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

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
- TS: An In-Depth Introduction to Drug Metabolism and Applications to Discovery and Development

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

REGISTER EARLY FOR MAXIMUM SAVINGS!

Plenary Keynote Introduction Sponsored by Syngene

Organized by Cambridge Healthtech Institute

DiscoveryonTARGET.com

#BostonDOT19

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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
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.
SPONSOR, EXHIBIT AND LEAD GEN OPPORTUNITIES

Comprehensive sponsorship packages allow you to achieve your objectives before, during, and long after the event. Signing on earlier will allow you to maximize exposure to hard-to-reach decision-makers.

Podium Presentations—Available within Main Agenda!
Showcase your solutions to a guaranteed, targeted audience. Package includes a 15 or 30-minute podium presentation on the scientific agenda, exhibit space, branding, full conference registrations, use of the event mailing list and more.

Luncheon Presentations
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 to 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:
- Hotel Room Keys
- Footprint Trails
- Staircase Ads
- Conference Tote Bags
- Literature Distribution (Tote Bag Insert or Chair Drop)
- Badge Lanyards
- Program Guide Advertisement
- Notepads
- Water Bottles
- Seating Area Sponsor
- Meter Boards
- Hanging Aisle Sign

Looking for additional ways to drive leads to your sales team?
CHI’s Lead Generation Programs will help you obtain more targeted, quality leads throughout the year. We will mine our database of 800,000+ life science professionals to your specific needs. We guarantee a minimum of 100 leads per program! Opportunities include:
- Live Webinars
- White Papers
- Market Surveys
- Podcasts and More!

To learn more about sponsorship and exhibit opportunities, please contact:
Rod Eymael  Manager, Business Development
781.247.6286  reymael@healthtech.com

2018 ATTENDEE DEMOGRAPHICS
Attendees included industry leaders, innovators and decision makers from many different backgrounds

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- Live Webinars
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- Podcasts and More!
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.

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

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

*For updated Plenary Keynote details, visit: DiscoveryOnTarget.com/plenary-keynotes
SC1: Immunology Basics: Focusing on Autoimmunity and Cancer
This short course provides an introduction to immunology and immunoncology 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, antibody generation, the molecular basis of pathogenic immune responses, 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. Schafer, 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
Additional Instructors to be Announced

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

SC7: 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
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, off-set 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

TS2: An In-Depth Introduction to Drug Metabolism and Applications to Discovery and Development
This lecture-based interactive seminar, which focuses on small molecule drug metabolism, will begin with a historical background to the origin of the field before reviewing the both well-recognized and more recently discovered drug metabolism pathways. In vitro assays used to access metabolic clearance and medicinal chemistry strategies for modifying structures to overcome metabolism-dependent clearance during lead-optimization will be discussed. The topic of drug toxicity will be discussed in the context of drugs that are toxic through bioactivation to reactive metabolites. Examples of drug structure-toxicity relationships and the relevance of idiosyncratic toxicity to drug candidates’ interaction with variable ambient physiology will be discussed. 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: John C.L. Erve, PhD, DABT, President, Jerve Scientific Consulting, Inc.

Guangqing Xiao, PhD, Director, DMPK, Sunovion Pharmaceuticals
Raman Sharma, PhD, Senior Scientist, Pfizer, Inc.

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
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 Presentation to be Announced

Sponsored by CELLECTA

12:25 pm Session Break

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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.

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, Scientist II, 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 Sponsored Presentation (Opportunity Available)

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 molecules hits from phenotypic screens is challenging due to the inherent complexity of the cellular systems involved. Comparison of multiple target identification 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-ISO11-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 Presentation to be Announced

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

Sponsored by
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.

- 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 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

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
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.

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 in 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 Sponsored Presentation (Opportunity Available)

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. Muta-tions 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.

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

RNA-PROTEIN COMPLEXES

8:40 Chairperson's Remarks
Razvan Nutiu, PhD, Investigator, Chemical Biology & Therapeutics, Novartis

8:45 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.

9:15 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.

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 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 Sponsored Presentation (Opportunity Available)

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 deliver oligo payloads to multiple cell types.

2:40 FANA ASO Therapy to Silence Foxp3, Impair Treg Function and Promote Anti-Tumor Immunity
Wayne Hancock, PhD, Professor of Pathology and Laboratory Medicine, University of Pennsylvania; Chief of the Division of Transplant Immunology, Children's Hospital of Philadelphia (CHOP)
Since Foxp3+ Treg cells limit host anti-tumor immunity, we tested the efficacy of FANA antisense-oligonucleotides that spontaneously enter cells. Unlike scrambled controls, Fopx3-specific FANAs decreased Foxp3 mRNA and protein expression and impaired Treg function in vitro. Comparable effects occurred in vivo. Mice receiving Fopx3 FANA had impaired tumor growth, with 50% clearing tumors and markedly reduced Foxp3+ Treg infiltration. Hence, FANA oligos modulate Foxp3 expression and Treg function, providing a major new approach to cancer immunotherapy.

3:10 Identification of Development Candidate eFT226, a First in Class Inhibitor of elf4A RNA Helicase
Justin Ernst, PhD, Director of Medicinal Chemistry, Effector Therapeutics
Dysregulated translation of specific mRNAs is an important driver of uncontrolled growth, immune evasion and metastasis in many types of cancer. elf4A (eukaryotic initiation factor 4A), an ATP-dependent DEAD-box RNA helicase and a key component of the elf4F complex, plays a crucial role in translational regulation of several oncogenes, rendering it a promising therapeutic target for the treatment of cancer. Flavagline natural products have been shown to inhibit elf4A by RNA-sequence specific formation of a stabilized elf4A/RNA/flavagline ternary complex; however, these compounds generally suboptimal drug-like properties. This presentation describes the design of and physicochemical property optimization in novel flavagline cores to support
intravenous delivery, culminating in clinical candidate eIF4A inhibitor eFT226.

3:40 **PATrOL-Enabled Therapies Targeting Mutant RNA Primary and Secondary Structures**

*Dietrich A. Stephan, PhD, Founder and CEO, NeuBase Therapeutics*

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.

4:10 **Close of Conference**
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 A Phenotypic Screen for 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, Associate 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, Associate Research Fellow, Structure Biology & Biophysics, Pfizer Global R&D

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.

12:10 pm Presentation to be Announced

12:25 Session Break

12:35 Luncheon Presentation

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

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.

3:00 Poster Competition Winner Announced

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

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 μM, 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.

9:05 Sponsored Presentation (Opportunity Available)

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 Presentation to be Announced
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

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
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.

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 penetration is significantly impacted by the physicochemical properties of the drugs. Compound properties associated with brain penetration 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 SPR Binding Studies of Small Molecule Inhibitors of PRMT5
Rebecca Eells, PhD, Senior Research Scientist I, Biophysical Assays, Reaction Biology Corporation

Sponsored by Reaction Biology

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.

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Sponsored by Reaction Biology
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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. Haner, 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 Tarloxitinib, a Hypoxia Activated Prodrug for EGFR and HER2
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. Tarloxitinib 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 proteinosome 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 (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 (CONT.)

2:05 Chairperson's Remarks
Nello Mainolfi, PhD, Founder and CSO, Kymera Therapeutics, Inc.

2:10 KEYNOTE PRESENTATION AND DISCUSSION: New Approaches to Challenging Targets in Cancer
Nathanael S. Gray, PhD, Professor of Biological Chemistry and Molecular Pharmacology, Dana-Farber Cancer Institute

The development of new anti-cancer therapies continues to be massively outpaced by the rapidly expanding knowledge into the biological mechanisms that underpin the development of cancer. One major obstacle is that many potentially interesting targets are challenging to drug. This lecture will focus on strategies using covalent inhibitors and small molecule degraders which hold the promise of making many previously challenging targets druggable. In particular, we will focus on the use of these approaches to target kinases and present some key advantages of small molecule degraders including potency, selectivity and abrogation of non-kinase activity-dependent functions. We will also describe efforts to target KRAS – a notorious and frequent oncogene that has been recalcitrant to small molecule approaches.

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 deg-radation 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 lig-ands 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
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.

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.

9:00 Organizer’s Welcome Remarks

9:05 Chairperson's Opening Remarks
Tanuja Koppal, PhD, Conference Director, Cambridge Healthtech Institute

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

10:05 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 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.

10:25 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.

10:55 Structures of the Substrate-Engaged Proteasome Reveal the Mechanism of Translocation and Activation
Andres Hernandez de la Peña, PhD, Postdoctoral Fellow, The Scripps Research Institute

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-translational deubiquitination mechanism that positions ubiquitin and the isopeptide scissile bond in the Rpn11 deubiquitinase.

9:00 Organizer’s Welcome Remarks

9:05 Chairperson's Opening Remarks
Tanuja Koppal, PhD, Conference Director, Cambridge Healthtech Institute

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

10:05 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 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.

10:25 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.

10:55 Structures of the Substrate-Engaged Proteasome Reveal the Mechanism of Translocation and Activation
Andres Hernandez de la Peña, PhD, Postdoctoral Fellow, The Scripps Research Institute

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Ubiquitin Ligase Mimic

4:35 Broad-Spectrum Proteome Editing with an Engineered Bacterial E3 Ligase

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 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, Progena, 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 UbiProTM 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.

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.

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9:05 Sponsored Presentation (Opportunity Available)

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

10:20 Use of Tip60 PROTACs in Cereblon-Knockin Mice
Wayne W. Hancock, MD, PhD, Professor, Pathology and Chief of Transplant Immunology, Children's Hospital of Philadelphia and University of Pennsylvania
Finding new ways to target histone acetyltransferases such as Tip60 is important for advances in immuno- oncology, and the PROTAC approach makes this possible. However, mice have a single amino acid substitution that blocks efficient iMID-dependent recruitment of the E3-ligase, Cereblon, limiting experimental studies. We report use of Tip60 PROTACs in WT vs. Cereblon-knock-in mice in which PROTAC-dependent recruitment is now rendered active, allowing use of murine models for testing of this and other PROTAC molecules.

10:50 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
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 Emerging Ubiquitin and Autophagy Targets Conference
Please click here to continue to the agenda for PROTACs and Targeted Protein Degradation
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. Prolysis-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:**

Choose 2 Short Courses and 2 Conferences/Training Seminars
- September 16 Pre-Conference Short Course: SC6: Biochemistry and Pharmacology of the Ubiquitin-Proteasome System
- 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

**WEDNESDAY, SEPTEMBER 18**

11:20 am Conference Registration Open

**PLENARY KEYNOTE PROGRAM**

Click here for full abstracts.

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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

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 Sponsored Presentation (Opportunity Available)

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

5:00 Pharmacokinetics Related Challenges of PROTACs
Upendra Dahal, PhD, Senior Scientist, Pharmacokinetics and Drug Metabolism, Amgen, Inc.

PROTACs are bifunctional molecules, designed to bind with target protein and E3 ligase to degrade 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.

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.
8:00 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, Culligen, 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
Nan Ji, PhD, Executive Director, Head of 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.

11:55 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: New Approaches to Challenging Targets in Cancer
Nathanael S. Gray, PhD, Professor of Biological Chemistry and Molecular Pharmacology, Dana-Farber Cancer Institute
The development of new anti-cancer therapies continues to be massively outpaced by the rapidly expanding knowledge into the biological mechanisms that underpin the development of cancer. One major obstacle is that many potentially interesting targets are challenging to drug. This lecture will focus on strategies using covalent inhibitors and small molecule degraders which hold the promise of making many previously challenging targets druggable. In particular, we will focus on the use of these approaches to target kinases and present some key advantages of small molecule degraders including potency, selectivity and abrogation of non-kinase activity-dependent functions. We will also describe efforts to target KRAS – a notorious and frequent oncogene that has been recalcitrant to small molecule approaches.
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
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.

9:10 Targeting GLP-1 for NASH
Karim 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
Firsoicosat (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 PPARα activity. In diet-induced obese mice, co-administration of fenofibrate, a PPARα 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 Combination Therapy for NASH
Marcos Pedrosa, MD, MPH, Global Program Clinical Head, Therapeutic Area Hepatology and Transplantation, Novartis Pharma AG

8:00 Organizer’s Welcome Remarks

NASH DRUG CANDIDATES

8:05 Chairperson’s Opening Remarks
Claus Kremoser, PhD, CEO, Phenex

8:10 FEATURED PRESENTATION: Thyroid Hormone Receptor Agonists
Rebecca Taub, MD, CMO & Executive Vice President, R&D, Madrigal Pharmaceuticals
I will present data from clinical studies of resmetirom (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.

8:40 FEATURED PRESENTATION: Parallel Development of Elafibranor and an in vitro Diagnostic (IVD) to Identify Patients for Drug Therapy
Dean Hum, PhD, CSO and COO, Genfit
Elafibranor is a first-in-class PPARα/δ agonist which has demonstrated in a Phase 2b study NASH resolution without the worsening of fibrosis while also improving cardio-metabolic risk. Furthermore, NASH resolution correlated with fibrosis improvement. Elafibranor is safe, tolerable and is now being investigated in Phase III. Additionally, GENFIT is developing a blood-based in vitro diagnostic to identify NASH patients who are at risk of disease progression and should be considered for therapeutic intervention – a key unmet clinical need.

10:05 Chairperson’s Remarks
Kendra K. Bence, PhD, Senior Director, Metabolism, Internal Medicine Research Unit (IMRU), Pfizer, Inc.

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 Presentation to be Announced

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 Translational Challenges in NASH
Brad Geddes, PhD, Senior Director, Innate Immunity Research Unit, GSK

This presentation will focus on recent FDA guidance regarding fibroside-centric primary endpoints for NASH clinical trials and its impact on preclinical development of potential NASH therapeutics.

5:05 Interactive Breakout Discussion Groups
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6:05 Welcome Reception in the Exhibit Hall with Poster Viewing (Sponsorship Opportunity Available)

7:10 Close of Day
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
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.

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: Targeting NASH
• September 18 Dinner Short Course: SC9: Targeted Protein Degradation Using PROTACs, Molecular Glues and More
• September 18-19 Conference: Targeting Fibrosis

WEDNESDAY, SEPTEMBER 18
11:20 am Conference Registration Open

PLENARY KEYNOTE PROGRAM
Click here for full abstracts.
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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 FEATURED PRESENTATION: An Overview of Fibrosis and the Hope of Pharmacologic Treatments
Bryan Fuchs, PhD, Senior Director, Research TA Head for GI & Liver Disease, Ferring Research Institute

3:25 Targeting Integrins for Fibrotic Diseases
Liangsu Wang, PhD, Vice President, Head of Biology, Morphic Therapeutics
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 Morphic 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 Sponsored Presentation (Opportunity Available)

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 αvβ1, αvβ3, and αvβ6. 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
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.
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 Sponsored Presentation (Opportunity Available)

12:00 Session Break

12:30 Luncheon Presentation (Sponsorship Opportunity Available) or 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 RIPK1 as a Liver Fibrosis Target
Allison Beal, PhD, Associate Fellow, Innate Immunity Research Unit, GSK
RIPK1 (receptor-interacting protein kinase-1) is a key homeostatic regulator of cell survival and cell death signaling pathways, particularly downstream of TNF signaling. RIPK1 is ubiquitously expressed and has complex, cellular context-dependent actions mediated by a combination of scaffold activity (survival) and kinase activity (cell death). I will discuss the role of RIPK1 in tissue injury and discuss why it is a promising target for modulating fibrosis.

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 Discovery and Development of NTZ as an Anti-Fibrotic Agent in NASH
Sunell Hosmane, PhD, Executive Vice President, Strategic Development, Genfit Nitazoxanide, or NTZ, is an approved anti-parasitic agent that has shown promising activity against fibrosis in preclinical disease models. We are currently evaluating NTZ in an investigator-initiated Phase 2 proof-of-concept clinical trial for the treatment of NASH-induced significant or severe fibrosis.

3:40 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.

4:10 Close of Conference
Please click here to return to the agenda for Targeting NASH
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
Daniela Cipolletta, PhD, Investigator III, Exploratory ImmunoOncology, Novartis

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 Cyclic Dinucleotides that Self-Assemble into Nanostructures as Potent STING 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 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
Jose M. Lora, PhD, VP, Research, 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, SYNBI1891, 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 responses 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 Presentation to be Announced

11:55 Sponsored Presentation (Opportunity Available)

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

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 blocking activity of 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 ongoing preclinical 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 Sponsored Presentation (Opportunity Available)

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

4:05 A Dual CD73-A2AR Antagonist to Reduce Adenosine in the TME
Murali Ramachandra, PhD, CSO, Aurigene Discovery Technologies Limited
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-tumor 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 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

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
GPCRs IN DISEASE

2:45 Organizer's Welcome Remarks

2:50 Chairperson's Opening Remarks
Ajay Yekkira, Co-Founder and CEO, 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 Talk Title to be Announced
Lisa Minor, Scientific Consultant, Multispan, Inc.

4:10 Sponsored Presentation (Opportunity Available)

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

5:00 LPAR1 Tool Compound with Signaling Bias Properties
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 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

2:00 Close of Plenary Keynote Program

WEDNESDAY, SEPTEMBER 18

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.

• 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

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

TABLE OF CONTENTS

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.
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 interaction in vitro, we converted the selectivity of MT7 towards M2R by structural biology. Furthermore, we solved the crystal structure of M1R-MT7 complex. This study suggests the possibility of designing GPCRs with strict subtype selectivity and allosteric mechanism. We present our structural and functional studies comparing unbiased ligands and well-characterized dimers of class C GPCRs such as GABA-B and glutamate receptors. The implications for drug discovery are discussed.

**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 have been studied extensively; however, the 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, their stability, kinetic features, and structural and functional asymmetry, of such metastable entities have implications for drug discovery.

**11:25 FEATURED PRESENTATION: Non-Traditional Aspects of Gas: Interaction with Ubiquitin and Regulation of GPCR Endosomal Sorting**

*Christine Lavoie, PhD, Professor, Department of Pharmacology and Physiology, University of Sherbrooke*

Although G proteins have been known for years, we found a novel motif in Gas that allows its interaction with ubiquitin, a key signal for receptor sorting to the lysosomal pathway. This presentation will cover the new role for Gas as an integral component of the ubiquitin-dependent endosomal sorting machinery of GPCRs and highlight the dual role of Gas in receptor trafficking and signaling for the fine-tuning of the cellular response.

**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.*

**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 potent GPCR pheromone inhibitors 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: Use of InCELL Pulse™ Cellular Thermal Shift Target Engagement Assays in Early Drug Discovery**

*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™ uses 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

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 Nanodiscs for GPCRs
Daniel Oprian, PhD, Professor, Biochemistry, Brandeis University

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.

3:55 Close of Conference
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, 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.
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
David Maurer, Principal 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.

12:25 Session Break

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

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 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.

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 (HCAbs) are presented and demonstrate that the effector functions of HCAbs 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.

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.
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.

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

9:05 Presentation to be Announced

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

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

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
**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.

**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

**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

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

**DISCOVERY STRATEGIES**

2:45 Organizer's Welcome Remarks

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

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.

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).
6:00 Enabling Protein-Based Antibody Discovery Using Stabilized GPCRs: The Hunt for Therapeutic mAbs Targeting CCR7
Chris Roth, PhD, Vice President, Innovation, Abilita Bio

GPCRs suffer from low expression, limited epitope exposure, and heterogeneity, all of which oppose antibody discovery efforts. Using our therapeutic target CCR7 as a case study, we show how the optimization of target properties by directed evolution can increase discovery options for tough targets. CCR7 was evolved to increase its yield and conformational stability, which enabled multiple discovery approaches, including protein-based animal immunization, and affinity maturation by yeast display.

6:30 Dinner Short Course Registration
Click here for details on short courses offered.

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

THURSDAY, SEPTEMBER 19

7:00 am Registration Open

7:30 Interactive Breakfast Breakout Discussion Groups

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 Wulf, 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 mediated 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.

12:35 Luncheon Presentation to be Announced

12:25 pm Session Break

12:35 Luncheon Presentation to be Announced

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 Integrated Discovery Approaches for Challenging Membrane Proteins**

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

Traditional antibody discovery processes often fail to deliver functional antibodies against complex multi-pass membrane proteins. A case study will be presented using multiple approaches – immunization, antibody display technologies, and high throughput screening – to identify and refine specific, functional antibodies against a challenging target, enabling incorporation of these antibodies into next-generation antibody formats.

**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
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.

### 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 Presentation to be Announced**

**12:25 pm Session Break**

**12:35 Luncheon Presentation to be Announced**

**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 Presentation to be Announced

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 Data Mining in Discovery Research ~ Learning from the Past
Jonas Lee, PhD, Scientist, Biologics, Amgen
Machine learning is becoming an integral part of therapeutic development. Although lot of efforts are focused on developing new technologies and data systems to capture new data, data mining and learning from past data is somewhat neglected. We mine, procure, and analyze ~25,000 antibody modality production (cloning, expression, purification) results from a past LIMS to develop a statistical model to plan production of different antibody modalities for discovery research.

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

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
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
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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
Noah Pefaur, PhD, Senior Scientist, AbbVie
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 disparate, 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 these unwanted properties can be fully ameliorated by paratope refinement.

3:55 Presentation to be Announced

4:10 Presentation to be Announced
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.

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 overrule the potency selection, predominant in protein engineering.
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 Presentation to be Announced

12:10 pm Sponsored Presentation (Opportunity Available)

12:25 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

Development Challenges of New Modalities and Complex Biotherapeutics

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 FCS 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.

3:40 **Targeting the STn Glycan in Ovarian Cancer Using a Highly Specific Anti-STn Antibody Drug Conjugate**

*Jeff Behrens, PhD, CEO, Siamab Therapeutics*

Sialyl-Tn (STn) is a tumor-associated carbohydrate antigen that is expressed in multiple solid tumors – ovarian, pancreatic, gastric, and others. STn is implicated in immune suppression, chemoresistance, and a cancer stem-cell phenotype. Carbohydrate antigens, including STn, pose unique challenges in antibody discovery; Siamab’s glycan array is a key tool used to overcome these challenges enabling the discovery of a panel of highly specific, high-affinity mAbs, currently formatted as an IND-ready ADC.

4:10 **Close of Conference**

Please click [here](#) to return to the agenda for Antibody Forum – Part 1: The Discovery Stage