even basic ones) about this rapidly-changing field.

2:55 Sponsored Presentation (Opportunity Available)

3:25 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

MACHINE LEARNING AND AI FOR ANTIBODY AND PROTEIN ENGINEERING

4:05 Designing Smart Nanobodies and Antibodies Using Neural-Networked Powered Alignment-Free Models

Deborah S. Marks, PhD, Associate Professor, Systems Biology, Harvard Medical School

Antibodies and nanobodies are highly valued molecular tools, used in research for isolating and imaging specific proteins, and in medical applications as therapeutics. However, for a large number of human and model-organism proteins, existing antibodies are non-existent or unreliable. Emerging experimental techniques enable orders-of-magnitude improvement in the number of sequences assayed for target affinity but are notoriously non-specific and not always well-folded. We have explored the use of generative deep probabilistic models for this design challenge.

4:35 Transitioning from Traditional Computational Modeling to Machine Learning and AI

Enkelejda Miho, PhD, Professor, Digital Life Sciences, FHNW University of Applied Sciences and Arts Northwestern Switzerland, Switzerland

The advent of large-scale data was followed by the consequential shift from one-at-a-time considerations to systems computational investigations. As a result, statistical analysis focused on the quantification of systems patterns. However, machine learning and deep learning have fast-forwarded analysis from the systems-level initial insights to application-driven results. We investigate the applicability of neural networks in longitudinal antibody sequences of personal immune repertoires and compare systems insights versus deep learning predictions.

5:05 Interactive Breakout Discussion Groups

Join a breakout discussion group. These are informal, moderated discussions with brainstorming and interactive problem solving, allowing participants from diverse backgrounds to exchange ideas and experiences and develop future collaborations around a focused topic. Visit the conference website for discussion topics and moderators.

6:05 Welcome Reception in the Exhibit Hall with Poster Viewing (Sponsorship Opportunity Available)

7:10 Close of Day

WEDNESDAY, SEPTEMBER 18

7:30 am Registration Open and Morning Coffee

HIGH-THROUGHPUT FUNCTIONAL SCREENING

8:00 Chairperson's Remarks

Enkelejda Miho, PhD, Professor, Digital Life Sciences, FHNW University of Applied Sciences and Arts Northwestern Switzerland, Switzerland

8:05 Simultaneous Pharmacokinetic Measurements of More than 100 Individual Binding Proteins by NestLink

Pascal Egloff, PhD, Platform Leader, University of Zurich, Switzerland

NestLink enables characterization of thousands of individual binding proteins at once. The technology was previously applied *in vitro* for the efficient identification high-affinity binders against integral membrane proteins in the cellular context. In this talk, I will show that NestLink can be applied *in vivo* as well, such as to simultaneously determine pharmacokinetic parameters of more than one hundred individual multi-specific binding proteins in a single model organism.

8:35 The Impact of Isotype on Antibody Screening

Ian Foltz, PhD, Scientific Director, Amgen

Successful screening of human antibody panels requires an understanding of the therapeutic design goals including specificity, functional activity and affinity. Antibody isotype differences can be leveraged in IgG2 antibodies to enhance agonist antibody screening and in IgG4 antibodies through Fab arm exchange for monovalent antibody screening. This presentation will outline some of the challenges and advantages of screening these antibody isotypes against design goals for therapeutic antibody development.

9:05 Immunizing Divergent Species as a MAB Discovery Strategy for Difficult Targets

Ross Chambers, PhD, Vice President of Antibody Discovery, Integral Molecular

The FDA's recent approval of a llama nanobody reflects increasing acceptance of nonrodent species for therapeutic antibody discovery. Using our MPS Antibody Discovery platform, we immunize chickens to produce antibodies against complex targets with an unprecedented success rate. Our antibody panels cover diverse epitopes, even for highly conserved proteins; react to human and rodent orthologs, avoiding the need for surrogate antibodies; and include rare functional and state-specific antibodies, enabling development of novel therapeutics.

9:35 Coffee Break in the Exhibit Hall with Poster Viewing

PANEL DISCUSSION

10:20 Membrane Protein Tools and Technologies – What Is Working and What Isn't?

Moderator: Kevin Heyries, PhD, Co-Founder, AbCellera, Canada



Panelists: John Blankenship, PhD, Senior Investigator and Group Leader, Antibody Discovery, Novartis

Brian Booth, PhD, Senior Scientist, Drug Discovery, Visterra

Benjamin Doranz, PhD, MBA, President and CEO, Integral Molecular

Heike Wulff, PhD, Associate Professor, Pharmacology, School of Medicine, University of California, Davis

The challenging nature of membrane proteins has often dictated that researchers employ a toolbox approach to this work, cycling through a wide range of methods and technologies to find the best fit for a specific project. Join this panel – shared between the Antibodies Against Membrane Targets and Antibody Forum audiences – for an interactive discussion of experiences with different discovery tools used in this space. You'll hear perspectives from both panelists and other audience members and have the opportunity to share your own questions and best practices.

11:20 Enjoy Lunch on Your Own

11:20 Conference Registration for Programs 1B-7B

PLENARY KEYNOTE PROGRAM

Click [here](#) for full abstracts.

12:20 pm Event Chairperson's Opening Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target 2019, Cambridge Healthtech Institute

12:30 Plenary Keynote Introduction

Anjan Chakrabarti, Vice President, Discovery Chemistry, Syngene International Ltd

Sponsored by
Syngene



12:40 Base Editing: Chemistry on a Target Nucleotide in the Genome of Living Cells

David R. Liu, PhD, Howard Hughes Medical Institute Investigator, Professor of Chemistry & Chemical Biology, Harvard University



1:20 PROTACs: Past, Present, and Future

Craig M. Crews, PhD, Professor, Chemistry; Pharmacology; Molecular, Cellular & Developmental Biology; Yale University

2:00 Close of Plenary Keynote Program

2:00 Dessert Break in the Exhibit Hall with Poster Viewing

2:45 Close of Antibody Forum – Part 1 Conference

Please click [here](#) to continue to the agenda for Antibody Forum – Part 2: Engineering and Development



Antibody Forum – Part 2

Engineering and Development

Discovery on Target's Antibody Forum offers R&D research scientists the opportunity to participate in a unique meeting format that encourages discussion and the exchange of best practices on the application of new science and technology for the discovery and development of novel biotherapeutics. The meeting will feature short presentations, panel discussions, facilitated roundtables and an audience layout that allows a sharing of ideas and experiences. **Part 2** picks up at the transition from Discovery into Development, examining the screening approaches used for candidate selection, engineering problem solving and approaches for challenging molecules and new modalities.

RECOMMENDED PREMIUM PACKAGE:

Choose 2 Short Courses and 2 Conferences/Training Seminars

- September 16 Pre-Conference Short Course: **SC3: Selection, Screening and Engineering for Affinity Reagents**
- September 17-18 Conference: **Antibody Forum – Part 1**
- September 18 Dinner Short Course: **SC8: GPCR Structure-Based Drug Discovery**
- September 18-19 Conference: **Antibody Forum – Part 2**

WEDNESDAY, SEPTEMBER 18

11:20 am Conference Registration Open

PLENARY KEYNOTE PROGRAM

Click [here](#) for full abstracts.

12:20 pm Event Chairperson's Opening Remarks

An-Dinh Nguyen, Team Lead, Discovery on Target 2019, Cambridge Healthtech Institute

12:30 Plenary Keynote Introduction

Anjan Chakrabarti, Vice President, Discovery Chemistry, Syngene International Ltd

Sponsored by
Syngene

12:40 Base Editing: Chemistry on a Target Nucleotide in the Genome of Living Cells

David R. Liu, PhD, Howard Hughes Medical Institute Investigator, Professor of Chemistry & Chemical Biology, Harvard University

1:20 PROTACs: Past, Present, and Future

Craig M. Crews, PhD, Professor, Chemistry; Pharmacology; Molecular, Cellular & Developmental Biology; Yale University

2:00 Close of Plenary Keynote Program

2:00 Dessert Break in the Exhibit Hall with Poster Viewing

TRANSITIONING FROM DISCOVERY TO DEVELOPMENT

2:45 Organizer's Welcome Remarks

2:50 Chairperson's Opening Remarks

Noah Pefaur, PhD, Senior Scientist, AbbVie

2:55 Deep Mutagenesis for Integrative Structure Determination, Binding Site Characterization, and Conformational Engineering of Dynamic Membrane Proteins

Erik Procko, PhD, Assistant Professor, Biochemistry, University of Illinois at Urbana-Champaign

When the directed evolution of mutant libraries is tracked with deep sequencing, the phenotypes of thousands of sequence variants can be determined simultaneously. This method, known as deep mutagenesis, has been applied in cell culture to dynamic membrane proteins with roles in mental health and immunity, including GPCRs, transporters, an MHC chaperone, and viral immunogens. The mutational landscapes help define ligand-binding sites, inform mechanism, assist engineering, and constrain computational modeling.

3:25 Monoclonality Does Not Mean Monospecificity – Paratope Refinement to Mitigate Antibody Polyspecificity

Jonny Finlay, PhD, CSO, Ultrahuman, United Kingdom

Antibodies are well known to become 'polyreactive' (randomly sticky) via excess charge or hydrophobicity. We have a much poorer understanding of what causes off-target reactivity to disperse, but selective, targets (polyspecificity). There is also a paucity of understanding in how this drives antibody toxicity. This will show that polyspecificity is an underappreciated phenomenon in therapeutic antibody development, but that these unwanted properties can be fully ameliorated by paratope refinement.

3:55 Rapid Assembly of Diverse Gene Variant Libraries Using Semiconductor Technologies

Sponsored by
GenScript
Make Research Easy

Irene Song, Scientific Advisor, GenScript USA Inc.

Optimization of therapeutics requires the use of high quality mutant libraries. Traditional methods for library construction suffer from limited control over codons, resulting in poor variant representation. Our advanced oligo synthesis platform allows for precise control over codon usage, creating a diverse and fully represented mutant library, improving screening efficiency.

4:10 Use of Mammalian Virus Display to Select Antibodies Specific for Complex Membrane Antigens

Sponsored by
VACCINEX

Ernest Smith, PhD, Senior Vice President & CSO, Vaccinex

We have developed a technology to enable direct incorporation of multipass membrane proteins into the membrane of a mammalian virus. Antigen expressing virus is easily purified for antibody selection. This method does not require any detergents or refolding and produces properly folded protein that is necessary for antibody selection.

4:25 Refreshment Break in the Exhibit Hall with Poster Viewing

5:00 Emerging Technologies to Evaluate Developability and Manufacturability

Aaron Beach, Investigator, Novartis Biologics Center, Novartis Institute for BioMedical Research, Inc.

The diversity and increasing complexity of new protein formats requires a change from former platform approaches often applied for antibodies. The Novartis developability assessment combines information about expression, aggregation propensity, process fit, stability, solubility, physicochemical properties, *in vivo* fitness and immunogenicity of potential candidates. This integrated approach prior to lead selection provides a thorough, yet resource efficient approach. The presentation will provide an overview about the concept and provide selected case studies.

5:30 Utilization of Throughput-Based Platforms to Identify Optimal Bispecifics

Noah Pefaur, PhD, Senior Scientist, AbbVie

Following entry of the DVD-Ig format into the clinic it has become a preferred format for bispecifics at AbbVie. As with any engineered biologic identification of potent molecules with favorable drug like properties frequently requires engineering and screening to identify optimal lead candidates. Here, we present a throughput-based strategy to increase project probability of success, reduce time spent on lead optimization, and increase the quality of identified leads.



Antibody Forum – Part 2

Engineering and Development

6:00 Creating a New Paradigm for Biotherapeutics: Attributes More Potent than Potency

Vishal Toprani, PhD, Scientist, Pharmaceutical Development, Alexion Pharmaceuticals, Inc.

The field of biotherapeutics is rapidly advancing into novel molecular formats from traditional antibody-based products. This shift to novel protein modalities will require addressing new types of liabilities and implementing modern technologies to evaluate the risk/benefit profiles of these molecules. This presentation will focus on using DOE approaches and automated high throughput biophysical tools, in combination with automated sample preparation to identify attributes that may overrun the potency selection, predominant in protein engineering.

6:30 Dinner Short Course Registration

Click [here](#) for details on short courses offered.

9:30 Close of Day

THURSDAY, SEPTEMBER 19

7:00 am Registration Open

7:30 Interactive Breakfast Breakout Discussion Groups

Grab a cup of coffee and join a breakout discussion group. These are informal, moderated discussions with brainstorming and interactive problem solving, allowing participants from diverse backgrounds to exchange ideas and experiences and develop future collaborations around a focused topic. Visit the conference website for discussion topics and moderators.

8:30 Transition to Sessions

ENGINEERING PROBLEM SOLVING

8:40 Chairperson's Remarks

Colby Souders, PhD, CTO, Abveris

8:45 Engineering Patient-Derived Anti-HIV Broadly Neutralizing Antibodies for Therapeutic Development

Nathan Thomsen, PhD, Senior Research Scientist, Gilead Sciences

Advances in discovery technology have led to the isolation of HIV broadly neutralizing antibodies (bNAbs) with exceptional breadth. These bNAbs hold promise for the treatment or cure of HIV, with many in clinical trials. Evolving alongside the virus within a single individual, HIV bNAbs diverge significantly from the human germline repertoire and present unique engineering challenges. Strategies to identify and mitigate development challenges in HIV bNAbs will be discussed.

9:15 Identification, Characterization & Engineering of Antibodies Directed against Complex Target Molecules

Christian Kunz, PhD, Director, Discovery Alliances & Technologies, MorphoSys AG, Germany

Methods generating highly specific antibodies against classical target molecules, as e.g. receptor tyrosine kinases or cytokines, are routinely established. Antibody compounds inhibiting these classical target classes are widely used in clinical development and as approved therapeutics. Innovative selection strategies have to be applied to broaden target space and bring new target classes, as GPCRs or HLA/Peptide complexes, into clinical development.

9:45 KEYNOTE PRESENTATION: Chemical and Physical Determinants of Drug-Like Monoclonal Antibodies

Peter M. Tessier, PhD, Professor, Pharmaceutical Sciences and Chemical Engineering, University of Michigan

Therapeutic antibodies display variable and difficult-to-predict levels of non-specific and self-interactions that lead to various drug development challenges, including abnormally high viscosity and fast antibody clearance. We are developing bioinformatics methods for predicting the overall specificity of antibodies in terms of their relative risk for displaying high levels of non-specific and self-interactions. We will report novel types of chemical descriptors that are strong predictors of antibody specificity.

10:15 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

PANEL DISCUSSION

10:55 Development Stage Problem Solving

Moderator: Colby Souders, PhD, CTO, Abveris

Panelists: Georg Fertig, PhD, Head, Screening & Functional Assays, Roche Pharmaceuticals, Germany

Jonny Finlay, PhD, CSO, Ultrahuman, United Kingdom

Peter M. Tessier, PhD, Professor, Pharmaceutical Sciences and Chemical Engineering, University of Michigan

Nathan Thomsen, PhD, Senior Research Scientist, Gilead Sciences

Discovery and Development stage scientists are under pressure to improve the quality of lead selections, avoid later stage liabilities and advance programs more rapidly to the clinic. Join our panel and your colleagues to hear about tools and technologies being used to achieve these goals and share ideas on how to respond to challenges at this critical point in the pipeline. The panel will include discussion by the panelists and provide the opportunity for participants to guide the discussion by offering perspectives and pose questions.

11:55 Overnight Target Engineering

Katie Lyons, Senior Scientist, Research & Development, SGI-DNA Inc.

Sponsored by
SGIDNA

Advancements in DNA synthesis and modification have yielded powerful new techniques for target engineering. As these techniques become more specialized, engineering becomes more resource-intensive. Here, we discuss a fully-automated workflow for protein engineering using SGI-DNA's BioXp™. The instrument generates Libraries, Clones, and Tiles from sequence information in an overnight run.

12:10 pm Just a Specific Target is Not Good Enough to Achieve Desired Effect; The Case of Vedolizumab (Entyvio®)

Pierre Eftekhari, PhD, Founder and CEO, Inoviem Scientific

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inoviem
scientific

Vedolizumab an antibody against ITGB7 is used for treatment of IBD. Molecular analysis of 31 IBD outpatients, in a prospective clinical study treated with Vedolizumab, showed that the efficient treatment could only be reached when ITGB7 interacts directly with 4 other proteins forming a signaling complex. In the absence of these proteins despite the presence of ITGB7 no therapeutic effect was observed. A therapeutic target is therefore defined as the presence of primary target within its corresponding signaling complex.

12:25 Session Break





12:35 Luncheon Presentation: Lead Optimization of Biologics Using Physics-Based Computational Methods

Eliud Oloo, PhD, Senior Principal Scientist, Schrödinger

In this presentation, we will describe how calculated properties derived from 3D structural analyses and simulation through physics-based methods are applied to not only optimize binding affinity and selectivity but also identify and mitigate potential liabilities in the development of biologics. Using such computational strategies to direct experimental focus can result in reductions in cost and timelines.

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

DEVELOPMENT CHALLENGES OF NEW MODALITIES AND COMPLEX BIOLOGICS

2:05 Chairperson's Remarks

Benjamin Smith, PhD, Scientist, Biologics Drug Discovery, CNS Delivery, Biogen

2:10 Strategies, Considerations and Challenges in Engineering Antibody-Drug Conjugates

Chen-Ni Chin, PhD, Director, Antibody Discovery, Mersana Therapeutics

Antibody-drug conjugates (ADCs) are a growing class of biopharmaceuticals designed to harness the targeting specificity of a mAb by linking it to highly potent drugs for delivery. In this talk we will discuss what it means to make an ADC through engineering the antibody as well as applying novel linker and payload technologies for the optimal pharmacological profile. Case studies will be presented.

2:40 Bispecific Antibodies – A Platform Approach for Generation and Screening in Final Format

Georg Fertig, PhD, Head, Screening & Functional Assays, Roche Pharmaceuticals, Germany

The generation of bi-functional bispecific antibodies requires the combination of two monospecific binders, which bind to the right epitope of the respective target in the right format. High-throughput generation and screening of such antibodies will be discussed in the context of an effective and robust technology platform, an automated production of bsAb binder-format combination matrices and the format, which defines the function.

3:10 Protein Engineering for Enhanced and Sustained CNS Exposure of Neuro-Therapeutic Antibodies

Benjamin Smith, PhD, Scientist, Biologics Drug Discovery, CNS Delivery, Biogen

The single domain antibody FC5 engages receptor-mediated transcytosis and is a promising BBB carrier. Here the humanization and stability engineering of FC5 and design of FC5 bispecifics with antibodies against neurodegenerative disease targets will be described. Enhanced BBB penetration of the bispecifics in an *in vitro* BBB model as well as CNS pharmacokinetics in rats and monkeys dosed at therapeutically relevant doses by systemic injections will be shown.

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SCHRÖDINGER

3:40 Screening Tools for Early Prediction of Development and Clinical Success

Colby Souders, PhD, CTO, Abveris

As industry-wide advancements in antibody drug discovery continue to push toward larger panels of candidates for early-stage characterization, more efficient identification of lead molecules through enhanced screening resolution is required. Integrating tools and methods into the overall characterization workflow enables reliable, high throughput selection of lead candidates more effectively than alternative traditional techniques. Comparisons across platforms, including traditional ELISA, flow cytometry, Octet and *in vivo* studies will be presented that provide enhanced prediction of downstream development and clinical success.

4:10 Close of Conference

Please click [here](#) to return to the agenda for Antibody Forum – Part 1: The Discovery Stage



PREMIUM PACKAGE (Choose 2 Short Courses and 2 Conferences/Training Seminars)

	Commercial	Academic, Government, Hospital-Affiliated
Registration after August 23, 2019	\$3,399	\$2,049

STANDARD PACKAGE (Choose 2 Conferences/Training Seminars, excludes Short Courses)

Registration after August 23, 2019	\$3,099	\$1,449
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SINGLE CONFERENCE PRICING (Choose 1 Conference/Training Seminar, excludes Short Courses)

Registration after August 23, 2019	\$2,049	\$1,119
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SHORT COURSE PRICING

One Short Course	\$749	\$429
Two Short Courses	\$1,049	\$729

September 16 2:00 - 5:00 pm ▼	September 18 7:00 - 9:30 pm ▼
SC1: Immunology Basics: Focusing on Autoimmunity and Cancer	SC8: GPCR Structure-Based Drug Discovery
SC2: Targeting of Ion Channels with Monoclonal Antibodies	SC9: Targeted Protein Degradation Using PROTACs, Molecular Glues and More
SC3: Selection, Screening and Engineering for Affinity Reagents	
SC4: How to Best Utilize 3D Cells, Spheroids and PDX Models in Oncology	
SC5: Applications of Artificial Intelligence and Machine Learning in Drug Discovery and Development	
SC6: Biochemistry and Pharmacology of the Ubiquitin-Proteasome System	

CONFERENCE PROGRAMS

September 17-18 ▼	September 18-19 ▼
C1A: Target Identification and Validation	C1B: RNA as a Drug Target
C2A: Lead Generation Strategies	C2B: Kinase Inhibitor Discovery
C3A: Emerging Ubiquitin and Autophagy Targets	C3B: PROTACs and Targeted Protein Degradation
C4A: Targeting NASH	C4B: Targeting Fibrosis
C5A: Immuno-Oncology: Emerging Targets and Therapeutics	C5B: GPCR-Based Drug Discovery
C6A: Antibodies Against Membrane Protein Targets - Part 1	C6B: Antibodies Against Membrane Protein Targets - Part 2
C7A: Antibody Forum - Part 1	C7B: Antibody Forum - Part 2
TS1: Targeting GPCRs for Drug Discovery	TS3: Introduction to Small Molecule Drug Discovery and Development
TS2: An In-Depth Introduction to Drug Metabolism and Applications to Discovery and Development	TS4: Practical Phenotypic Screening

CONFERENCE DISCOUNTS

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

Group Discounts: Special rates are available for multiple attendees from the same organization and for NIH/Government employees. For more information on group and government discounts contact Jeff Knight, jknight@healthtech.com, 781-247-6264.

Alumni Discount - SAVE 20%: CHI appreciates your past participation at Discovery On Target. 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 Submission - Discount (\$50 Off): Poster abstracts are due by August 16, 2019. Once your registration has been fully processed, we will send an email containing a unique link allowing you to submit your poster abstract. If you do not receive your link within 5 business days, please contact iring@healthtech.com. *CHI reserves the right to publish your poster title and abstract in various marketing materials and products.

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FINAL WEEKS TO REGISTER



ADDITIONAL REGISTRATION DETAILS

Each registration includes all conference sessions, posters and exhibits, food functions, and access to the conference proceedings link.

Handicapped Equal Access: In accordance with the ADA, Cambridge Healthtech Institute is pleased to arrange special accommodations for attendees with special needs. All requests for such assistance must be submitted in writing to CHI at least 30 days prior to the start of the meeting.

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