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A Division of Cambridge Innovation Institute

EVENT FEATURES

340+ Speakers
17 Conference Programs
2 Training Seminars
7 Symposia
7 Short Courses
70+ Exhibiting Companies
1,200+ Attendees

FINAL AGENDA

15th Annual

Discovery on TARGET

The Industry's Preeminent Event on Novel Drug Targets

September 25-29, 2017 • The Westin Copley Place • Boston, MA

PLENARY KEYNOTE SPEAKERS

Jeffrey V. Ravetch, M.D., Ph.D.
Professor and Head, Laboratory of Molecular Genetics & Immunology
The Rockefeller University

Raymond J. Deshaies, Ph.D.
Senior Vice President, Discovery Research
Amgen

CONFERENCE PROGRAMS & SYMPOSIA

Cancer Immunotherapy

- » Immunomodulatory Small Molecules
- » Microbiome in Immuno-Oncology
- » NK Cell-Based Cancer Immunotherapy
- » Targeting Tumor Myeloid Cells

Target-Based Discovery & Validation

- » Targeting Histone Methyltransferases & Demethylases
- » Targeting the Ubiquitin Proteasome System
- » Lead Generation Strategies
- » CRISPR for Disease Modeling & Target Discovery
- » GPCR-Based Drug Discovery
- » Next-Generation Histone Deacetylase Inhibitors
- » Kinase Inhibitor Discovery
- » Target Identification Strategies

Hot & Emerging

- » Targeting Autophagy
- » Targeting HBV
- » Targeting the Microbiome
- » NASH & Fibrosis
- » Autoimmune & Inflammation Drug Targets
- » Targeting Ocular Disorders
- » CNS & Neurodegenerative Targets
- » Tackling Rare Diseases

Biologics & Beyond

- » Constrained Peptides & Macrocyclics
- » Antibodies Against Membrane Protein Targets - PART 1
- » Antibodies Against Membrane Protein Targets - PART 2
- » Emerging Oligonucleotide Therapeutics

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- Cover
- Conference At-A-Glance
- Short Courses
- Training Seminars
- Plenary Keynotes
- Agenda
  - Symposia
  - Cancer Immunotherapy Channel
  - Target-Based Discovery & Validation Channel
  - Hot & Emerging Channel
  - Biologics & Beyond Channel
- Hotel/Travel
- Sponsorship & Exhibit
- Registration

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15th Annual

Discovery on TARGET

September 25-29, 2017 • The Westin Copley Place • Boston, MA

#BostonDOT17

ABOUT THE EVENT

Cambridge Healthtech Institute's 15th Annual Discovery on Target, "The Industry's Preeminent Event on Novel Drug Targets," will once again gather over 1,200 drug discovery professionals in Boston, MA, this September 25-29, 2017. The event brings forth current and emerging "hot" targets, technologies and validation strategies for the development of novel small molecules and biologics.

CONFERENCE AT-A-GLANCE

Pre-Conference Symposia

Monday, September 25	Immunomodulatory Small Molecules*	Targeting Autophagy*	Microbiome in Immuno-Oncology*	Constrained Peptides and Macrocyclics*	Targeting HBV*
	Pre-Conference Dinner Short Courses*				

Main Conference Meetings

Tuesday, September 26	Targeting Histone Methyltransferases and Demethylases	Targeting the Ubiquitin Proteasome System	Targeting the Microbiome	Lead Generation Strategies	NASH and Fibrosis	CRISPR for Disease Modeling and Target Discovery	NK Cell-Based Cancer Immunotherapy	Antibodies Against Membrane Protein Targets - Part 1	GPCR-Based Drug Discovery
Wednesday, September 27	Targeting Histone Methyltransferases and Demethylases	Targeting the Ubiquitin Proteasome System	Targeting the Microbiome	Lead Generation Strategies	NASH and Fibrosis	CRISPR for Disease Modeling and Target Discovery	NK Cell-Based Cancer Immunotherapy	Antibodies Against Membrane Protein Targets - Part 1	GPCR-Based Drug Discovery
	Next-Generation Histone Deacetylase Inhibitors	Kinase Inhibitor Discovery	Autoimmune and Inflammation Drug Targets	Target Identification Strategies	Emerging Oligonucleotide Therapeutics	Targeting Ocular Disorders	Targeting Tumor Myeloid Cells	Antibodies Against Membrane Protein Targets - Part 2	Training Seminars
	Dinner Short Courses*								
Thursday, September 28	Next-Generation Histone Deacetylase Inhibitors	Kinase Inhibitor Discovery	Autoimmune and Inflammation Drug Targets	Target Identification Strategies	Emerging Oligonucleotide Therapeutics	Targeting Ocular Disorders	Targeting Tumor Myeloid Cells	Antibodies Against Membrane Protein Targets - Part 2	Training Seminars

Post-Conference Symposia

Thursday, September 28 & Friday, September 29	CNS and Neurodegenerative Targets*	Tackling Rare Diseases*

Separate registration is required for short courses and symposia.

Conference Channels

- CANCER IMMUNOTHERAPY
- TARGET-BASED DISCOVERY & VALIDATION
- HOT & EMERGING
- BIOLOGICS & BEYOND

Training Seminars

(Concurrent)

- Data Visualization for Effective Drug Discovery Decisions
- Introduction to Small Molecule Drug Discovery and Development

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Cambridge 25 YEARS HEALTHTECH Institute
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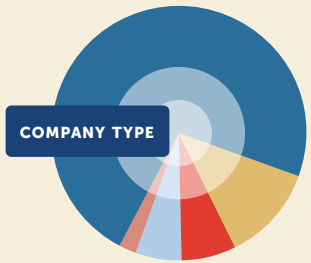
THE INDUSTRY'S PREEMINENT EVENT ON NOVEL DRUG TARGETS

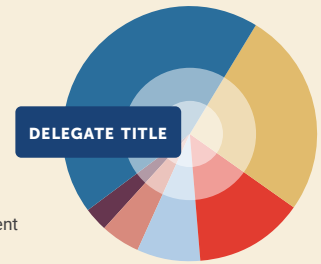
Spanning five days, Discovery on Target brings forth current and emerging "hot" targets, technologies and validation strategies for the development of novel small molecules and biologics. Now in its 15th year, Discovery on Target continues to gather a diverse body of over 1,200 attendees from around the world to network, share ideas, and discuss cutting-edge science and technology. The 2017 event features a special focus on cancer immunotherapy, expansion of coverage to include peptides and oligonucleotides, lead generation and target validation strategies, as well as advances in targeting the microbiome, protein homeostasis, autoimmunity and autophagy.

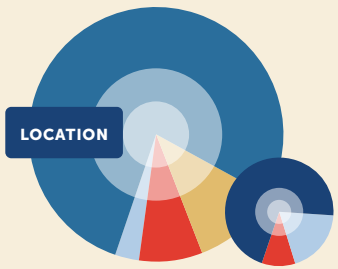
2017 EVENT FEATURES

- **340+ speakers** presenting across 17 conference tracks, 2 training seminars and 7 symposia
- **New coverage** of immunomodulatory small molecules, targeting tumor myeloid cells, microbiome in immuno-oncology, autophagy, fibrosis, constrained peptides and macrocyclics, oligonucleotide therapeutics, HBV, CNS targets, lead generation and target identification strategies
- **7 short courses** to provide additional training and education to brush up on your knowledge or expand your horizons
- **Exhibit hall of 70+ companies** with novel technologies and solutions
- **Plenary keynote program** unified by an underlying theme on meeting the new challenges of novel drug development
- **Poster sessions** featuring cutting-edge, ongoing research
- **Student fellowships** offering discounted registration for young researchers looking to make a difference
- **1,200+ international delegates** focusing on preclinical research and the challenges and opportunities in early drug discovery and development
- **Sponsored talks** by leading technology and service providers showcasing new offerings
- **Dedicated poster viewing** and interactive panel discussions for active networking

2016 ATTENDEE DEMOGRAPHICS







For additional information regarding sponsorship & exhibit opportunities, please contact:

Rod Eymael
Manager, Business Development
781.247.6286
reymael@healthtech.com

PLENARY KEYNOTE PROGRAM » Wednesday, September 27, 12:35 - 2:00 pm

NOVEL DRUG DISCOVERY: WHERE ARE WE NOW?

AMONG THE VARIOUS therapeutic strategies currently under development, few have managed to garner the interest of drug developers as quickly as modulating the immune system and proteostasis. Due to the remarkable clinical response of first-generation cancer immunotherapies, and success in harnessing the proteostasis machinery of the Ubiquitin Proteasome System (UPS) for targeted protein degradation, significant efforts are currently underway to explore the wealth of possibilities targeting immune and proteostasis pathways.

Discovery on Target's 2017 Plenary Keynote Program features lectures and discussion from two renowned and distinguished scientists: Dr. Jeffrey Ravetch, who will discuss his work on the diverse downstream pro-inflammatory, anti-inflammatory and immunomodulatory consequences of the engagement of type I and type II Fc receptors; and Dr. Raymond Deshaies, who will show for the first time that the activity of p97/VCP•Npl4•Ufd1 is enhanced by mutations that cause multisystem proteinopathy.

» Click here for more details.

Jeffrey V. Ravetch, M.D., Ph.D.
Professor and Head, Laboratory of Molecular Genetics & Immunology
The Rockefeller University

Raymond J. Deshaies, Ph.D.
Senior Vice President, Discovery Research
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Our dinner short courses are designed to be instructional, interactive and provide in-depth information on a specific topic. They allow for one-on-one interaction and provide a great way to explain more technical aspects that would otherwise not be covered during our main presentations. Attendees enjoy dinner with each short course as part of their registration.

MONDAY, SEPTEMBER 25

6:30-9:00 PM | PRE-CONFERENCE DINNER SHORT COURSES

SC2: GPCR Structure-Based Drug Discovery
Recent breakthroughs in obtaining high-resolution structures of G Protein-Coupled Receptors (GPCRs) are rapidly impacting the pharmaceutical industry. This course will review how newly elucidated GPCR crystal structures have informed our current understanding of GPCR function. The instructors will explore how this new structural information is guiding rational drug design approaches for targeting GPCRs. This course will also review the role of conformational dynamics in GPCR function and structural biology techniques for studying the conformational dynamics of GPCRs, including the burgeoning field of applying nuclear magnetic resonance (NMR) to study GPCR structure and dynamics.
Instructors: Matthew Eddy, Ph.D., Postdoctoral Fellow, Ray Stevens Laboratory, The Bridge Institute, University of Southern California
Huixian Wu, Ph.D., Principal Scientist, Structural and Molecular Sciences, Discovery Sciences, Pfizer Inc. Groton

SC5: 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. The topics to be covered include: 1) Antibody discovery, including methods to generate monoclonal antibodies and antigen preparation strategies, 2) Assays to enable isolation of binding antibodies, including use of recombinant stable cell lines, 3) *in vitro* assays to measure functional activity of the antibody, including use of electrophysiology platforms and ion flux methods, and 4) Review of promising ligand-gated and voltage-gated ion channel targets and antibodies in development.
Instructor: Trevor Wilkinson, Ph.D., Associate Director, Antibody Discovery and Protein Engineering, MedImmune Ltd., United Kingdom

SC6: Covalent Fragments: Applications in Target-Based and Phenotypic Screens
The course will cover the design principles of covalent fragment libraries, target-based and phenotypic screens using covalent fragments, strategies to grow fragments into drug leads, and case studies. Topics to be covered include design principles of covalent fragment libraries, target-based and phenotypic screens using covalent fragments and current technologies to conduct those screens, strategies and considerations to grow covalent fragments into drug leads, coupling covalent fragment growth with selectivity profiling in cells, using covalent fragments as toolkits to discover novel drug targets in phenotypic screens, and photocrosslinking methods to identify fragment drug targets in cells.
Instructor: Alexander Statsyuk, Ph.D., Assistant Professor, Department of Pharmacological and Pharmaceutical Sciences, University of Houston

WEDNESDAY, SEPTEMBER 27

7:00-9:30 PM | DINNER SHORT COURSES

SC9: Impact of Convergence of Immunotherapy and Epigenetics on Drug Discovery
In recent years, the understanding of both the immunotherapy and epigenetics of cancer has increased. This course will provide some details of how immunotherapy and epigenetic pathways interact and how they can be exploited to enhance the efficacy of current cancer treatments. The instructors will review recent scientific evidence and preclinical data that support the development of combination therapies and offer their perspectives on challenges that may have to be tackled along the way.
Instructors: Alan P. Kozikowski, Ph.D., CEO and President, StarWise Therapeutics LLC
Alejandro Villagra, Ph.D., Assistant Professor, Department of Biochemistry and Molecular Medicine, School of Medicine and Health Sciences, The George Washington University
Wayne W. Hancock, M.D., Ph.D., Professor of Pathology and Chief of Transplant Immunology, Children's Hospital of Philadelphia and University of Pennsylvania

SC10: Introduction to Allosteric Modulators and Biased Ligands of GPCRs
Aimed at scientists working on or moving into the field of G protein-coupled receptors (GPCRs), this course will provide information on the identification and validation of allosteric, pathway-biased drugs including emerging screening approaches and practical tips and tools for ligand identification and validation. Allosteric modulators and pathway-biased ligands represent novel therapeutic approaches for achieving more selective actions with regards to GPCRs. The protein structural basis underlying the drug activity of allosteric modulators and the emerging opportunities for computer-aided discovery of allosteric and biased ligands will also be covered.
Instructors: Annette Gilchrist, Ph.D., Professor, Pharmacology, Midwestern University
Sid Topiol, Ph.D., CSO, 3D-2drug, LLC; Professor and Director, Structural and Computational Drug Discovery, Stevens Institute of Technology

SC12: 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 screening programs. This presentation will cover a range of relevant topics with a goal of providing practical information to help prosecute such programs more effectively.
Instructor: Fabien Vincent, Ph.D., Associate Research Fellow, Hit Discovery and Lead Profiling Group, Pfizer

**Separate registration is required for short courses and symposia.*

SC13: Introduction to Targeted Covalent Inhibitors
Covalent inhibitors of kinases have re-emerged as a drug design strategy due to more examples of their safety and efficacy in patients. Covalent inhibitors have the advantage of increased selectivity and longer action of duration but there are still important issues about their design and application that need to be better understood. This course will cover practical as well as theoretical issues that a medicinal chemist needs to keep in mind in developing covalent inhibitors.
Instructors: Brain Gerstenberger, Ph.D., Principal Scientist, Inflammation & Immunology: Medicinal Chemistry, Pfizer Inc.
Mark Schnute, Ph.D., Associate Research Fellow, Biotherapeutics Chemistry & Immunoscience Research, Pfizer Global R&D

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**Separate registration is required for short courses and symposia.*

Training SEMINARS

By Cambridge Healthtech Institute

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

**For detailed agendas and further details, please visit conference website*

SEPTEMBER 27 - 28, 2017

WEDNESDAY 3:30 - 6:30 PM & THURSDAY 9:00 AM - 5:00 PM

TS1: Data Visualization for Effective Drug Discovery Decisions

Instructor: Georges Grinstein, Ph.D., Research Professor, Center for Data Science, College of Information and Computer Sciences, University of Massachusetts, Amherst MA and Consultant

This 1.5-day lecture-based seminar focuses on strategies to help biopharma organizations effectively utilize data to better identify new potential drug candidates and develop them into effective, approved and reimbursed medicines more quickly. This potential cannot be unlocked without addressing key issues including data collection, management and integration of complex and disparate datasets, scalability, analysis and visualization tools in order to identify multiple drug targets (not just single drug targets) to work together as a network. This seminar will explore these issues and the role that a modern approach to this process can have on drug design to identify biomarkers and discover targets for potential therapies.

TS2: Introduction to Small Molecule Drug Discovery and Development

Instructors: H. James Harwood Jr., Ph.D., Founder and CEO, Delphi BioMedical Consultants, LLC

Geraldine Harriman, Ph.D., Founder and CSO, HotSpot Therapeutics, Inc.

This 1.5-day 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.

TRAINING SEMINAR INFORMATION

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.

Cambridge 25 YEARS HEALTHTECH Institute
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PLENARY KEYNOTE PROGRAM » Wednesday, September 27, 12:35 - 2:00 pm

NOVEL DRUG DISCOVERY: WHERE ARE WE NOW?

The 2017 Discovery on Target Plenary Keynote Program will take place on Wednesday, September 27, from 12:35 – 2:00 pm at the Westin Copley Hotel. We are delighted and honored to have two renowned and distinguished scientists join the program: Dr. Jeffrey Ravetch, who will discuss his work on the diverse downstream pro-inflammatory, anti-inflammatory and immunomodulatory consequences of the engagement of type I and type II Fc receptors; and Dr. Raymond Deshaies, who will show for the first time that the activity of p97/VCP•Npl4•Ufd1is enhanced by mutations that cause multisystem proteinopathy.

12:35 - 2:00 PM PLENARY KEYNOTE PROGRAM

12:35 pm Event Chairperson's Opening Remarks
Kip Harry, Senior Conference Director, Cambridge Healthtech Institute

12:40 Diversification of Antibody Effector Function
Jeffrey V. Ravetch, M.D., Ph.D., Theresa and Eugene M. Lang Professor; Head, Leonard Wagner Laboratory of Molecular Genetics and Immunology, The Rockefeller University
Antibodies produced in response to a foreign antigen are characterized by polyclonality, not only in the diverse epitopes to which their variable domains bind but also in the various effector molecules to which their constant regions (Fc domains) engage. Thus, while Fab-antigen interactions are crucial to the specificity of the antibody response, there is a crucial role for the Fc domain in mediating the diverse effector properties triggered by antigen recognition, even for processes traditionally attributed solely to recognition by the Fab, such as neutralization of toxins and viruses. Specific interactions of the IgG Fc domain with distinct receptors expressed by diverse immune cell types result in the pleiotropic effector functions for IgG, including the clearance of pathogens and toxins, lysis and removal of infected or malignant cells, modulation of the innate and adaptive branches of immunity to shape an immune response, and initiation of anti-inflammatory pathways that actively suppress immunity. The Fc domain mediates these diverse effector activities by engaging two distinct classes of Fc receptors (type I and type II) on the basis of the distinct conformational states that the Fc domain may adopt. These conformational states are regulated by the differences among antibody subclasses in their amino acid sequence and by the complex, biantennary Fc-associated N-linked glycan. I will discuss the diverse downstream proinflammatory, anti-inflammatory and immunomodulatory consequences of the engagement of type I and type II Fc receptors in the context of infectious, autoimmune, and neoplastic disorders.

1:20 Ubiquitin- and ATP-Dependent Unfoldase Activity of p97/VCP•Npl4•Ufd1 Is Enhanced by Mutations that Cause Multisystem Proteinopathy
Raymond J. Deshaies, Ph.D., Senior Vice President, Discovery Research, Amgen
p97 is a 'segregase' that plays a key role in numerous ubiquitin-dependent pathways. p97 extracts proteins from membranes or macromolecular complexes to enable their proteasomal degradation; however, the complex nature of p97 substrates has made it difficult to directly observe the mechanistic basis for this activity. We developed a soluble p97 substrate—Ub-GFP modified with K48-linked ubiquitin chains—for *in vitro* p97 activity assays. We demonstrate for the first time that wild type p97 can unfold proteins and that this activity is dependent on the p97 adaptor Npl4•Ufd1, ATP hydrolysis, and substrate ubiquitination, with branched chains providing maximal stimulation. Remarkably, p97 mutants that cause disease in humans unfold substrate faster, suggesting that excess activity may underlie pathogenesis.

2:00 Close of Plenary Keynote Program

PLENARY KEYNOTE BIOGRAPHIES

Jeffrey V. Ravetch, M.D., Ph.D.
Theresa and Eugene M. Lang Professor; Head, Leonard Wagner Laboratory of Molecular Genetics and Immunology, The Rockefeller University
Jeffrey V. Ravetch, M.D., Ph.D. is currently the Theresa and Eugene Lang Professor at the Rockefeller University and Head of the Leonard Wagner Laboratory of Molecular Genetics and Immunology. Dr. Ravetch, a native of New York City, received his undergraduate training in molecular biophysics and biochemistry at Yale University, earning his BS degree in 1973, working with Donald M. Crothers on the thermodynamic and kinetic properties of synthetic oligoribonucleotides. He continued his training at the Rockefeller University – Cornell Medical School M.D./Ph.D. program, earning his doctorate in 1978 in genetics with Norton Zinder and Peter Model, investigating the genetics of viral replication and gene expression for the single-stranded DNA bacteriophage f1. In 1979, he earned his M.D. from Cornell University Medical School. He pursued postdoctoral studies at the NIH with Phil Leder where he identified and characterized the genes for human antibodies and the DNA elements involved in switch recombination. From 1982 to 1996, Dr. Ravetch was a member of the faculty of Memorial Sloan Kettering Cancer Center and Cornell Medical College. His laboratory has focused on the Fc domain of antibodies and the receptors it engages, determining the mechanisms by which this domain enables antibodies to mediate their diverse biological activities *in vivo*. His work established the novel structural basis for Fc domain functional diversity and the pre-eminence of FcR pathways in host defense, inflammation and tolerance, describing novel inhibitory signaling pathways to account for the paradoxical roles of antibodies as promoting and suppressing inflammation. His work has been widely extended into clinical applications for the treatment of neoplastic, inflammatory and infectious diseases.

Raymond J. Deshaies, Ph.D.
Senior Vice President, Discovery Research, Amgen
Dr. Deshaies received his Ph.D. degree in biochemistry from UC-Berkeley and was a Lucille P. Markey Postdoctoral Scholar at UCSF. His honors include the American Society for Cell Biology–Promega Early Career Life Scientist of the Year Award for 1999, appointment as a Fellow of the American Association for the Advancement of Science, election to the American Academy for Arts and Sciences (2011), and election to the National Academy of Sciences (2016). Dr. Deshaies's lab at Caltech investigates the cellular machinery that mediates protein degradation by the ubiquitin-proteasome system. In addition to his academic work, Dr. Deshaies co-founded Proteolix in 2003. Proteolix initiated development of Kyprolis (approved by FDA, July 2012) and was acquired by Onyx in 2009. In 2011, Dr. Deshaies co-founded Cleave Biosciences. Cleave initiated Phase I clinical trials in 2014 with a molecular scaffold whose development was initiated in the Deshaies laboratory.

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CONFERENCE & SYMPOSIA CHANNELS

Take advantage of Discovery on Target's program channels to explore the 1.5-day main program conferences and pre- and post-conference symposia that align with your research. » *Click the links below to jump to the agenda for each program.*

Cancer Immunotherapy

- Immunomodulatory Small Molecules Symposium*
- Microbiome in Immuno-Oncology Symposium*
- NK Cell-Based Cancer Immunotherapy
- Targeting Tumor Myeloid Cells

Target-Based Discovery & Validation

- Targeting Histone Methyltransferases & Demethylases
- Targeting the Ubiquitin Proteasome System
- Lead Generation Strategies
- CRISPR for Disease Modeling & Target Discovery
- GPCR-Based Drug Discovery
- Next-Generation Histone Deacetylase Inhibitors
- Kinase Inhibitor Discovery
- Target Identification Strategies

Hot & Emerging

- Targeting Autophagy Symposium*
- Targeting HBV Symposium*
- Targeting the Microbiome
- NASH & Fibrosis
- Autoimmune & Inflammation Drug Targets
- Targeting Ocular Disorders
- CNS & Neurodegenerative Targets Symposium*
- Tackling Rare Diseases Symposium*

Biologics & Beyond

- Constrained Peptides & Macrocyclics Symposium*
- Antibodies Against Membrane Protein Targets - PART 1
- Antibodies Against Membrane Protein Targets - PART 2
- Emerging Oligonucleotide Therapeutics

**Separate registration is required for short courses and symposia.*

Symposia*

September 25 - 29, 2017

Back by popular demand are focused, one-day pre- and post-conference symposia, designed to highlight areas of discovery research currently capturing the interest of developers, and poised to grow in importance over the next few years. Pre- and post-conference symposia complement topics covered during main conference meetings, and can be combined to provide a robust and comprehensive five days of unique programing based on personal interest.

*Click the links below to jump to the agenda for each symposium.**

September 25

- Immunomodulatory Small Molecules
- Targeting Autophagy
- Microbiome in Immuno-Oncology
- Constrained Peptides and Macrocyclics
- Targeting HBV

September 28-29

- CNS and Neurodegenerative Targets
- Tackling Rare Diseases

Separate registration is required for short courses and symposia.

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Cancer Immunotherapy

September 25 - 28, 2017

While a large portion of cancer immunotherapies focus on antibodies targeting T-cells, developers are now exploring newer therapeutic agents and approaches. The Cancer Immunotherapy channel highlights cutting-edge discovery approaches harnessing NK cells for improved cell therapies, tailoring the microbiome for immune response, and targeting myeloid infiltrates in the tumor microenvironment, as well as the discovery and design of new immunomodulatory small molecules.

*Click the links below to jump to the agenda for each conference or symposium.**

September 25

- Immunomodulatory Small Molecules
- Microbiome in Immuno-Oncology

September 26-27

- NK Cell-Based Cancer Immunotherapy

September 27-28

- Targeting Tumor Myeloid Cells

Separate registration is required for short courses and symposia.

Target-Based Discovery & Validation

September 26 - 28, 2017

The Target-Based Discovery and Validation channel covers the latest scientific and technological advances enabling the discovery of small molecules targeting GPCRs, kinases, epigenetic proteins and protein degradation. New for 2017 are Lead Generation and Target Identification Strategies, complementary meetings focused on exploring new tools, techniques, and approaches for increased preclinical efficiency.

Click the links below to jump to the agenda for each conference.

September 26-27

- Targeting Histone Methyltransferases and Demethylases
- Targeting the Ubiquitin Proteasome System
- Lead Generation Strategies
- CRISPR for Disease Modeling and Target Discovery
- GPCR-Based Drug Discovery

September 27-28

- Next-Generation Histone Deacetylase Inhibitors
- Kinase Inhibitor Discovery
- Target Identification Strategies

25 YEARS Cambridge HEALTHTECH Institute
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Hot & Emerging

September 25 - 29, 2017

The Hot and Emerging channel follows major trends in drug discovery, particularly outside of oncology. These meetings focus more broadly on addressing the significant interest in developing therapies to impact the microbiome, autophagy, ocular disorders, inflammation, fibrosis, autoimmunity, and rare diseases. New for 2017 is a focus on identifying new mechanisms and targets for neurodegenerative and CNS diseases, as well as the discovery of improved agents to treat Hepatitis B.

*Click the links below to jump to the agenda for each conference or symposium.**

September 25

- Targeting Autophagy
- Targeting HBV

September 26-27

- Targeting the Microbiome
- NASH and Fibrosis

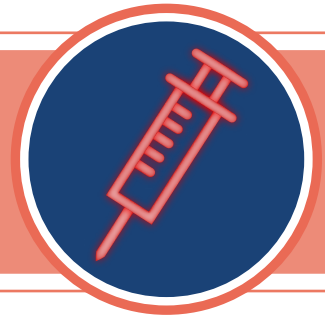
September 27-28

- Autoimmune and Inflammation Drug Targets
- Targeting Ocular Disorders

September 28-29

- CNS and Neurodegenerative Targets
- Tackling Rare Diseases

**Separate registration is required for short courses and symposia.*



Biologics & Beyond

September 25 - 28, 2017

Bridging the gap between small molecules and the growing interest in biologic discovery, the Biologics and Beyond channel explores complex transmembrane proteins (GPCRs and ion channels) as antibody drug targets, the utilization of macrocyclics and constrained peptides to provide 'middle-sized' compounds with advantages over traditional agents, and the discovery of a new generation of oligonucleotide therapeutics to address a broader range of targets.

*Click the links below to jump to the agenda for each conference or symposium.**

September 25

- Constrained Peptides and Macrocyclics

September 26-27

- Antibodies Against Membrane Protein Targets - PART 1

September 27-28

- Antibodies Against Membrane Protein Targets - PART 2
- Emerging Oligonucleotide Therapeutics

**Separate registration is required for short courses and symposia.*

Inaugural | September 25, 2017

Immunomodulatory Small Molecules

Discovery and Development of Small Molecules for Cancer Immunotherapy

First-generation cancer immunotherapy agents being developed or approved are mainly monoclonal antibodies that block protein-protein interactions between T cell checkpoint receptors and their ligands. Recently, discovery efforts have expanded to focus on the development of immune-modulatory small molecules, particularly for synergistic combinations with checkpoint antibodies, and addressing a wide array of new immune-modulatory targets.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Immunomodulatory Small Molecules
- September 26-27 Conference: NK Cell-Based Cancer Immunotherapy
- September 27-28 Conference: Targeting Tumor Myeloid Cells
- September 27 Short Course: Impact of Convergence of Immunotherapy and Epigenetics on Drug Discovery
- September 28-29 Symposium: Tackling Rare Diseases

MONDAY, SEPTEMBER 25

7:00 am Registration Open and Morning Coffee

KINASE, UBIQUITIN AND EPIGENETIC INHIBITORS FOR CANCER IMMUNOTHERAPY

7:55 Welcome Remarks
Kip Harry, Senior Conference Director, Cambridge Healthtech Institute

8:00 Chairperson's Opening Remarks
Jonathan Pachter, Ph.D., CSO, Translational Research, Verastem

8:10 Immunologic Effects of Clinical Stage FAK and PI3K-Delta/Gamma Inhibitors
Jonathan Pachter, Ph.D., CSO, Translational Research, Verastem
The efficacy and long term survival observed with our FAK inhibitor in combination with PD-1 antibody across preclinical models has led to 3 ongoing clinical trials combining our FAK inhibitor defactinib with anti-PD-1 and anti-PD-L1 in solid tumor indications. Additionally, in preclinical models, PI3K-delta inhibition has been shown to confer selective inhibition of Tregs, while PI3K-gamma inhibition confers selective inhibition of MDSCs. Accordingly, immuno-oncology applications of our Phase III PI3K-delta/gamma inhibitor duvelisib will be discussed.

8:40 A Novel Dual PI3K/BRD4 Inhibitor, SF2523 for Combinatorial Activation of Anti-Tumor Immunity in Cancer Via the Orthogonal Inhibition of MYCN and MYC
Donald Durden, M.D., Professor, Department of Pediatrics, University of California, San Diego; Director of Operations, SignalRx Pharmaceuticals
We have developed a dual inhibitory chemotype which blocks MYC via two orthogonal independent pathways: 1) PI3K inhibition induces MYCN degradation and 2) BRD4 blocks MYCN transcription. We demonstrate that this small molecule, SF2523, blocks MYCN transcription and induces MYCN degradation and abrogates the macrophage immunosuppressive effects on tumor immunity via the blockade of the M1-M2 transition *in vivo*.

9:40 Networking Coffee Break with Poster Viewing

10:10 A First-in-Class Selective Class IIa Histone Deacetylase (HDAC) Inhibitor, TMP195
Michael Nolan, Ph.D., Director, GlaxoSmithKline
We recently reported that a first-in-class selective class IIa HDAC inhibitor (TMP195) influenced human monocyte responses to colony stimulating factors CSF-1 and CSF-2 *in vitro*. Here, we utilize a macrophage-dependent autochthonous mouse model of breast cancer to demonstrate that *in vivo* TMP195 treatment alters the tumor microenvironment and reduces tumor burden and pulmonary metastases through macrophage modulation. TMP195 induces recruitment and differentiation of highly phagocytic and stimulatory macrophages within tumors.

10:40 Inhibition of Kinase-Mediated Signaling in Myeloid Cells Suppresses Peritumoral Immune Suppression in Pancreas Cancer
Michael Burnet, Ph.D., Managing Director, Oncology Discovery, Synovo GmbH

11:10 Enjoy Lunch on Your Own

SMALL MOLECULES TARGETING PD-1, IDO1, TDO2, AND STING

1:10 pm SPEAKER CANCELLATION: Chairperson's Remarks
Lijun Sun, Ph.D., Associate Professor, Harvard Medical School; Director, Center for Drug Discovery and Translational Research, Beth Israel Deaconess Medical Center

1:20 SPEAKER CANCELLATION: Design and Synthesis of IDO1 and TDO2 Inhibitors
Lijun Sun, Ph.D., Associate Professor, Harvard Medical School; Director, Center for Drug Discovery and Translational Research, Beth Israel Deaconess Medical Center
We conducted *in silico* screens to identify novel and selective IDO1 and TDO2 inhibitors, respectively. Enzymatic hIDO1 and hTDO2 assays were utilized to confirm inhibitory activity and selectivity. Among the confirmed inhibitors, a series of oxan-4-carboxamides selectively inhibited hIDO1, while a series of substituted 9H-fluorenes were identified as TDO2 selective inhibitors (IC50: 1 μM). In this presentation, we will discuss the *in silico* approach and provide updates on characterization data of the inhibitors.

1:50 Development of SB 11285, a Highly Potent STING Agonist for Application in Immuno-Oncology
R.P. (Kris) Iyer, Ph.D., Co-Founder & CSO, Spring Bank Pharmaceuticals
Immunotherapy has emerged as a transformative approach for the treatment of cancer. Evidence suggests that the activation of Stimulator of Interferon Genes (STING) pathway in tumor cells and/or immune

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cells induces type I Interferon production leading to apoptosis of tumor cells as well as induction of adaptive immune response thereby providing a powerful anti-cancer strategy. Herein, we describe the discovery of highly potent and selective first-in-class STING agonist SB 11285 for application in immuno-oncology.

2:20 **Small Molecule Ubiquitin Protease (USP7) Inhibitors with Immune Cell Based Anti-Tumor Activity Superior to that of Biologicals**
Tauseef R. Butt, Ph.D., President and CEO, Progenra, Inc.
In immune competent animal models, USP7 inhibitors are potent anti-tumor agents, not only blocking tumor growth but also eliminating tumor metastasis. These results constitute the first example of a small molecule single agent that works by targeting both the tumor itself and the host immune system and also by eliminating tumor metastasis. In animal models, the USP7 inhibitor demonstrates activity that is superior to that of PD1 and CTLA4 antibodies.

2:50 **Networking Refreshment Break with Poster Viewing**

NOVEL IMMUNOMODULATORY SMALL MOLECULES

3:30 **Chairperson's Remarks**
David Ferguson, Ph.D., Professor, Medicinal Chemistry, University of Minnesota

3:30 **Selective Activation of Toll-Like Receptor 7 and 8 in the Design of Cancer Vaccines**
David Ferguson, Ph.D., Professor, Medicinal Chemistry, University of Minnesota
The basic structural features of small molecule ligands that confer selectivity to Toll-like receptors 7 and 8 will be discussed in the context of immunomodulation and the design of cancer vaccines. An SAR analysis will be presented to identify structural features that confer selectivity to TLR7 and TLR8 and ligand specific activation of key cytokines in producing antigen specific cellular responses in model systems. Finally, *in vivo* data will be shown that demonstrates the potential of TLR7/8 stimulation in designing advanced vaccines for cancer treatment.

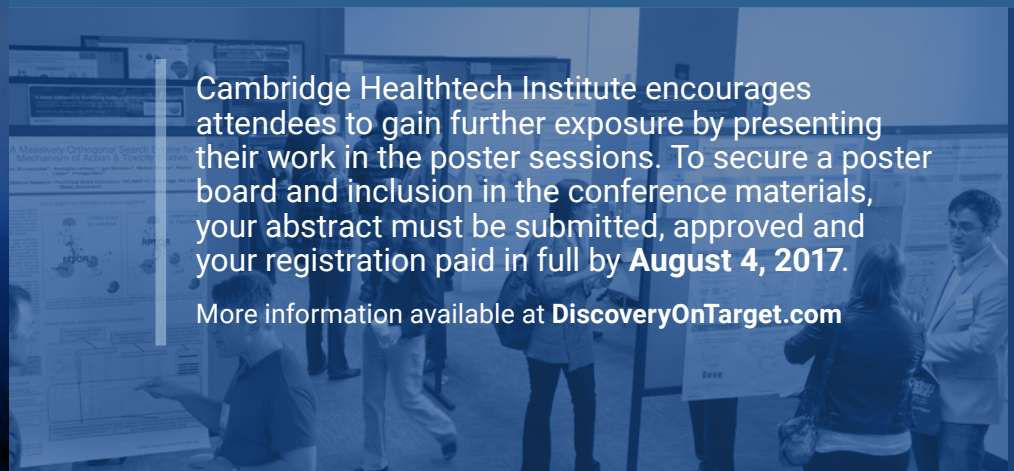
4:00 **Anti-Cancer Therapy by Inducing Immunogenicity in Tumors with Small Molecules**
Weiwen Ying, Ph.D., Co-Founder and President, Drug Discovery, Capten Therapeutics
Capten Therapeutics is developing a new class of drugs that enhance the immunogenicity of cancer cells in a novel way. Our technology uses analogs of the active substance in natural produces to bond with proteins in cancer cells to produce highly immunogenic haptenated proteins. These haptenated proteins stimulate an adaptive immune response that opens the door to effective therapeutic options.

4:30 **Novel Natural Immunomodulatory Peptide Synergistic with Chemotherapy**
Raghu Pandurangi, Ph.D., Founder & President, Drug Design, Sci-Engi-Medco Solutions, Inc.
Loss of immunity protein beta defensin is responsible for the onset of cancer. A fragment of beta defensin modulates immunofunction which when delivered selectively to cancer cells resulted in the regression of tumor. The peptide fragment also synergizes with standard FDA-approved chemotherapeutics *in vitro/ in vivo*. This novel peptide can be used as neoadjuvant to chemotherapy to expand the therapeutic index of existing treatments.

5:00 **Close of Symposium**

5:00 **Pre-Conference Dinner Short Course Registration**
Click here for details on short courses offered.

Dedicated Poster Sessions for Symposia and Conference Programs



Cambridge Healthtech Institute encourages attendees to gain further exposure by presenting their work in the poster sessions. To secure a poster board and inclusion in the conference materials, your abstract must be submitted, approved and your registration paid in full by **August 4, 2017**.

More information available at **DiscoveryOnTarget.com**

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- 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

25 YEARS Cambridge HEALTHTECH Institute
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Inaugural | September 25, 2017

Targeting Autophagy

Advances in Pharmaceutically Modulating Autophagy in Disease

Autophagy is a highly regulated and complex process of destroying damaged proteins and organelles under stressful conditions. Stemming from the pioneering work of Professor Yoshinori Ohsumi, who was awarded the 2016 Nobel Prize in Physiology and Medicine, dysregulation of the autophagy process has been established to play a role in neurodegenerative diseases and cancers. Consequently, the discovery of novel therapeutic agents targeting various stages along this process has emerged as a promising new approach for drug developers.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Targeting Autophagy
- September 25 Short Course: Covalent Fragments: Applications in Target-Based and Phenotypic Screens
- September 26-27 Conference: Targeting the Ubiquitin Proteasome System
- September 27-28 Conference: Kinase Inhibitor Discovery
- September 27 Short Course: Introduction to Targeted Covalent Inhibitors
- September 28-29 Symposium: CNS and Neurodegenerative Targets

MONDAY, SEPTEMBER 25

7:00 am Registration Open and Morning Coffee

ADVANCES IN OUR UNDERSTANDING OF AUTOPHAGY IN DISEASE

7:55 Welcome Remarks
Kip Harry, Senior Conference Director, Cambridge Healthtech Institute

8:00 Chairperson's Opening Remarks
Nicholas Cosford, Ph.D., Associate Director, Translational Research & Professor, Cancer Metabolism and Signaling Networks Program, NCI-Designated Cancer Center, Sanford Burnham Prebys Medical Discovery Institute

8:10 KEYNOTE PRESENTATION: Targeting Autophagy in Cancer
Eileen White, Ph.D., CSO, Deputy Director & Associate Director, Basic Science, Rutgers Cancer Institute of New Jersey
Macroautophagy (autophagy) degrades proteins, other macromolecules, and organelles, in lysosomes and recycles the breakdown products to promote survival in stress and starvation. Autophagy is upregulated in some cancers and promotes survival and malignancy, suggesting that targeting autophagy in cancer may be therapeutically advantageous. Autophagy promotes tumor cell autonomous cancer in preclinical models by suppressing p53, apoptosis, senescence, and immune responses, and also by promoting metabolism and proliferation.

9:10 A Membrane-Associated Signaling Complex for Controlling Peroxisome Fate
Vlad Denic, Ph.D., Professor, Molecular and Cellular Biology, Harvard University
Eukaryotic cells maintain the quality of their organelles by controlling organelle turnover by autophagy. Recent work has shown that autophagy receptor proteins induce organelle destruction by triggering local autophagosome initiation upon activation by cytosolic kinases. It has remained unclear, however, how receptor activation is regulated. We hypothesized that receptor activation is controlled locally by organelle resident proteins to enable quality control decisions. I will present our evidence for this hypothesis in the context of selective autophagy of peroxisomes in the budding yeast *S. cerevisiae* and discuss implications of this work for drug targeting of mammalian pexophagy associated with certain Zellweger Spectrum disorders.

9:40 Networking Coffee Break with Poster Viewing

10:10 Context-Specific Regulation and Function of Autophagy, Therapeutic Food for Thought
Eric H. Baehrecke, Ph.D., Professor, Department of Molecular, Cell and Cancer Biology, University of Massachusetts Medical School
Autophagy is an important cellular response to stress, and plays essential roles in development, immunity, cancer and neurodegeneration. Thus, autophagy is considered a promising target for disease therapies. Pioneering studies of yeast led to the identification of conserved core factors that regulate autophagy, but the role of autophagy in specific cell contexts within multi-cellular organisms has not been rigorously studied. Recent studies of how autophagy is regulated and contributes to distinct cell fates will be presented.

10:40 Selected Poster Presentation

11:10 Enjoy Lunch on Your Own

THERAPEUTICALLY MODULATING AUTOPHAGY

1:10 pm Chairperson's Remarks
Eric H. Baehrecke, Ph.D., Professor, Department of Molecular, Cell and Cancer Biology, University of Massachusetts Medical School

1:20 The Investigation of Autophagy in Cancer Using Chemical Biology
Nicholas Cosford, Ph.D., Associate Director, Translational Research & Professor, Cancer Metabolism and Signaling Networks Program, NCI-Designated Cancer Center, Sanford Burnham Prebys Medical Discovery Institute
Despite recent breakthroughs in the understanding of how ULK1 is activated by nutrient deprivation, how ULK1 promotes autophagy remains poorly understood. Using various chemical biology approaches, we identified and characterized a potent ULK1 small molecule inhibitor. The compound SBI-0206965 is a highly selective ULK1 kinase inhibitor *in vitro* and suppresses ULK1-mediated phosphorylation events

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in cells, regulating autophagy and cell survival. This presentation will describe our efforts to date on the validation of autophagy inhibition.

1:50 Targeting Autophagy in Cancer
Jeff MacKeigan, Ph.D., Professor, College of Human Medicine, Michigan State University
In recent years, autophagy has emerged as an important therapeutic target. In response to environmental, therapeutic, and oncogenic stress, cancer cells upregulate autophagy and also demonstrate an increased dependence upon this intracellular recycling process. Many cancers still lack targeted therapeutic options, and autophagy inhibitors are a promising and emerging anti-cancer target. We present the therapeutic development of autophagy inhibitors from early lysosomotropic agents to next-generation lysosome-targeted drugs to kinase-directed targets.

2:20 Targeting the Lysosome in Cancer
Ravi Amaravadi, M.D., Associate Professor, Medicine, University of Pennsylvania
The anti-tumor efficacy of the second-generation dimeric chloroquine Lys05 has now been demonstrated by a number of laboratories. A new series of third-generation longer linkered dimeric chloroquines such as DC661 demonstrate substantial improvements in potency compared to Lys05. Finally the dimeric quinacrine DQ661 concurrently inhibits mTOR and autophagy. The molecular target of dimeric chloroquine derivatives was pulled down using multiple DC and DQ-photoaffinity probes. This lysosomal enzyme could play a critical role in multiple oncogenic pathways.

2:50 Networking Refreshment Break with Poster Viewing

3:30 Inhibitors of Vps34 in Cancer Treatment
Jessica Martinsson, Ph.D., Vice President, Medicinal Chemistry, Sprint Bioscience AB
We have developed potent and selective inhibitors of Vps34 with excellent drug properties. The compounds are potent inhibitors of autophagy, affecting cellular metabolism and oxygen consumption. With these compounds, we have shown the relevance of autophagy inhibition in TNBC and investigated its role in immune response.

4:00 Discovery of Novel TAOK2 Inhibitor Scaffolds from High-Throughput Screening
Malia B. Potts, Ph.D., Assistant Member, Cell and Molecular Biology, St. Jude Children's Research Hospital
A synthetic lethal screen performed using a NSCLC (non-small cell lung cancer) cell line, and a second screen identifying potential modulators of autophagy have implicated TAOK2 as a potential cancer therapeutic target. Using a 200,000 compound high throughput screen, we identified three specific small molecule compounds that inhibit the kinase activity of TAOK2. These compounds also showed inhibition of autophagy. Based on SAR (structure-activity relationship) studies, we have predicted the modifications on the reactive groups for the three compounds.

4:30 Targeting Autophagy for Cancer Therapy
Natalie Roy D'Amore, Ph.D., Director, Early Discovery Oncology, Takeda Pharmaceuticals

5:00 Close of Symposium

5:00 Pre-Conference Dinner Short Course Registration
Click here for details on short courses offered.

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Inaugural | September 25, 2017

Microbiome in Immuno-Oncology

Role of a Healthy Gut Microbiome in Cancer Prevention

Understanding the relationship between the human microbiome and cancer could be instrumental in transforming immune-modulating therapies, since a certain immunotherapy is reliant on the gut's microflora. Cambridge Healthtech Institute's inaugural symposium on Microbiome in Immuno-Oncology tracks both the scientific and clinical progress being made to discover and develop microbiome-derived biomarkers, drug targets, and bioactive molecules as potential treatments for cancer. Through interactive sessions and panel discussions, leading researchers and thought leaders will discuss how their work in this emerging field has and will continue to have tremendous impact on cancer and improve clinical outcomes for patients.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Microbiome in Immuno-Oncology
- September 26-27 Conference: Targeting the Microbiome
- September 27-28 Conference: Autoimmune and Inflammation Drug Targets
- September 27 Short Course: Impact of Convergence of Immunotherapy and Epigenetics on Drug Discovery
- September 28-29 Symposium: CNS and Neurodegenerative Targets

MONDAY, SEPTEMBER 25

7:00 am Registration Open and Morning Coffee

MECHANISMS OF IMMUNE SYSTEM-DIRECTED THERAPIES FOR CANCER

7:55 Welcome Remarks
Cindy Crowninshield, RDN, LDN, HHC, Senior Conference Director, Cambridge Healthtech Institute

8:00 Chairperson's Opening Remarks
William Loging, Ph.D., Associate Professor of Genomics & Head, Production Bioinformatics, Genetics and Genomics Sciences, Icahn School of Medicine at Mount Sinai; Editor, Bioinformatics and Computational Biology in Drug Discovery and Development

8:10 Targeting the Microbiome in I/O
Rodolphe Clerval, Chief Business Officer, Vice President US Operations, Enterome Bioscience
Enterome discovers and develops microbiome derived molecules in immunology (IBD & I/O). Our approach is based on complete genetic and functional analysis of the microbiome. First clinical product candidate in IBD based on novel disease-modifying mechanism of action.

8:40 Molecular Impacts of Immune Modulating Drugs on Cancer Patients
William Loging, Ph.D., Associate Professor of Genomics & Head, Production Bioinformatics, Genetics and Genomics Sciences, Icahn School of Medicine at Mount Sinai; Editor, Bioinformatics and Computational Biology in Drug Discovery and Development, Cambridge University Press, 2016
The area of Immuno-Oncology provides a novel strategy for cancer treatment by utilizing the patient's immune system to combat tumor growth. We investigated the impact of specific immune modulating drugs on patients with diagnosed tumors in order to understand the molecular changes that take place at the pathway level. These data are correlated to phenotypic effect and provide insights into the mechanism of immune system directed therapies for cancer.

9:10 Microbiome in Immuno-Oncology
Lata Jayaraman, Ph.D., Head, Tumor Immunotherapy, Seres Therapeutics
The human gut microbiome is a diverse, dynamic, and complex ecosystem that contains many different types of micro-organisms. Gut microbiota modulate several host processes including metabolism, inflammation and immune and cellular responses. Recent studies have shown that the microbiome can also influence the development of cancer, and equally importantly, tumor response to therapy, especially immunotherapy. It is therefore not inconceivable that therapeutic utility of the microbiome to enhance clinical response is a distinct possibility in the not-so-distant future. This presentation will cover the challenges and advantages of developing the microbiome as a drug.

9:40 Networking Coffee Break with Poster Viewing

10:10 The Breast Tissue Microbiome: Associations with Cancer and Cancer Risk
Tina Hieken, M.D., Surgical Oncologist and Associate Professor of Surgery, Mayo Clinic College of Medicine
Breast tissue contains a complex microenvironment including epithelium, stroma and a mucosal immune system, providing evidence for an intrinsic breast tissue microbiome. Our pilot data has confirmed the existence of this breast tissue microbiome, distinct from that of breast skin and other microbial niches, with demonstrable differences in benign and malignant disease states using culture-independent genomic analysis of sterile human samples. We are expanding our analyses and exploring relationships between the microbiome of breast tissue, other body niches and the immune microenvironment in an effort to develop a biome-based approach to individualized breast cancer risk prediction and identify a platform for novel breast cancer prevention therapies.

10:40 Presentation to be Announced

11:10 Sponsored Presentation *(Opportunity Available)*

11:40 Enjoy Lunch on Your Own

INFLUENCES OF INFLAMMATION AND NUTRITION IN MICROBIOME AND CANCER

1:10 pm Chairperson's Remarks
Bonnie Feldman, D.D.S., MBA, Digital Health Analyst and Chief Growth Officer, DrBonnie360

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1:20 Alimentary Effect in Microbiome and Cancer
Antonio Rezusta, Professor, Section Head, Microbiology, Hospital Universitario Miguel Servet
This presentation discusses microbiota management in the prevention and treatment of cancer. Topics covered will include 1) the interest in knowing which microorganisms favor colon cancer, 2) the influence that can modify the microbiota in the prevention of cancer, 3) the influence that modifying the flora can have on the response to chemotherapy, and 4) the consequences for any cancer treatment of antimicrobial resistance.

1:50 Influences of Inflammation, Vitamin D Receptor, and Gut Microbiome in Cancers
Jun Sun, Ph.D., AGA Fellow, Associate Professor, Division of Gastroenterology and Hepatology, Department of Medicine, University of Illinois at Chicago
Vitamin D deficiency is implicated in the pathology of over 17 types of cancers. Vitamin D exerts its regulatory roles in immunity, host defense, and inflammation via vitamin D receptor (VDR). We have demonstrated that VDR deletion leads to dysbiosis and human VDR gene variation shapes gut microbiome. Here, we will discuss influences of inflammation, VDR, and microbiome in cancers.

2:20 Microbial Allies across the Cancer Continuum: Getting to Know Our Fiber-Fermenting Friends
Carrie R. Daniel-MacDougall, Ph.D., MPH, Assistant Professor, Department of Epidemiology, Division of Cancer Prevention and Population Sciences, The University of Texas MD Anderson Cancer Center
The gut microbiome's role in inflammation, immunity, and carcinogenesis extends beyond specific pathogens to the wider community of beneficial, commensal bacteria, nurtured by fiber and resistant starch-rich "prebiotic" plant foods (e.g., *Faecalibacterium prausnitzii*, *Roseburia* and *Ruminococcus* species). Building on longstanding, evidence-based dietary recommendations for chronic disease prevention, targetable diet-microbiota relationships stand at the interface of cancer prevention, treatment, and survival strategies.

2:50 Networking Refreshment Break with Poster Viewing

PROMISING APPLICATIONS IN THERAPEUTIC ONCOLOGY: CURRENT PRACTICES AND EMERGING PLATFORMS, DEVICES, AND THERAPIES

3:30 Cancer Moonshot: Obtaining patents on Oncologic Therapies
Joe Kovarik, J.D., Patent Attorney with Bioscience Focus and Shareholder, Sheridan Ross, P.C.
The ability to expedite the patent process for particular cancer therapies is an important aspect of current therapeutic Oncology. The ability to obtain funding for research, as well as the prospects for commercialization, are intimately tied to the ability to obtain patent protection. Mr. Kovarik, a patent attorney/inventor, will review what is required to participate in the "Cancer Immunotherapy Pilot Program" at the USPTO, providing real world examples of how this new program enables researchers to obtain an issued patent in a fraction of the time typically required under the conventional patent process.

4:00 Targeting Microbial b-Glucuronidases with Symbiotic Drugs to Improve Cancer Therapy
Bret Wallace, Ph.D., Scientist, Symberix, Inc.
Many toxic compounds are inactivated by liver cells and subsequently reactivated by gut microbiota. We recently showed that *E. coli* GUS is one of several structurally distinct b-glucuronidases expressed in the human gut microbiome (i.e., human GUSome). We describe here potential uses of new symbiotic drugs that target harmful components of the human GUSome to improve cancer therapy. This includes prevention of chemotherapy-induced diarrhea, improvement of chemotherapy survival outcomes, and cancer prevention. The GUSome is an emerging platform of druggable microbiome targets with promising applications in therapeutic oncology.

4:30 KEYNOTE PRESENTATION: Microbiome Therapeutics in Immuno-Oncology: Current Practices to Future Therapies
Zain Kassam, M.D., MPH, FRCPC, CMO, OpenBiome; Gastroenterologist, Epidemiologist and Research Affiliate, MIT Center for Microbiome Informatics & Therapeutics

5:00 Close of Symposium

5:00 Pre-Conference Dinner Short Course Registration
Click here for details on short courses offered.

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Inaugural | September 25, 2017

Constrained Peptides and Macrocyclics

Cell-Penetrating Middle-Sized Molecules for Better Therapeutics

Constrained peptides and macrocyclics represent a relatively new class of drug compounds that are smaller than biologics or protein therapeutics but bigger than the 'small molecule' class of traditional drugs. Their 'middle size' and the synthetic or natural constraints that give them a ring structure is supposed to make them the Goldilocks or 'just right' set of new therapeutic modalities because they should be small enough to cross the cell membrane, unlike biologics, and therefore not be limited to only acting on cell-surface targets and they have the potential to be developed into oral therapeutics. At the same time these molecules are large enough to have the safety/tolerability advantage of biologics and the ability to better disrupt protein-protein interactions and therefore are more useful for targeting the 'undruggable' protein complexes that much of new drug discovery is taking aim at. Join us at Cambridge Healthtech Institute's Inaugural Constrained Peptides and Marocyclics symposium to witness how this class is living up to its promise and discuss the challenges that lie ahead.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Constrained Peptides and Macrocyclics
- September 26-27 Conference: Lead Generation Strategies
- September 27-28 Conference: Autoimmune and Inflammation Drug Targets
- September 27 Short Course: Introduction to Targeted Covalent Inhibitors
- September 28-29 Symposium: Tackling Rare Diseases

MONDAY, SEPTEMBER 25

7:00 am Registration Open and Morning Coffee

MAKING MACROCYCLICS PEPTIDE-LIKE

7:55 Welcome Remarks
Anjani Shah, Ph.D., Conference Director, Cambridge Healthtech Institute

8:00 Chairperson's Opening Remarks
Lauren Monovich, Ph.D., Senior Investigator, Global Discovery Chemistry, Novartis

8:10 Properties of Peptidic Macrocycles beyond the Rule-of-5
Alan M. Mathiowetz, Ph.D., Director, Pfizer Worldwide Medicinal Chemistry – Cardiovascular and Metabolic Diseases
Peptidic macrocycles with properties beyond the Rule-of-5 (BRo5) have the potential to be effective modulators of difficult targets. Oral delivery of such molecules is challenging, however, and requires a balance of competing properties such as permeability, clearance, and potency. This talk provides an overview of structure/property trends we have found spanning multiple series of BRo5 macrocycles and highlights both promising and challenging areas.

8:40 ADME Considerations for Non-peptidic Macrocycles
Adrian Whitty, Ph.D., Professor, Biochemistry, Boston University
The last several years have seen a significant upsurge of interest in the use of synthetic macrocycles in drug discovery, and particularly in their potential as inhibitors of difficult targets such as protein-protein interactions. I will discuss progress towards understanding what structural and physicochemical properties of synthetic non-peptidic macrocycles confer good pharmaceutical properties, and particularly good aqueous solubility coupled with passive membrane permeability.

9:10 Peptidic and Non-Peptidic Macrocycles for Challenging Targets in Drug Discovery
Steffen Weinbrenner, Ph.D., Head Drug Discovery, Drug Discovery, Polyphor Ltd.
The talk will give insight into how macrocycles as new therapeutic modalities are complementing the chemical space and help to identify chemical matter for difficult targets and target classes. A particular focus will be given how macrocycles offer chemical matter beyond the rule of 5, still being cell penetrating and orally bioavailable. A case study on macrocycle MedChem optimization will be presented.

9:40 Networking Coffee Break with Poster Viewing

MAKING PEPTIDES CYCLIC

10:10 Facile Peptide Cyclization and Bicyclization via Iminoboronate Chemistry
Jianmin Gao, Ph.D., Associate Professor, Chemistry, Boston College
We recently reported a powerful strategy for peptide cyclization which takes advantage of formation and reduction of iminoboronates (J. Am. Chem. Soc., 2016, 138, 2098). Assisted by the boronic acid substituent, intramolecular iminoboronate formation readily proceeds under physiological conditions to allow for spontaneous peptide cyclization and bicyclization. While formation of iminoboronate is reversible, peptide (bi) cyclization can be made permanent via mild reduction. The resulting (bi)cyclic peptides display novel amino-boronate motifs that can promote structural rigidification and facilitate target recognition. Importantly, this iminoboronate-based cyclization allows for facile generation of libraries of peptide macrocycles, which can be applied to ligand discovery for a variety of targets.

10:40 Design of Technology-Compatible Cyclic Peptide Scaffolds with Oral Bioavailability
Lauren Monovich, Ph.D., Senior Investigator, Global Discovery Chemistry, Novartis
Traditionally, permeable macrocyclic peptides have been identified by discrete synthesis and careful side

**Separate registration is required for short courses and symposia.*

chain variation of privileged, natural product scaffolds. More recently, the basic principles governing passive permeability were applied to the prospective design of macrocyclic peptide scaffolds with oral bioavailability. However, there remains the broad challenge of chemical diversity sufficient to enable regular identification of novel protein ligands. Herein, we present macrocyclic peptide scaffolds with ribosomal library-compatible amino acids and experimentally validated oral bioavailability.

11:10 Sponsored Presentation *(Opportunity Available)*

11:40 Enjoy Lunch on Your Own

CASE STUDIES OF MACROCYCLIC PEPTIDES FOR SPECIFIC TARGETS

1:10 pm Chairperson's Remarks
Maxwell D. Cummings, Ph.D., Senior Principal Scientist, Computational Chemistry, Discovery Sciences, Janssen R&D

1:20 FEATURED PRESENTATION: Macrocyclized Extended Peptides for Tankyrase Inhibition
Heike Laman, Ph.D., Associate Professor, Department of Pathology, University of Cambridge

1:50 Discovery of Potent Cyclophilin Inhibitors Based on Structural Simplification of Sanglifehrin A
Vicky Steadman, Ph.D., Director of Drug Discovery, Cypralis
Sanglifehrin, a complex macrocyclic natural product (MW>1000, 17 chiral centers), is a potent inhibitor of cyclophilins, a target for HCV. Through a structure-guided medicinal chemistry approach, potent, simplified and drug like macrocyclic inhibitors of cyclophilin were identified (MW~500 and 4 chiral centers). The design, synthesis and biological activity of these partially peptidic macrocycles will be discussed.

2:20 Ipglycermides: Novel Macrocyclic Peptide Inhibitors of Microorganism Phosphoglycerate Mutase
James Inglese, Ph.D., Director, Assay Development and Screening Technologies, National Center for Advancing Translational Sciences (NCATS), NIH
This presentation will describe the discovery and mechanism of action of the first inhibitor class for an essential glycolytic enzyme, co-factor independent phosphoglycerate mutase (iPGM), an important target in several infectious organisms, including parasitic nematodes, trypanosomes and the gram positive bacteria *Staphylococcus aureus*. The enzyme has been considered "undruggable" due to unsuccessful attempts to identify inhibitors from small molecule high throughput screening (HTS). As an alternative approach to HTS we sought to explore the exceedingly vast chemical space available from nucleic acid-encoded cyclic peptide libraries.

2:50 Networking Refreshment Break with Poster Viewing

CASE STUDIES OF MACROCYCLIC PEPTIDES FOR SPECIFIC TARGETS *(Cont.)*

3:30 Targeting Intracellular Protein-Protein Interactions with Structure-Based Designed Macrocyclic Peptides
David J. Earp, J.D., Ph.D., President and CEO, Circle Pharma
Circle Pharma deploys a structure–based design/synthetic chemistry platform for macrocycle therapeutic discovery that incorporates prediction of intrinsic cell permeability as a key step in the design workflow. While this platform is target-agnostic, Circle's internal pipeline is directed to intracellular protein-protein interactions that are key drivers in oncology pathways, including p53:MDM2/4, MCL1:BH3, cyclinA:cdk2 and beta-catenin:TCF4. Examples of Circle's development work will be presented.

4:00 A Macrocyclic Peptide for Complement-Mediated Diseases
Doug Treco, Ph.D., Director, President, CEO and Co-Founder, RA Pharma
Inappropriate activation of complement C5 leads to RBC destruction in the rare, acquired disease paroxysmal nocturnal hemoglobinuria (PNH), and has been implicated in other serious indications. RA101495 is a potent, synthetic, macrocyclic peptide that binds C5 and inhibits its activation through a novel mechanism. A Phase I study in healthy volunteers has been completed, supporting the advancement of this product into Phase II studies in patients with PNH and other indications.

4:30 Design and Application of a DNA-Encoded Macrocyclic Peptide Library
Zhengrong Zhu, Ph.D., Scientific Leader, PTS-DDS-NCE, GlaxoSmithKline
A DNA-encoded macrocyclic peptide library was designed and synthesized with 2.5×1012 members composed of 4-20 natural and unnatural amino acids. Affinity-based selection was performed against two therapeutic targets, VHL and RSV N protein. Based on selection data some peptides were selected for resynthesis without DNA tag and their activity was confirmed.

5:00 Close of Symposium

5:00 Pre-Conference Dinner Short Course Registration
Click here for details on short courses offered.

**Separate registration is required for short courses and symposia.*

Inaugural | September 25, 2017

Targeting HBV

New Drug Development for Hepatitis B and Other Infectious Diseases

Hepatitis B is a viral infection of the liver that is a major global health problem and can lead to death from liver fibrosis or liver cancer. The current treatments of daily nucleoside inhibitors only work in half the population and interferon, the other main treatment, has significant side effects making chronic usage difficult. However, the future of potential new treatments for HBV looks promising. Spurred by the recent success in developing direct acting antivirals that in combination have been able to cure hepatitis C, the antiviral drug development industry has re-focused its attention on HBV. However HBV has a few unique challenges such its covalently closed circular (ccc) DNA that is very resistant to destruction and can lead to 'reservoirs' of the virus remaining in treated cells. Join fellow infection disease researchers at Cambridge Healthtech Institute's Inaugural Targeting HBV symposium to learn the latest and discuss the 'behind the scenes' medicinal chemistry and discovery innovations that are enabling progress.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Targeting HBV
- September 26-27 Conference: NASH and Fibrosis
- September 27-28 Conference: Autoimmune and Inflammation Drug Targets
- September 28-29 Symposium: Tackling Rare Diseases

MONDAY, SEPTEMBER 25

7:00 am Registration Open and Morning Coffee

TARGETING HBV PROTEINS

7:55 Welcome Remarks
Anjani Shah, Ph.D., Conference Director, Cambridge Healthtech Institute

8:00 Chairperson's Opening Remarks
Richard Colonno, Ph.D., CSO, Assembly Biosciences

8:10 Targeting HBV Surface Antigen with Nucleic Acid Polymers (NAPs): Updates on Pharmacology, Toxicity and Achieving Functional Cure of HBV and HDV Infection
Andrew Vaillant, Ph.D., CSO, Replicor
NAPs have a unique ability to eliminate circulating HBsAg, potentiating the ability of immunotherapy to achieve functional control of HBV and HDV infection. Recent breakthroughs in modeling NAP effects *in vitro* and updated pre-clinical and clinical data continue to advance the understanding of how NAPs work and their clinical impact against HBV and HDV infection.

8:40 HBV Capsid Assembly Inhibitors
Rene Rijnbrand, Ph.D., Vice President, Biology, Arbutus
AB-423 is an HBV capsid inhibitor that has shown *in vitro* and *in vivo* antiviral activity. AB-423 has been shown to impact the HBV life cycle at two distinct stages: the formation of novel core particles, required for the formation of rcDNA, and the unpacking of the rcDNA from these particles, required for cccDNA formation. AB-423 acts additively to synergistically with siRNA and nucleoside inhibitors.

9:10 Targeting HBV Core Protein to Achieve Higher Cure Rates
Richard Colonno, Ph.D., CSO, Assembly Biosciences
With HBV cure rates below 5%, additional novel therapies are needed. HBV Core protein (Cp) plays a critical role in multiple steps related to the generation of cccDNA, a key viral moiety responsible for infection and maintenance of chronic infection. We are developing a series of novel CpAMs (Cp Allosteric Modifiers) that target Cp and reduce cccDNA levels in infected cells via multiple mechanisms.

9:40 Networking Coffee Break with Poster Viewing

TARGETING HBV PROTEINS *(Cont.)*

10:10 RNAi Interference: A New Tool in the Toolbox for Treatment of HBV
Amy Lee, Ph.D., Senior Director, In vivo Pharmacology, Arbutus
ARB-1467 and ARB-1740 are RNAi therapeutics currently in Phase II MAD clinical studies. These agents are designed to inhibit viral replication, cleave HBV transcripts, and lower all viral antigens. Reducing HBV proteins, particularly HBsAg, is expected to abrogate viral suppression of immune function and facilitate reinvigoration of the host response/ defense. Preclinical studies suggest that combination of RNAi with standard-of-care drugs can enhance control of HBV.

10:40 RNAi in HBV, the Next Backbone Therapy for Use in Combinations?
Bruce Given, M.D., COO, Head of R&D, Arrowhead Pharmaceuticals
Arrowhead was the first broadly used RNAi studied in HBV. Based on our experience in treatment of naïve and experienced patients, we believe that RNAi will become a backbone therapy, together with NUCs, in the next generation of combination therapies seeking functional cure.

11:10 Sponsored Presentation *(Opportunity Available)*

11:40 Enjoy Lunch on Your Own

TARGETING VIRUS/HOST INTERACTIONS

1:10 pm Chairperson's Remarks
Rene Rijnbrand, Ph.D., Vice President, Biology, Arbutus

1:20 KEYNOTE PRESENTATION: Targeting HBV: Integrating Approaches
Pierre Raboisson, Ph.D., Head, IDV Europe Discovery, Janssen

**Separate registration is required for short courses and symposia.*

Cambridge HEALTHTECH Institute
25 YEARS
A Division of Cambridge Innovation Institute

RECORD ATTENDANCE EXPECTED:
RESERVE YOUR SPOT TODAY!

Cover
Conference At-A-Glance
Short Courses
Training Seminars
Plenary Keynotes
Agenda
Symposia
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Target-Based Discovery & Validation Channel
Hot & Emerging Channel
Biologics & Beyond Channel
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1:50 CANCELLED: Entry Inhibition as a Therapeutic Concept for the Treatment of Hepatitis B and D Virus Infections
Stephan Urban, Ph.D., Professor, Department of Infectious Diseases, Translational Virology, University Hospital Heidelberg
Entry inhibition is an interesting, potentially curative opportunity to treat viral infections. The development of Myrcludex B as a potent inhibitor of the HBV/HDV receptor NTCP opened a novel therapeutic option to treat chronically infected patients. In my talk, I will discuss the current state of the art of entry inhibition for HBV/HDV and discuss, if such strategies might become important for future therapeutic regiments.

2:20 Targeting HBx and Smc5/6 Interactions
Dara Burdette, Ph.D., Research Scientist II, Discovery Virology, Gilead Sciences
The structural maintenance of chromosome 5/6 complex (Smc5/6) is a restriction factor that represses hepatitis B virus (HBV) transcription. HBV counters this restriction by expressing X protein (HBx), which targets Smc5/6 for degradation shortly after HBV infection. While the mechanism of transcriptional suppression remains to be elucidated, our data indicate that Smc5/6 restricts HBV when localized to ND10 and without inducing an innate immune response.

2:50 Networking Refreshment Break with Poster Viewing

IMMUNOMODULATORS FOR HBV AND BEYOND

3:30 Achieving Functional Cure in HBV: The Dinucleotide SB 9200 as an Immuno-Modulatory Anti-HBV Agent
R. P. (Kris) Iyer, Ph.D., Co-Founder and CSO, Spring Bank Pharmaceuticals, Inc.
Over 350 million people worldwide are infected with chronic hepatitis B (CHB). While life-long therapy with direct-acting nucleoside and nucleotide antivirals (DAAs) effectively suppress viral replication, development of resistance and toxicity to DAAs remain a significant problem. In CHB, the cellular innate and adaptive immune responses critical for antiviral defense are disabled. SB 9200, a novel synthetic dinucleotide, activates cellular viral sensors RIG-I and NOD2, restores the production of IFNs, ISGs and antiviral cytokines, and shows potent *in vitro* and *in vivo* antiviral activity. SB 9200 is being currently evaluated both as a monotherapy and in combination with Viread® in global Phase II clinical trials.

4:00 CRV431: Exploring the Cyclophilin Inhibitor Mode of Action in HBV
Robert T. Foster, Pharm.D., Ph.D., CSO, ContraVir Pharmaceuticals Inc. and Professor, Pharmacy & Pharmaceutical Sciences, University of Alberta, Canada
CRV431 is a proprietary host targeting cyclophilin inhibitor designed for the treatment of hepatitis B viral infection. The detailed mode of action of CRV431 is being examined and has thus far been shown to abrogate binding between cyclophilin A and two important viral proteins, HBsAg and HBx. These proteins play a vital role in the pathogenesis of infection and the propagation of liver disease.

4:30 Therapeutic Development for HIV and Emerging Diseases: Targeting TLR7 and other Approaches
James B. Whitney, Ph.D., Assistant Professor, Harvard Medical School, the Ragon Institute of MGH, MIT, and Harvard and the Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center

5:00 Close of Symposium

5:00 Pre-Conference Dinner Short Course Registration
Click here for details on short courses offered.

**Separate registration is required for short courses and symposia.*

Cambridge 25 YEARS HEALTHTECH Institute
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Cambridge 25 YEARS HEALTHTECH Institute
A Division of Cambridge Innovation Institute

6th Annual | September 26-27, 2017

Targeting Histone Methyltransferases and Demethylases

Inhibitors, Tools and Strategies for Modulating Histone Methylation

Targeting the histone methylome as a therapeutic strategy continues to capture the interest of developers due to the genetic and expression abnormalities displayed in a variety of human cancers, as well as the chemically tractable nature of modifying enzymes. Over the past few years, developers have intensely pursued these targets, resulting in the rapid entry of histone methyltransferase (HMT) and histone demethylases (HDM) inhibitors into the clinic. Recently, interest in developing inhibitors against arginine methyltransferase enzymes, targeting of protein-protein interactions of enzyme complexes, and designing HMT and HDM inhibitors for combination cancer immunotherapy have provided new avenues for continued development.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Immunomodulatory Small Molecules
- September 25 Short Course: Covalent Fragments: Applications in Target-Based and Phenotypic Screens
- September 26-27 Conference: Targeting Histone Methyltransferases and Demethylases
- September 27-28 Conference: Next-Generation Histone Deacetylase Inhibitors
- September 27 Short Course: Impact of Convergence of Immunotherapy and Epigenetics on Drug Discovery
- September 28-29 Symposium: CNS and Neurodegenerative Targets

TUESDAY, SEPTEMBER 26

7:00 am Registration Open and Morning Coffee

ADVANCES IN THE DISCOVERY OF HISTONE METHYLTRANSFERASE INHIBITORS

8:00 Welcome Remarks
Kip Harry, Senior Conference Director, Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks
Dafydd Owen, Ph.D., Associate Research Fellow, Pfizer

8:10 KEYNOTE PRESENTATION: Discovery of Selective Inhibitors for Histone Methyltransferases
Jian Jin, Ph.D., Professor, Departments of Pharmacological Sciences and Oncological Sciences, Icahn School of Medicine at Mount Sinai
Histone methyltransferases (HMTs) have received great attention as a new class of potential therapeutic targets. High-quality selective inhibitors of HMTs will permit biological and disease hypotheses concerning these enzymes to be tested with high confidence in cell-based and/or animal models. Our laboratory has made significant progress on discovering selective inhibitors of HMTs by pursuing three complementary structure-based inhibitor discovery approaches. Our recent discoveries of selective HMT inhibitors using these approaches will be presented.

8:40 Structure of the PRC2 Complex: Implications for Inhibitor Discovery
Karen A. Maegley, Ph.D., Associate Research Fellow, Pfizer
Several inhibitors of PRC2 activity have shown efficacy in EZH2-mutated lymphomas and are currently in clinical development, although the molecular basis of inhibitor recognition remains unknown. The crystal structures of the inhibitor-bound wild-type and Y641N PRC2 illuminate an important role played by a stretch of 17 residues in the N-terminal region of EZH2 in inhibitor recognition and the potential development of mutation-mediated drug resistance. This work provides new insights for the design and development of next-generation PRC2 inhibitors.

9:10 Crosstalk Affects Activity of Histone Methyltransferases
Masoud Vedadi, Ph.D., Principal Investigator, Molecular Biophysics, Structural Genomics Consortium; Assistant Professor, Department of Pharmacology and Toxicology, University of Toronto
Histone methyltransferases (HMTs) are involved in a broad range of biological processes. Their roles in regulation of gene expression have been extensively studied in relation to diseases including cancers. Here we will discuss the data indicating how the activities of some HMTs are affected by crosstalk between methylation and other histone posttranslational modifications.

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

NOVEL HISTONE METHYLTRANSFERASE INHIBITORS

10:25 An S-Adenosyl Methionine-Inspired Chemical Probe for SMYD2
Dafydd Owen, Ph.D., Associate Research Fellow, Pfizer
Research into Histone Methyltransferases (HMTs) has benefitted from the disclosure of high-quality chemical probes from the scientific community. Higher-quality tools, available with no restriction on use, enable the small molecule perturbation cell biology as we study the role and function of poorly understood targets in human disease. While chemical probes for HMTs have been identified binding in both the substrate and co-factor sites, molecules that predominantly compete with the co-factor S-Adenosyl Methionine (SAM) are in the minority. The talk will discuss why that may be and disclose an inhibitor of SMYD2 that was designed starting from SAM as the initial screening hit.

10:55 Development of Sinefungin Derivatives as Selective Protein Methyltransferases Inhibitors
Xiaochuan Cai, Ph.D., Research Scientist, Lou Lab, Chemical Biology Program, Memorial Sloan Kettering Cancer Center
Our recent progress highlights the development of sinefungin analogues as selective PMT inhibitors, guided by molecular rationale based on *in silico* simulation and X-ray crystallography. Here we concluded that even closely related PMTs can adopt distinct conformational states, though not necessarily for the apo-enzymes, and thus be selectively recognized by small molecule inhibitors.

11:25 Fragment-Based Discovery of WDR5-MLL1 Disruptors
Shaun Stauffer, Ph.D., Research Assistant Professor, Pharmacology; Associate Director, Medicinal Chemistry, Vanderbilt University
Fragment-based screening methods coupled with X-ray crystallography offer the potential for rapid optimization of high-affinity ligands for target protein. We have utilized this approach to afford small molecule disruptors of the WDR5-MLL1 complex with subnanomolar affinity.

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

TARGETING THE PPI OF PRC2

1:50 Chairperson's Remarks
Masoud Vedadi, Ph.D., Principal Investigator, Molecular Biophysics, Structural Genomics Consortium; Assistant Professor, Department of Pharmacology and Toxicology, University of Toronto

1:55 Targeting the PRC2 Complex through a Novel Protein-Protein Interaction Inhibitor of EED
Chaohong Sun, Ph.D., Senior Principal Research Scientist; Head, Fragment Based Drug Discovery, and Global Protein Sciences-Small Molecule, AbbVie
In this talk, we will present our discovery of A-395, a first-in-class antagonist of PRC2 protein-protein interactions (PPI). A-395 binds potently to EED, thereby allosterically inhibiting activity of PRC2 complex. It showed potent cellular activity and comparable *in vivo* activities to known EZH2 enzymatic inhibitors and furthermore, retained potent activity against cell lines resistant to the catalytic inhibitors, suggesting potential clinical benefits of this novel mechanism of targeting PRC2 complex.

2:25 Using Fragments to Find New Ways to Inhibit MethylTransferases
Gregg Siegal, Ph.D., Lecturer, Faculty of Science, Leiden Institute of Chemistry, Leiden University
The small size of fragments enables them to be used as probes of surface features that more lead-like compounds would miss. Careful design of biophysical binding assays can be used to efficiently sort out different binding sites and, where the target is an enzyme, the biological activity of hits can usually be determined rapidly. Using such an approach, we have discovered two novel small molecule binding sites on Dot1L and a new, non-nucleotide scaffold that targets the SAM co-factor site. The mode of action of these compounds was confirmed through X-ray crystallography studies. This is a perfectly general approach that can be used against an array of pharmaceutically relevant targets.

2:55 Selected Poster Presentation: LSD1 Modulation by Allosteric Ligands
Bremberg Ulf, Ph.D., CSO, Beactica AB

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

TARGETING JMJC-DOMAIN CONTAINING HISTONE DEMETHYLASE

4:05 FEATURED PRESENTATION: Metabolic Regulation of Histone Lysine Demethylases
Udo Oppermann, Ph.D., Professor, Molecular Biology; Director, Molecular Laboratory Sciences, Botnar Research Centre; Principal Investigator, Epigenetics and Metabolism, Structural Genomics Consortium, University of Oxford
Several classes of chromatin modifying enzymes utilize as cofactors metabolic intermediates such as S-adenosylmethione, acetyl-CoA, 2-oxoglutarate or NAD+, respectively, whose concentrations are subject to nutritional status and impact on global protein acetylation and methylation patterns. In this presentation our ongoing work will be presented that is related to metabolic regulation, inhibitor development and dependencies of histone demethylases in the context of chromatin modification.

4:35 Targeting JARID1/KDM5 Demethylases in Breast Cancer and Melanoma
Jian Cao, Ph.D., Associate Research Scientist, Department of Pathology, Yale School of Medicine
We have discovered novel mechanisms by which the KDM5 family histone demethylases regulate gene expression and promote tumorigenesis in breast cancer and melanoma. We also developed and evaluated inhibitors with selective specificity against the KDM5 family members, as well as pan-KDM5 inhibitors. These inhibitors could be further developed to target KDM5 histone demethylases in breast cancer and melanoma.

INTERACTIVE BREAKOUT DISCUSSION GROUPS

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

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. Details on the topics and moderators are available on the conference website.

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

7:10 Close of Day

WEDNESDAY, SEPTEMBER 27

7:30 am Registration Open and Morning Coffee

DISCOVERY AND DEVELOPMENT OF LSD1 INHIBITORS

8:00 Chairperson's Remarks
Udo Oppermann, Ph.D., Professor, Molecular Biology; Director, Molecular Laboratory Sciences, Botnar Research Centre; Principal Investigator, Epigenetics and Metabolism, Structural Genomics Consortium, University of Oxford

8:05 FEATURED PRESENTATION: Investigation of GSK2879552 in Combination with ATRA in AML
Helai Mohammad, Ph.D., Scientific Leader, Fellow, Cancer Epigenetics DPU, GlaxoSmithKline
GSK2879552, an inhibitor of lysine demethylase 1 (LSD1), can promote differentiation and inhibit the growth of human acute myeloid leukemia (AML) cells. Treatment of non APML-AML cell lines with the combination of GSK2879552 and ATRA results in enhanced growth inhibition and cytotoxic response. Supra-additive effects were observed upon evaluation of cell surface markers associated with myeloid differentiation and caspase activation, a hallmark of apoptotic cell death.

8:35 INCB059872, LSD1 Specific Inhibitor, as a Potential Therapeutic Agent for Advanced Malignances
Sang Hyun Lee, Ph.D., Principal Scientist, Pharmacology, Incyte Corporation
LSD1 functions as an epigenetic eraser, and its overexpression is associated with many human cancers. We have previously reported that a LSD1 specific inhibitor, INCB059872, potently inhibits tumor cell growth in preclinical models of AML and SCLC. This presentation will focus on the exploration of the potential therapeutic utility of INCB059872 in additional cancer indication and in novel combination therapeutic strategies.

9:05 Coffee Break in the Exhibit Hall with Poster Viewing

10:20 Development of Lysine-Specific Demethylase Inhibitors for Oncological and Neurodegenerative Disease
Tamara Maes, Ph.D., Co-Founder, Vice President & CSO, Oryzon Genomics S.A.
Here we will discuss the advances in the development of ORY-1001, a potent selective inhibitor of LSD1, for the treatment of leukemia and other malignancies; and of ORY-2001, a dual inhibitor of LSD1 and MAO-B, for the treatment of neurodegenerative diseases. ORY-1001/RG6016 has finalized in a Phase I/IIa trial in recurrent or recalcitrant acute leukemia and is currently in a Phase I trial for small cell lung cancer. A Phase I trial with ORY-2001 to assess the compounds' tolerability, pharmacokinetics and pharmacodynamics in healthy young and elderly volunteers is nearing finalization and the compound is being moved forward in neurodegenerative diseases including Alzheimer's and multiple sclerosis.

10:50 Chemical Probes Targeting Histone Modification for Cancer Research and Therapy
Yongcheng Song, Ph.D., Associate Professor, Department of Pharmacology, Baylor College of Medicine

11:20 Enjoy Lunch on Your Own

12:35 pm Plenary Keynote Program
(click here for details)

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

2:45 Close of Conference

Cambridge 25 YEARS HEALTHTECH Institute
A Division of Cambridge Innovation Institute

11th Annual | September 27-28, 2017

Next-Generation Histone Deacetylase Inhibitors

New Biology. New Chemistries. New Combinations.

Histone deacetylases (HDACs) have proven to be a promising target for drug intervention, and there are a number of HDAC inhibitors (HDACi) currently being tested at various preclinical and clinical stages. HDACi were primarily developed as anti-tumor agents for cancer, but many are now being explored for treating neurologic, immunologic, metabolic, inflammatory and cardiovascular disorders. More recently, they are being developed as combination treatments along with small molecule cancer immunotherapy agents. This conference on Next-Generation Histone Deacetylase Inhibitors tracks both the scientific and clinical progress being made to better understand the cellular function of this complex drug target family.

RECOMMENDED ALL ACCESS PACKAGE:

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- September 26-27 Conference: Targeting Histone Methyltransferases and Demethylases
- September 27-28 Conference: Next-Generation Histone Deacetylase Inhibitors
- September 27 Short Course: Impact of Convergence of Immunotherapy and Epigenetics on Drug Discovery
- September 28-29 Symposium: CNS and Neurodegenerative Targets

WEDNESDAY, SEPTEMBER 27

11:50 am Conference Registration Open

12:35 pm Plenary Keynote Program
(click here for details)

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

INSIGHTS INTO EMERGING HDAC BIOLOGY

2:45 Welcome Remarks
Tanuja Koppal, Ph.D., Conference Director, Cambridge Healthtech Institute

2:50 Chairperson's Opening Remarks
Timothy A. McKinsey, Ph.D., Associate Professor and Associate Division Head for Translational Research, Director, Consortium for Fibrosis Research and Translation, Department of Medicine, Division of Cardiology, University of Colorado Denver

2:55 Photo-Activatable HDAC Inhibitors for Modulating Inflammation
Pamela Chang, Ph.D., Assistant Professor, Department of Microbiology and Immunology, Cornell University
The immune system is an essential component of host defense that is mediated by inflammatory molecules produced by immune cells. These inflammatory mediators are regulated at the transcriptional level by chromatin-modifying enzymes including histone deacetylases (HDACs). Here we describe a strategy to regulate inflammation and immunity with photo-controlled HDAC inhibitors, which can be selectively delivered to target cells by light irradiation to minimize off-target effects.

3:25 HDAC Inhibitors for Non-Oncology Indications: Focus on Heart, Kidney and Fat
Timothy A. McKinsey, Ph.D., Associate Professor and Associate Division Head for Translational Research, Director, Consortium for Fibrosis Research and Translation, Department of Medicine, Division of Cardiology, University of Colorado Denver
Obesity is a major risk factor for the development of diabetes, heart failure and chronic kidney disease. I will discuss our recent findings that suggest novel roles for specific HDAC isoforms in the control of obesity, glucose tolerance and cardiorenal disease, and the potential for isoform-selective HDAC inhibitors for the treatment of heart, kidney and metabolic dysfunction.

3:55 Drug Safety for Epigenetic Drugs: What Should Be Done?
Kevin S. Sweder, Ph.D., DABT, Director, The Forensic and National Security Sciences Institute, Center for Science & Technology, Syracuse University
The ability of non-genotoxic agents to induce cancer has been documented and a reassessment of testing for environmental and human safety is required. Drug safety testing has relied on genetic toxicology assays designed to detect DNA damage leading to mutation and cancer, which are not suitable for compounds that function through epigenetic changes. How then might we predict long-term downstream effects through epigenetic mechanisms?

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

5:00 Selective HDAC Inhibition in Pulmonary Arterial Hypertension
Hyung J. Chun, M.D., FAHA, Associate Professor of Medicine, Section of Cardiovascular Medicine, Yale School of Medicine
Pulmonary arterial hypertension (PAH) is a rare disease involving the remodeling of the pulmonary arterioles that leads to increased pulmonary vascular resistance and right heart failure. Emerging studies have demonstrated efficacy of HDAC inhibitors as a therapeutic strategy in experimental models of PAH. Recent evidence supporting the role for selective HDAC class IIA inhibition will be discussed.

5:30 HDAC6 Inhibitors, Autophagy, Mitochondrial Movement, and Disease Modification
Alan P. Kozikowski, Ph.D., CEO and President, StarWise Therapeutics LLC
In this lecture I will present information on the design, synthesis, and testing of ligands that are highly selective for HDAC6 inhibition and show the effects of these compounds in animal models of diseases such as Rett syndrome, Alzheimer's disease, Charcot Marie Tooth disease, cancer, and stroke.

6:00 Close of Day

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

THURSDAY, SEPTEMBER 28

7:30 am Registration Open

8:00 Interactive Breakout Discussion Groups with Continental Breakfast
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. Details on the topics and moderators are available on the conference website.

HDACİ FOR CANCER IMMUNOTHERAPY AND COMBINATION THERAPIES

9:00 Chairperson's Remarks
Stephen Shuttleworth, Ph.D., COO and CSO, Karus Therapeutics Ltd.

9:05 Epigenetic Targeting of Foxp3+ Treg Cells to Promote Anti-Tumor Immunity
Wayne W. Hancock, M.D., Ph.D., Professor of Pathology and Chief of Transplant Immunology, Children's Hospital of Philadelphia and University of Pennsylvania
HDACs such as HDAC1, HDAC2 and HDAC3 function as part of large multi-molecular complexes. We have begun to study the effects of targeting individual HDACs or co-associated proteins within these complexes. This presentation will deal with our successful targeting of individual members of the CoREST complex during cancer and inflammatory responses.

9:35 Epigenetic Priming with New HDAC Class I Inhibitor 4SC-202 Sensitizes Tumor for Anti-PD-1/PD-L1 Therapy
Svetlana Hamm, Ph.D., Head of Translational Pharmacology, 4SC AG
Epigenetic drugs were shown to increase immunogenicity and recognizibility of tumors by immune cells, and there is growing evidence that combination of epigenetic modulators with different cancer immunotherapies results in increased clinical benefit. We have found that 4SC-202, a new oral HDAC class I inhibitor, modulates inflammatory networks in the tumor microenvironment, strongly increases tumor infiltration with tumoricidal cytotoxic T cells and synergizes with anti-PD1/PD-L1 therapy.

10:05 Improving Cancer Immunotherapy with Selective HDAC Inhibitors
Alejandro Villagra, Ph.D., Assistant Professor, Department of Biochemistry and Molecular Medicine, School of Medicine and Health Sciences, The George Washington University
A considerable number of reports have analyzed the role of the specific inhibition of HDACs in cancer as well as processes of immune regulation. This new collection of information has helped the rational design of improved anti-cancer drug candidates to be used as stand-alone or as combination partners in immunotherapeutic approaches. In here, we will discuss the new functional roles of HDAC6 and other HDAC inhibitors as immune regulators in cancer and immune cells, and the new combination strategies being tested to improve immunotherapy.

10:35 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

11:20 Promise of HDAC and IKK Inhibition as Combination Therapy for Solid Tumors
Ivana Vancurova, Ph.D., Professor of Biological Sciences, Department of Biology, Laboratory of Cancer Immunology, St. John's University
We present evidence that may explain the decreased efficacy of HDAC inhibition (HDI) in ovarian cancer (OC), based on our data demonstrating that HDI increases IKK-dependent interleukin-8 expression, which induces OC cell proliferation. Combination of HDI and IKK inhibitors significantly reduces tumor growth in mice, compared to either drug alone, suggesting that IKK inhibitors may increase HDI effectiveness in OC and other solid tumors characterized by increased IL-8 expression.

11:50 Design and Development of KA2507, an Orally-Active HDAC6-Selective Inhibitor with Tumor Immunotherapeutic Activity
Stephen Shuttleworth, Ph.D., COO and CSO, Karus Therapeutics Ltd.

12:20 pm Enjoy Lunch on Your Own

1:50 Refreshment Break in the Exhibit Hall with Poster Viewing

EXPLOITING NEW CHEMISTRIES AND SCREENING PLATFORMS

2:35 Chairperson's Remarks
Ralph Mazitschek, Ph.D., Assistant Professor, Harvard Medical School; Co-Director of the Chemical Biology Platform, Center for Systems Biology, Massachusetts General Hospital

2:40 Non-Catalytic Inhibitors Target the Zinc-Finger Ubiquitin-Binding Domain of HDAC6
Matthieu Schapira, Ph.D., Principal Investigator, Structural Genomics Consortium, University of Toronto
Virtual and fragment-based screens identified a novel class of inhibitors targeting the unique zinc-finger ubiquitin-binding domain of HDAC6. Crystal structures in complex with these screening hits provide a framework for structure-based optimization.

3:10 FEATURED PRESENTATION: Novel Insights about Deacetylation by HDAC6
Patrick Matthias, Ph.D., Senior Group Leader, Friedrich Miescher Institute for Biomedical Research (FMI)
We will present the crystal structure of the two catalytic domains of Histone deacetylase 6 (HDAC6), in complex with the pan-HDAC inhibitor, trichostatin A (TSA) to 1.6Å resolution. The structural backbone of each catalytic domain is highly similar to each other and has overall similarity to other deacetylase domains. We propose a detailed model explaining how HDAC6 can uniquely deacetylate tubulin. We will also discuss the identification of novel substrates and the implications for understanding the activity of this enzyme.

3:40 Session Break

3:55 The Importance of Non-Catalytic Domains of HDAC6 for Interactions with Tubulin
Cyril Bařinka, Ph.D., Principal Investigator, Laboratory of Structural Biology, Institute of Biotechnology, Vestec, Czech Republic
We will present data on interactions between human HDAC6 and tubulin/microtubules. By using single-molecule TIRF microscopy we identified structural features governing HDAC6 binding to assembled microtubules. Furthermore, we detailed the influence of HDAC6 on microtubule assembly and dynamics. Our data show that structural motifs beyond the HDAC6 catalytic domains play an important role in HDAC6/tubulin interactions and influence microtubule dynamics.

4:25 Light-Controlled Epigenetics
Ralph Mazitschek, Ph.D., Assistant Professor, Harvard Medical School; Co-Director of the Chemical Biology Platform, Center for Systems Biology, Massachusetts General Hospital

4:55 Close of Conference

5th Annual | September 26-27, 2017

Targeting the Ubiquitin Proteasome System

Modulating Protein Homeostasis by Targeting DUBs and E3 Ligases

The ubiquitin proteasome system (UPS) is an essential and highly regulated mechanism operating to tightly control intracellular protein degradation and turnover. Advances in our understanding of the role and molecular mechanisms of UPS components in disease and the development of high-quality chemical tools and novel inhibitors have taken the Ubiquitin Proteasome System from an improbable target class to one of the most robust and exciting arenas for the discovery of novel drugs. Over the past years, we have seen the generation of several DUB inhibitors poised for clinical development, novel approaches and inhibitors disrupting the protein-protein interactions of E3 ligases, and most recently, hijacking the UPS for targeted protein degradation.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Targeting Autophagy
- September 25 Short Course: Covalent Fragments: Applications in Target-Based and Phenotypic Screens
- September 26-27 Conference: Targeting the Ubiquitin Proteasome System
- September 27-28 Conference: Kinase Inhibitor Discovery
- September 27 Short Course: Introduction to Targeted Covalent Inhibitors
- September 28-29 Symposium: CNS and Neurodegenerative Targets

TUESDAY, SEPTEMBER 26

7:00 am Registration Open and Morning Coffee

HARNESSING THE UPS FOR TARGETED PROTEIN DEGRADATION

7:55 Chairperson's Opening Remarks
Ingrid E. Wertz, M.D., Ph.D., Senior Scientist, Discovery Oncology and Early Discovery Biochemistry, Genentech, Inc.

8:00 Session Introduction and Remarks
Craig M. Crews, Ph.D., Lewis B. Cullman Professor of Molecular, Cellular, and Developmental Biology; Professor, Chemistry & Pharmacology, Yale University

8:10 FEATURED PRESENTATION: Targeted Protein Degradation by Small Molecules
Alessio Ciulli, Ph.D., Professor, Chemical & Structural Biology, School of Life Sciences, University of Dundee
The application of small molecules to induce selected protein degradation is emerging as a transformative new modality of chemical intervention in drug discovery. We have previously shown that linking a VHL ligand that we had discovered with a pan-BET inhibitor creates highly selective PROTAC molecule MZ1. MZ1 triggers preferential intracellular degradation of Brd4, leaving the homologous BET members untouched, and exhibits greater anti-proliferative activity in leukemia cell lines than pan-BET inhibition.

8:40 Target Protein Degradation for New Therapeutics
Shaomeng Wang, Ph.D., Warner-Lambert/Parke-Davis Professor, Medicine; Professor, Medicine, Pharmacology and Medicinal Chemistry; Director, Center for Therapeutics Innovation, University of Michigan
Recently, a new small-molecule approach has been employed to target degradation of BET proteins through the design of bifunctional, Proteolysis-Targeting Chimera (PROTAC) molecules. Based upon our new classes of highly potent small-molecule BET inhibitors, we have designed and optimized highly potent and efficacious small-molecule degraders of BET proteins. We have performed critical and extensive evaluation of our BET degraders for their therapeutic potential and mechanism of action in models of acute leukemia and solid tumors.

9:10 Targeted Protein Degradation via Redirecting the Action of CRL4 E3 Ligases
Brian Cathers, Ph.D., Executive Director, Co-Leader & Head, Drug Discovery, Protein Homeostasis Thematic Center of Excellence, Celgene
Distinct cereblon binding molecules evoke different phenotypic responses yet bind the same target. Solution of the ligand bound CRBN complex provides a rationale for distinguishing "gain of function" targeting of key substrates including the transcription factors Aiolos and Ikaros, the protein kinase CK1α, or the translation termination factor GSPT1. Is it possible to harness the action of a single E3 ligase and direct its actions toward new and different substrates? Are other ligases able to be co-opted in a similar fashion?

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

KEYNOTE SESSION

10:25 KEYNOTE PRESENTATION: Covalent Inhibitors and Degraders of Challenging Targets in Cancer
Nathanael Gray, Ph.D., Professor, Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School; Professor, Cancer Biology, Dana-Farber Cancer Institute
This presentation will discuss new pharmacological strategies towards targeting kinases and other targets. Small molecules capable of inducing protein degradation through the recruitment of E3 ligases will be discussed with a focus on kinases. A general approach for identifying the most easily degradable kinase targets will be presented. Chemical design principles for developing degraders will be discussed. New approaches for developing covalent kinase inhibitors will also be discussed.

11:10 KEYNOTE PRESENTATION: PROTACs: The Chemical Equivalent of CRISPR
Craig M. Crews, Ph.D., Lewis B. Cullman Professor of Molecular, Cellular, and Developmental Biology; Professor, Chemistry & Pharmacology, Yale University
Induced protein degradation offers several advantages over traditional inhibition strategies and has emerged recently as a potential therapeutic option. For the past 16 years, we have helped develop this fast growing field, shepherding our initial chemical biology concept into a drug development strategy that is on the verge of clinical validation. PROTACs with high target selectivity, potency, and oral bioavailability will be discussed as well as a system to address the 'PROTACability' of particular E3 ligases.

11:55 Selected Poster Presentation: Induced Degradation of Bcl-xL: A Protac Approach to Target the Achilles' Heel of Senescent Cells
Xuan Zhang, Research Scientist, College of Pharmacy, University of Arkansas for Medical Sciences

12:10 Enjoy Lunch on Your Own

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

DESIGN AND DEVELOPMENT OF NOVEL DUB INHIBITORS

1:50 Chairperson's Remarks
Gerald Gavory, Ph.D., Head, Biology, Alma Discovery

1:55 Ubiquitin -Omics for Target Discovery in Human Disease
Benedikt Kessler, Ph.D., Professor of Biochemistry and Life Science Mass Spectrometry, Target Discovery Institute, Nuffield Department of Medicine, University of Oxford
Mass spectrometry can now cover the proteome in the ten thousand range, and ubiquitylation can be profiled in the thousands, covering enough depth to interrogate DUB and E3 ligase substrates. The ubiquitin-specific protease USP7 was suggested as a potential drug target for Multiple Myeloma, where the treatment with small molecule USP7 inhibitors overcomes resistance to clinical proteasome inhibitors. We have utilized activity-based profiling, chemical proteomics and structural analysis to determine the potency of novel deubiquitylating enzyme inhibitors.

2:25 Developing a Quantitative Profiling Platform to Evaluate Endogenous Deubiquitinase Activity
Ingrid E. Wertz, M.D., Ph.D., Senior Scientist, Discovery Oncology and Early Discovery Biochemistry, Genentech, Inc.
Here we describe the development of an analysis platform that combines DUB ABPs with chemical multiplexing, targeted mass spectrometry, novel internal reaction standards, and a customized statistical analysis program. Our strategy allows us to quantitate changes in DUB activity across a theoretically unlimited number of samples in a high-throughput manner. We illustrate the efficacy of this technology by evaluating the activity of disease-relevant DUBs, in analyzing DUB inhibitor selectivity, and in evaluating how compounds impact DUB activity.

2:55 An Integrated Chemistry and Assay Platform to Enable and Support Ubiquitin-System Targeted Drug Discovery
Sponsored by UBIQUIGENT
Jason Brown, Ph.D., Scientific Director, Ubiquigent Ltd.

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

4:05 Small Molecule Ubiquitin Protease (USP7) Inhibitors with Immune Cell Based Anti-Tumor Activity Superior to that of Biologicals
Tauseef R. Butt, Ph.D., President and CEO, Progenra, Inc.
In immune competent animal models, USP7 inhibitors are potent anti-tumor agents, not only blocking tumor growth but also eliminating tumor metastasis. These results constitute the first example of a small molecule single agent that works by targeting both the tumor itself and the host immune system and also by eliminating tumor metastasis. In animal models, the USP7 inhibitor demonstrates activity that is superior to that of PD1 and CTLA4 antibodies.

4:35 Development and Further Exploitation of UbiPlex - A Proprietary Drug Discovery Platform for DUBs
Gerald Gavory, Ph.D., Head, Biology, Alma Discovery
We will describe our latest efforts and developments in targeting members of the DUB family using USp7, USP19 and new DUBs as case examples. UbiPlex delivered the first genuine and highly potent and selective inhibitors of multiple DUBs hence demonstrating the druggability and tractability of this so far refractory target class.

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. Details on the topics and moderators are available on the conference website.

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

7:10 Close of Day

WEDNESDAY, SEPTEMBER 27

7:30 am Registration Open and Morning Coffee

DIVERSE STRATEGIES MODULATING THE UPS

8:00 Chairperson's Remarks
Benedikt Kessler, Ph.D., Professor, Biochemistry and Life Science Mass Spectrometry, Target Discovery Institute, Nuffield Department of Medicine, University of Oxford

8:05 Mining the Deubiquitinase Family for Novel Drugs Utilizing FORMA's Drug Discovery Engine
Stephanos Ioannidis, Ph.D., Head, Early Portfolio, FORMA Therapeutics
The deubiquitinating enzymes (DUBs), by their reversal of the ubiquitination/polyubiquitination process, are key enzymes regulating protein homeostasis. As such, modulators of DUB function have the potential to be important therapeutics in oncology, immunology, neurodegenerative and other medical disorders involving pathological or dysregulated proteins. FORMA Therapeutics deploys multiple drug discovery screening platforms to explore broad target families on scale. Panels of functional cellular and enzymatic assays, including related target family selectivity screens, were established to mine the DUBome for novel chemical matter. Early chemistry activities exploited use of automated parallel synthesis for confirmed chemical matter, applying computational and crystallographic insights into structurally novel series as well as DUB hopping chemical scaffolds across the target family. As part of a fully integrated R&D team, FORMA engages key collaborators and collaborative networks to assist in the interrogation of biological hypotheses, target validation and selection of preferred mechanisms of action for

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advancement. FORMA's novel approach to DUBs resulted in the identification of a novel chemical series that potently inhibits USP7.

8:35 Targeting Ubiquitin-Like Protein Activation
Lawrence Dick, Ph.D., Director, Biochemistry, Oncology Drug Discovery Unit, Takeda Pharmaceuticals International Co.
Pevonedistat (aka TAK-924 or MLN4924) is an inhibitor of the NEDD8 activating enzyme (NAE) currently in a Phase II trial for patients with higher-risk MDS, CML and low-blast AML (NCT02610777). Pevonedistat resembles the nucleotide substrate of NAE and it inhibits NAE by a mechanism termed "substrate-assisted inhibition" in which the NAE-NEDD8 thioester form of the enzyme catalyzes formation of a NEDD8-pevonedistat adduct that remains tightly bound to the enzyme. The activating enzymes for UBL conjugation pathways share a common enzymatic mechanism so that in principle, substrate-assisted inhibition can be applied to ubiquitin, SUMO, and the other UBL conjugation pathways. In practice, we have discovered a specific inhibitor of ubiquitin activation, TAK-243 (aka MLN7243), and a SUMO activating enzyme specific inhibitor, ML-792.

9:05 Selected Poster Presentation: Evaluation and Characterization of Small Molecule Inhibitors of Deubiquitinating Enzyme USP14 as Potential Anti-Cancer Agents
Stina Lundgren, Ph.D., Senior Research Scientist, Medivir AB

9:20 Selected Poster Presentation: Targeting Deubiquitinases (DUBs) in Lung Cancer Using Activity Based Protein Profiling (ABPP)
Shikha Mahajan, Research Scientists, Moffitt Cancer Center

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

TARGETING THE PPIs OF E3 LIGASES

10:20 HECT E3 and RBR E3 Ligases as Drug Targets to Treat Cancer and Neurodegenerative Diseases: Basic Science and New Screening Technologies
Alexander Statsyuk, Ph.D., Assistant Professor, Department of Pharmacological and Pharmaceutical Sciences, University of Houston
E3 ligases (>600 known) are the key mediators of protein degradation pathways, and E3 ligase inhibitors or activators are promising drug leads. In addition, E3 ligases can be executors that mediate the degradation of PROTAC targets. In this presentation, we specifically discuss emerging biochemical mechanisms and biological roles of HECT and RBR E3 ligases, their therapeutic potential to treat cancers and neurodegenerative diseases, and current screening technologies to discover initial drug leads for this class of drug targets.

10:50 Inhibition of an E2/E3 Protein-Protein Interaction as a Novel Strategy to Interfere with E3 Ligase Activity
Kamyar Hadian, Ph.D., Principal Investigator & Head, Assay Development and Screening Platform, HelmholtzZentrum München
This lecture will give insights into the discovery of a novel E2/E3 protein-protein interaction small molecule inhibitor that we were able to validate and characterize in a variety of biochemical as well as cell-based assays including primary mouse and human cells. More importantly, we can show that this first-in-class inhibitor is effective in preclinical autoimmune mouse models for psoriasis as well as rheumatoid arthritis.

11:20 Enjoy Lunch on Your Own

12:35 pm Plenary Keynote Program
(click here for details)

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

2:45 Close of Conference

STUDENT FELLOWSHIP

Full-time graduate students and Ph.D. candidates are encouraged to apply for the Discovery on Target Student Fellowship. Applications are due by July 14, 2017.

- Interested students must complete the online application for the 2017 Student Fellowship.
- Fellows are required to present a scientific poster. A poster title and abstract are due at the time of the application.
- All applications will be reviewed by the scientific review committee and students will be notified if they were accepted for the 2017 Student Fellowship.
- Accepted 2017 Student Fellows will receive a discounted conference rate of $195*, which must be paid in full by August 4, 2017. Credit card information is requested at the time of the application and will be charged upon application approval.
- This fellowship is limited to 20 students and is for the Standard Package (Main Conference Only*), September 26-28, 2017.
- All accepted 2017 Student Fellows will be asked to help promote the conference onsite at their college, and throughout their social media networks.
- Students not accepted for the 2017 Student Fellowship can register at a discounted rate of $295*, and will not be required to present a poster.

**This discounted rate cannot be combined with any other discounts for this event. Your discounted registration does not grant access to any of the short courses, training seminars or symposia. It also does not include hotel, travel or meals.*

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10th Annual | September 27-28, 2017

Kinase Inhibitor Discovery

Emerging Targets, Tools and Development Strategies

The human kinome is a large and highly druggable class of targets spanning numerous disease indications, and accounts for a significant portion of drug discovery efforts. Kinase inhibitor discovery remains a very active area as developers are exploring more deeply into the human kinome, 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.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Immunomodulatory Small Molecules
- September 25 Short Course: Covalent Fragments: Applications in Target-Based and Phenotypic Screens
- September 26-27 Conference: Targeting the Ubiquitin Proteasome System
- September 27-28 Conference: Kinase Inhibitor Discovery
- September 27 Short Course: Introduction to Targeted Covalent Inhibitors
- September 28-29 Symposium: CNS and Neurodegenerative Targets

WEDNESDAY, SEPTEMBER 27

11:50 am Conference Registration Open

12:35 pm Plenary Keynote Program
(click here for details)

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

ADVANCES IN COVALENT KINASE DISCOVERY AND DESIGN

2:45 Welcome Remarks
Kip Harry, Senior Conference Director, Cambridge Healthtech Institute

2:50 Chairperson's Opening Remarks
Doriano Fabbro, Ph.D., CSO, Piqur Therapeutics

2:55 Opportunities and Pitfalls in Characterizing Covalent Kinase Inhibitors during Lead Optimization
Christopher Harris, Ph.D., Associate Director, AbbVie
This presentation will discuss a category of experiments that qualitatively confirm the mechanism of action, but are not otherwise enlightening. However, measuring apparent binding (K_i) and reactivity (k_{inact}) components, or their ratio (k_{inact}/K_i), can inform optimization of these components. We will discuss how to measure such at scale. Lastly, this talk will address selectivity: comparing covalent vs. non-covalent selectivity, and how failing to account for time dependence misrepresents off-target liabilities.

3:25 Discovery of the Covalent FGFR1-4 Inhibitor PRN1371 for the Treatment of Solid Tumors
Michael Bradshaw, Ph.D., Associate Director, Principia Biopharma
We have developed a selective, irreversible covalent inhibitor of FGFR1-4, PRN1371, by targeting a cysteine residue within the kinase domain. PRN1371 demonstrates highly selective and long lasting inhibition of FGFR which extends beyond drug clearance from circulation. Strong inhibition was also sustained toward clinically relevant FGFR mutations and translocations. In addition, durable tumor regression was obtained in multiple rodent xenograft models and was sustained even using an intermittent dosing strategy that provided drug holidays.

3:55 3DM Protein-Family Analysis Platform Applied to the Kinase Protein-Family
Sponsored by bio-prodict
Henk-Jan Joosten, Ph.D., CEO, Bio-Prodict
Vast amounts of data are available for protein-families (e.g., sequences, literature, structural-, alignment-, SNP-, mutation-, patent-, binding data). 3DM, a protein-superfamily analysis platform, automatically collects and integrates all data and contains many state-of-the-art analysis tools. 3DM is used by many companies, including large pharma, to guide structure-based drug design.

4:10 Sponsored Presentation *(Opportunity Available)*

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

KINASE INHIBITORS FOR CANCER IMMUNOTHERAPY COMBINATIONS

5:00 Design and Development of a Novel, Selective PI3K-p110β/δ Inhibitor, KA2237, for the Treatment of Cancer
Stephen Shuttleworth, Ph.D., COO and CSO, Karus Therapeutics Ltd.

5:30 Discovery of a PI3Kβ/δ Inhibitor for the Treatment of PTEN-Deficient Tumors: Building PI3Kβ Potency in a PI3Kδ-Selective Template
Stephane Perreault, Ph.D., Research Scientist II, Medicinal Chemistry, Gilead Sciences, Inc.
The design, optimization, and *in vivo* evaluation of a novel series of PI3Kβ/δ inhibitors in which PI3Kβ potency was built in a PI3Kδ-selective template will be presented. This work led to the discovery of a highly selective PI3Kβ/δ inhibitor displaying excellent pharmacokinetic profile and efficacy in a human PTEN-deficient LNCaP prostate carcinoma xenograft tumor model. Phosphoinositide 3-kinase β (PI3Kβ) signaling is required to sustain cancer cell growth in which the tumor suppressor phosphatase and tensin homolog (PTEN) has been deactivated.

6:00 FEATURED PRESENTATION: Inhibition of PI3K and Tubulin
Doriano Fabbro, Ph.D., CSO, Piqur Therapeutics
The PI3K signaling pathway is frequently activated in tumors. PQR309 is a selective dual inhibitor of PI3K and mTOR (currently in Phase I) in cancer patients. The preclinical pharmacology

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and toxicology of PQR309 is presented, including its activity in lymphoma preclinical models. In addition, we elucidate structural factors defining the PI3K inhibitory activity and tubulin-binding of PQR309 derivatives.

6:30 Close of Day

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

THURSDAY, SEPTEMBER 28

7:30 am Registration Open

8:00 Interactive Breakout Discussion Groups with Continental Breakfast
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. Details on the topics and moderators are available on the conference website.

OPTIMIZING NEXT-GENERATION KINASE INHIBITORS

9:00 Chairperson's Remarks
Gerhard Müller, Ph.D., CSO, Gotham Therapeutics

9:05 Target Residence Time-Guided Optimization of TTK Kinase Inhibitors
Guido J.R. Zaman, Ph.D., Managing Director & Head of Biology, Netherlands Translational Research Center B.V. (NTRC)
We studied NTRC 0066-0, a selective inhibitor of TTK, together with eleven TTK inhibitors from different chemical classes developed by others. Parallel testing showed that the cellular activity of the TTK inhibitors correlates with their binding affinity and, more strongly, with target residence time. X-ray structures revealed that the most potent inhibitors induce a unique structural conformation. Based on this insight, new TTK inhibitors were developed with longer target residence times and very potent anti-proliferative activity.

9:35 Structure-Based Design of Long Residence Time into Novel Kinase Inhibitors
Gerhard Müller, Ph.D., CSO, Gotham Therapeutics
The presentation focuses on the engineering of binding kinetic signatures into "deep-pocket-directed" scaffolds for achieving high-efficacy kinase inhibitors. We will demonstrate that a thorough understanding of the precise pharmacophoric requirements on the target's binding site is essential to pre-engineer the desired slow off-rates into new, thus literature-unprecedented scaffolds that qualify as privileged structures for the target family of kinases. The details of the so-called "retro-design" approach for type II kinase inhibitors will be exemplified by hit-to-lead and lead optimization campaigns that yielded novel and highly efficacious inhibitors for a variety of kinases. Special emphasis will be laid on optimizing selectivity of inhibitors against CDK8, a novel and interesting anti-cancer target.

10:05 KEYNOTE PRESENTATION: Selective Targeting of Kinase Catalytic and Non-Catalytic Function
Stefan Knapp, Ph.D., Professor, Department of Pharmaceutical Chemistry, Goethe Institut, Frankfurt
Advances in kinase structural biology led to an excellent structural coverage of the human kinase family and provided insight into the remarkable domain plasticity of the catalytic domain. Our laboratory contributed 75 of the currently ~200 known crystal structures, enabling a family-wide structural analysis for rational design of inhibitors. In this talk I will summarize strategies that led to the development of highly selective inhibitors. I will discuss the discovery of novel inhibitor binding sites including allosteric sites and the exploitation of unusual structural features for the design of highly selective kinase inhibitors including irreversible inhibitors. Structural aspects optimizing inhibitor residence times and mechanisms leading to slow off-rate binding kinetics will also be discussed.

10:35 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

KINASE INHIBITORS FOR CNS AND NEURODEGENERATIVE DISORDERS

11:20 Discovery of MLi-2, a Potent, Selective and Brain Penetrant LRRK2 Inhibitor
Jack D. Scott, Ph.D., Principal Scientist, Merck
Starting from a high-throughput screen (HTS), a series of indazole kinase inhibitors was identified. Optimization of these inhibitors based on ligand efficiency (LE), hepatocyte stability and kinome selectivity led to the identification of MLi-2, a very potent and selective LRRK2 inhibitor that showed robust CNS activity in rodent pharmacodynamic studies. Subsequently MLi-2 has been used to identify previously unknown substrates of LRRK2.

11:50 SPEAKER CANCELLATION: Leucettines, a Class of DYRK1A Inhibitors, as Drug Candidates for the Treatment of Cognitive Deficits Associated with Alzheimer's Disease and Down Syndrome
Laurent Meijer, Ph.D., CEO & CSO, ManRos Therapeutics
There is growing evidence implicating the DYRK1A kinase in the onset and development of neurodegenerative pathologies such as Alzheimer's disease (AD) and Down syndrome (DS). Leucettines, derived from the marine sponge natural product Leucettamine B, represent an archetype of DYRK1A inhibitors. Medicinal chemistry optimization and detailed characterization of Leucettines at the molecular, biochemical, cellular and animal models levels have been carried out extensively. Leucettines are able to cross the blood-brain barrier, to normalize DYRK1A activity, to modify specific phosphorylation patterns and to restore normal cognitive functions in three DS and three AD animal models. These encouraging results advocate for further development of a Leucettine drug candidate as a potential therapeutic agent to treat neurodegenerative diseases and possibly other diseases.

12:20 pm Enjoy Lunch on Your Own

1:50 Refreshment Break in the Exhibit Hall with Poster Viewing

DATA-DRIVEN DESIGN OF KINASE INHIBITORS

2:35 Chairperson's Remarks
Guido J.R. Zaman, Ph.D., Managing Director & Head of Biology, Netherlands Translational Research Center B.V. (NTRC)

2:40 Data-Driven Design of Kinase Inhibitors with Controlled Polypharmacology
Dmitri Kireev, Ph.D., Professor, Chemical Biology & Medicinal Chemistry; Director, Computational Biophysics & Molecular Design, Center for Integrative Chemical Biology and Drug Discovery, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill
The presented multidisciplinary study is centered around a novel computational approach based on FRAgments in Structural Environments (FRASE). The approach was applied to develop inhibitors of closely related immunotherapeutic cancer targets MER, AXL and Tyro3. The efficacy and specificity of our new leads have been investigated and confirmed in multiple biochemical, cellular and animal models, including kinome-wide polypharmacology profiling, acute lymphoblastic leukemia (ALL), melanoma and NSCLC cell lines, as well as a pharmacodynamic study in mice.

3:10 Ligand- and Structure-Based Methods in Predicting Kinase Activity and Selectivity
Istvan Enyedy, Ph.D., Senior Scientist, Drug Discovery, Biogen
Ligand-based methods are fast and may be useful for large-scale modeling like filtering large databases or predicting kinase selectivity. For example, Kriging is useful for predicting the activity of compounds of interest when enough experimental data is available. The fake ligands derived from ATLAS solvent mapping are negative images of the binding site and show promise in identifying active compounds when used as queries in ROCS. These methods can successfully complement hybrid and structure-based methods like POSIT, HYBRID, and FRED.

3:40 Session Break

CASE STUDIES IN KINASE INHIBITOR DESIGN

3:55 Using a Vector-Free Microfluidic CellSqueeze Platform
Jonathan Gilbert, Ph.D., Director, Strategic Partnerships, SQZ Biotechnologies
Pfizer collaborated with SQZ to employ a newly discovered vector-free microfluidic platform, which enables us to deliver membrane impermeable small molecules into cells and subsequently assess their cellular activity by various functional assays. As a proof-of-concept, we demonstrated that, upon "squeezing", a cell impermeable JAK inhibitor probe effectively inhibits the phosphorylation of STAT5 in PBMCs. Finally we show that a series of cell-impermeable JAK inhibitors becomes more potent after squeezing.

4:25 Discovery of a Novel, Highly Potent, and Selective Thieno[3,2-*d*]pyrimidinone-Based Cdc7 Inhibitor with a Quinuclidine Moiety (TAK-931) as an Orally Active Investigational Anti-Tumor Agent
Osamu Kurasawa, Ph.D., Principal Scientist, Medicinal Chemistry, Takeda Pharamaceutical Co. Ltd.
A structure-based approach to circumvent formaldehyde adduct formation culminated in the discovery of TAK-931, possessing a quinuclidine moiety, as a preclinical candidate. In this presentation, the design, synthesis, and biological evaluation of this series of compounds will be presented.

4:55 Close of Conference

Cambridge 25 YEARS HEALTHTECH Institute
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3rd Annual | September 26-27, 2017

Targeting the Microbiome

Discovering Druggable Targets for Microbiome-Therapeutic Development

Cambridge Healthtech Institute's 3rd Annual Targeting the Microbiome tracks the scientific and clinical progress being made to discover and develop microbiome-derived biomarkers, drug targets, and bioactive molecules to improve disease treatment and human health. Through interactive sessions and panel discussions, leading researchers and thought leaders will discuss novel therapeutic targets based on microbiome R&D and the potential of translational interventions, as well as, patent eligibility and investment opportunities.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Microbiome in Immuno-Oncology
- September 26-27 Conference: Targeting the Microbiome
- September 27-28 Conference: Autoimmune and Inflammation Drug Targets
- September 27 Short Course: Impact of Convergence of Immunotherapy and Epigenetics on Drug Discovery
- September 28-29 Symposium: CNS and Neurodegenerative Targets

TUESDAY, SEPTEMBER 26

7:00 am Registration Open and Morning Coffee

TARGETING THE GUT MICROBIOME IN HEALTH & DISEASE: MARKET TRENDS, DATA ANALYSIS, AND STANDARDS

8:00 Welcome Remarks
Cindy Crowninshield, RDN, LDN, HHC, Senior Conference Director, Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks
Sudeep Basu, Ph.D., Practice Leader, TechVision-Innovation Services, Frost & Sullivan

8:10 Human Microbiome Growth Opportunities and Predictions
Sudeep Basu, Ph.D., Practice Leader, TechVision-Innovation Services, Frost & Sullivan
This presentation focuses on recent development in the areas of microbiome-driven therapeutics. An overview of key research groups, disease focus areas and trends will be provided. The discussion will encompass a review of select technologies, markets and products as well.

8:40 The Human Microbiome: Data Challenges and Solutions
Andreas M. Kogelnik, M.D., Ph.D., Director, Open Medicine Institute
Human microbiome analysis is the study of microbial communities found in and on the human body. The goal of human microbiome studies is to understand the role of microbes in health and disease. High throughput methods have enabled increasingly relevant studies with increasing clinical impact that is both surprising and broad-reaching at times. There remains enormous work to be done for data analysis and for application of these technologies.

9:10 Standards for Microbiome and Metagenomics: Supporting the Commercial Translation of Microbiome Science
Scott Jackson, Ph.D., Molecular Genetics and Microbial Genomics, National Institute of Standards and Technology
At NIST, we are improving microbiome science and supporting the National Microbiome Initiative by developing standards for microbiome measurements that will enable federal, academic, and industry labs to reliably reproduce and advance each other's results. Microbiome standards will support research investigations and commercial translation of microbiome science by providing measurement assurance tools: standardized protocols, reference materials, validated measurements and critically evaluated reference data.

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

NOVEL THERAPEUTIC TARGETS BASED ON MICROBIOME R&D, PART I

10:25 Designing Targeted Next Generation Microbial Therapeutics for Inflammatory Diseases
Nikole Kimes, Ph.D., President and CSO, Siolta Therapeutics
The burgeoning field of microbial therapeutics represents an exciting class of biologics that hold great potential for the prevention and treatment of inflammatory diseases. Siolta Therapeutics is particularly focused on the rational design of a mixed-species microbial consortium to treat childhood asthma through the reengineering of the gut microbiome. Our multifaceted approach utilizes patient stratification, immune phenotyping, and rationally designed microbial consortia to provide next generation microbial therapeutics.

10:55 Role of Probiotics to Prevent Viral Chronic Diseases
Imad Al Kassaa, Ph.D., Associate Professor, Microbiology, Lebanese University; Researcher, Laboratoire Microbiologie Sante et Environnement (LMSE)
In this presentation, we discuss the possible role of probiotic strains in chronic viral infections and their benefits in therapy strategies against infectious diseases. Data from numerous studies has shown that the use of probiotic as therapeutic agents is safe and inexpensive and can avoid the need for invasive treatment for several chronic viral infections caused by HIV, HCV, HTLV, HPV, CVB4, etc.

11:25 Subtractive Assembly Approaches for Identification of Disease-Associated Microbial Marker Genes
Yuzhen Ye, Ph.D., Associate Professor, Computer Science, Indiana University, Bloomington
We have developed novel computational approaches for identification of disease-associated microbial marker genes from metagenomic and metatranscriptomic datasets. Application of our approaches to the microbiome datasets associated with type II diabetes and liver cancer demonstrated that our approaches provide simplified yet efficient solutions for identification of disease-related microbial marker genes.

11:55 Gaining Key Functional Insights into the Microbiome Through Metabolomics
Sponsored by METABOLON
Kendra Hightower, Ph.D., Study Director, Metabolon
There is increasing evidence that the microbiome plays an important role in human health and disease. Gaining an understanding of host-microbe interaction and the mechanisms through which the microbiome influences human health can provide new avenues for microbiome research and therapeutic intervention. A key readout of the host-microbe interaction is the metabolome. We will describe how implementing a metabolomics approach to survey the metabolites that broker the host-microbe interaction can enhance insight into this association.

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

1:50 Chairperson's Remarks

1:55 The 7-Day Forecast for Our Health Storm: Exploring the Connection between the Oral Microbiome and Immune-Mediated Inflammatory Diseases, and Personalized Nutrition
Bonnie Feldman, D.D.S., MBA, Digital Health Analyst and Chief Growth Officer, DrBonnie360
The status of our oral health may be an early indicator of other systemic diseases such as diabetes, heart disease, stroke, rheumatoid arthritis and other autoimmune diseases. This talk will present the latest research done on the connection of the oral microbiome to chronic and autoimmune diseases, as well as discuss implementation of the research on the emerging field of personalized nutrition.

2:25 FEATURED PRESENTATION: MycroFriends – Targeting the Microbiome to Help Consumers Nurture and Improve Their Health
George Cigale, Co-Founder & CEO, Mycrobiomics, Inc.
Mycrobiomics helps people get healthier through research, education and coaching on the connection between your microbiome, nutrition and lifestyle choices, and overall health. Our first consumer service launched recently in beta at www.mycrofriends.com. Mycrobiomics was founded in 2015 by George Cigale, Founder and former CEO of Tutor.com and Dr. Harlan Weisman, former President of J&J Pharmaceutical R&D. We are based in NYC and backed by seed investments from Mayo Clinic Ventures and Bloomberg Beta.

2:55 FEATURED PRESENTATION: Patent and Regulatory Update for Microbiome Research
John M. Conley, J.D., Ph.D., William Rand Kenan, Jr. Professor of Law, University of North Carolina, Chapel Hill; Counsel, Robinson Bradshaw & Hinson

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

TARGETING THE GUT MICROBIOME IN HEALTH & DISEASE: COLLABORATION AND INVESTMENT OPPORTUNITIES

4:05 PANEL DISCUSSION: From Microbiome to Market: Exploring Global Scope of Microbiome and Successful Collaboration, Reimbursement, and Business Investment Models
Moderator: Keith F. Batchelder, M.D., CEO and Founder, Genomic Healthcare Strategies
Panelists:
David Donabedian, Ph.D., Venture Partner, Longwood Fund; Chief Executive Officer and Co-founder of Longwood portfolio Company Axial Biotherapeutics
Jonathan Freeman, Chief Business Officer, Vedanta
Denise Kelly, Ph.D., Microbiome Venture Advisor, Seventure Partners
Greg Sieczkiewicz, J.D., Ph.D., Chief IP Counsel, MPM
Cameron Wheeler, Ph.D., Principal, Deerfield Management
This microbiome to market panel discussion serves as a critical ending to the first day of this meeting. Today's agenda has covered themes related to market trends, data analysis, standards, IP challenges, and targeting next generation microbial therapeutics. This panel discussion is appropriate for you if you are working in research, science or industry and have questions about translation opportunities or the kinds of business and financial models that investors find attractive. Leading investors will gather to discuss the areas of the microbiome they are looking at and why. We will explore the global scope of microbiome and successful collaboration, reimbursement, and business investment models between science, business, healthcare, and government in bringing live microbial products to market. We will also discuss balancing venture activities, external R&D, and long-term market opportunities. Join us for a lively and interactive discussion of the how's and what's of bringing your microbiome product or service to market.

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. Details on the topics and moderators are available on the conference website.

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

7:10 Close of Day

WEDNESDAY, SEPTEMBER 27

7:30 am Registration Open and Morning Coffee

NOVEL THERAPEUTIC TARGETS BASED ON MICROBIOME R&D, PART II

8:00 Chairperson's Remarks
Bonnie Feldman, D.D.S., MBA, Digital Health Analyst and Chief Growth Officer, DrBonnie360

8:05 Precision Microbiota Applications in Clinical Therapy and Diagnosis
Georg Gerber, M.D., Ph.D., MPH, FASCP, Assistant Professor of Pathology, Harvard Medical School; Member of the Faculty, Harvard-MIT Health Sciences & Technology; Co-Director, Massachusetts Host-Microbiome Center, and Director of the Computational Unit; Associate Pathologist, Center for Advanced Molecular Diagnostics; Department of Pathology, Brigham & Women's Hospital
The microbiota, or compending of organisms living on and in us, provide essential functions for normal health and physiology. They also contribute to a variety of diseases. This non-human organ is also increasingly being used to develop and target new therapies for a variety of conditions, from *Clostridium difficile* colitis, to treatment of IBD, and other autoimmune, allergic and metabolic diseases.

8:35 Discovering Microbiome-Related Nutritional Biomarkers for Chronic Diseases Using Multi-Omics and Transgenic Model Technologies
Kanakaraju Kaliannan, M.D., Senior Research Fellow, Laboratory for Lipid Medicine and Technology (LLMT), Massachusetts General Hospital
The modern chronic disease epidemic has coincided with the rise of nutritional imbalances in the Western diet, including excessive intake of omega-6 fatty acids and insufficient intake of omega-3 fatty acids. Our combined use of multi-omics technologies with novel transgenic mouse models has demonstrated critical links between the omega-6/omega-3 fatty acid imbalance and chronic disease, and has discovered microbiome-derived biomarkers for disease assessment. Targeting the microbiome is a key approach for developing effective therapeutics for chronic disease.

9:05 Simple Gut Microbiome Metabolite Blood Screen for Wellness and Risk Markers
Sponsored by IXCELA
Wayne Matson, Ph.D., Chief Scientist & Co-Founder, Research & Development, Ixcela, Inc.
Ixcela has developed a fingerprick blood test for metabolomic profiling and monitoring of gut health-related risk factors. The test allows self-sampling (25-50 uL), and employs HPLC coupled Electrochemical Detection. Theoretical and developmental rationale; test characteristics; specific metabolite importance; and outcome data from multiple studies is presented.

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

10:20 Clinical Development of Ammonia Oxidizing Bacteria for Systemic and Dermatologic Targets
Larry Weiss, CMO, AOBiome, LLC
AOBiome is a clinical stage microbiome therapeutics company in Phase II development with a range of systemic and dermatologic therapeutic targets including acne, hypertension, allergic rhinitis, and migraine headache. Our intervention is based on restoring ammonia oxidizing bacteria (AOB), and autotrophic ancestral keystone commensal bacteria. This bacteria oxidize physiologic ammonia to nitrite and nitric oxide restoring host control over local and systemic inflammation, hemodynamics, and cellular energy metabolism. We will present scientific and clinical data.

10:50 Targeting the Intestinal Microbiome with Colon-Specific Pharmaceutical Vehicles - Revisiting
Abraham Rubinstein, Ph.D., Professor, Institute for Drug Research, The Hebrew University of Jerusalem School of Pharmacy
The enormous number of microorganisms inhabiting the human intestine, mainly the large bowel, is a source for diverse enzymatic activity that can be exploited for drug delivery and imaging purposes. Polymeric vehicles, susceptible to enzyme-driven hydrolysis have been suggested and tested clinically in the context of local treatment of colon-mucosa associated diseases and imaging.

11:20 Enjoy Lunch on Your Own

12:35 pm Plenary Keynote Program
(click here for details)

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

2:45 Close of Conference

Cambridge 25 YEARS HEALTHTECH Institute
A Division of Cambridge Innovation Institute

2nd Annual | September 27-28, 2017

Autoimmune and Inflammation Drug Targets

Towards Oral-Based Therapeutics

Many autoimmune and immune-related inflammation disorders are chronic conditions for which the development of orally-delivered therapeutics, usually small-molecule-based, is a sought-after goal because of their convenience of administration and lower cost to the patient, especially for a potentially lifelong therapy. While much progress in the field of immunotherapy has been made with injectable, protein-based therapeutics such as biologics, those therapeutic modalities can only act on cell surface proteins. However, a wealth of new knowledge of immune-related intracellular signaling pathways, partly spurred by the success of biologics, is revealing new intracellular targets against which cell-penetrable therapeutics can be developed. Cambridge Healthtech Institute's 2nd Annual Autoimmune and Inflammation Drug Targets conference will cover the advancement of promising oral-based drug candidates and emerging intracellular drug targets for combatting autoimmune and inflammatory disease.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Immunomodulatory Small Molecules
- September 26-27 Conference: NASH and Fibrosis
- September 27-28 Conference: Autoimmune and Inflammation Drug Targets
- September 27 Short Course: Impact of Convergence of Immunotherapy and Epigenetics on Drug Discovery
- September 28-29 Symposium: Tackling Rare Diseases

WEDNESDAY, SEPTEMBER 27

11:50 am Conference Registration Open

12:35 pm Plenary Keynote Program
(click here for details)

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

TARGETING ROR NUCLEAR RECEPTORS

2:45 Welcome Remarks
Anjani Shah, Ph.D., Conference Director, Cambridge Healthtech Institute

2:50 Chairperson's Opening Remarks
Dinesh V. Patel, Ph.D., President & CEO, Protagonist Therapeutics

2:55 Pharmacology of Targeting ROR in Autoimmunity
Joseph Wahle, Ph.D., Senior Scientist, Immunology and Respiratory Disease Research, Boehringer Ingelheim
The IL-23/Th17 axis is of great importance in the inflammation and autoimmunity field as confirmed by the efficacy of multiple biologics targeting this pathway. A key regulator of this axis is the RORC, and inhibitors of this transcription factor hold great promise in autoimmunity. This presentation will give an overview of the *in vitro* and *in vivo* pharmacologic support and rationale for targeting ROR in autoimmunity.

3:25 Pharmacology and Preclinical Safety Studies Related to Pharmacological Inhibition of RORC
Christine Guntermann, Ph.D., Project Team Head, Autoimmunity, Transplantation and Inflammation, Novartis Institutes for BioMedical Research
RORC is a master regulator of Th17 cells and represents a promising target for therapeutic intervention against autoimmune diseases. However, RORC deficiency also leads to metastatic thymic T cell lymphomas in mice. We identified potent and selective RORC inhibitors that impaired Th17 differentiation, IL-17A production, and showed good *in vivo* efficacy. In a longer-term safety study, we found that RORC inhibition recapitulates the early thymic aberrations found in RORC-deficient mice. While RORC inhibition will likely be an effective therapy for Th17-mediated diseases, T cell lymphoma development with chronic therapy remains an apparent risk.

3:55 Selected Poster Presentations:

Design and Synthesis of a Potent and Selective CBP Inhibitors
Alex Muthengi, Ph.D. Candidate, Department of Chemistry, Laboratory of Wei Zhang, University of Massachusetts Boston

IL6/STAT3 and Multiple Sclerosis
Yuhong Yang, M.D., Research Associate Professor, Department of Neurology, Ohio State University

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

INFLAMMATORY BOWEL DISEASE

5:00 FEATURED PRESENTATION: Emerging Oral Therapies for Inflammatory Bowel Disease: Clinical Programs Targeting SMAD7, S1P1R and PDE4
Kamal Puri, Ph.D., Director, Inflammation & Immunology, Celgene Corporation
Inflammatory bowel disease is a chronic inflammatory disorder of the digestive tract. It is a common disease and the incidence is rising globally. Despite current therapeutics, many patients do not obtain remission and some patients develop fibrotic strictures and require surgery. Celgene has several programs at various stages of clinical development including Mongersen, Ozanimod, and Apremilast. The scientific rationale and emerging clinical data will be discussed.

5:30 Anti-NKG2D Antibody for the Treatment of Crohn's Disease and Considerations for Small Molecule Approaches
Tatiana Ort, Ph.D., Director, Immunology Research, Janssen Research & Development
NKG2D, an activating receptor expressed by T and innate lymphoid cells, is linked to stress-induced gut inflammation and mucosal damage. JNJ64304500 is a first in class anti-NKG2D antagonizing antibody that showed efficacy signal in a Phase IIa trial in patients with Crohn's disease. The mechanism of action of JNJ64304500 and considerations for small molecule approaches to target NKG2D pathway will be discussed.

6:00 PTG-100, an Oral Peptide in Development for IBD
David Liu, Ph.D., CSO and Head, R&D Protagonist Therapeutics
PTG-100 is an oral GI-restricted peptide antagonist of α4β7 integrin currently in a global Phase IIb trial with ulcerative colitis patients with active moderate-to-severe disease. As a potent, reversible, and specific inhibitor of α4β7, it blocks T cell trafficking in the gastrointestinal (GI) system where there is rapid local target engagement as demonstrated by the blood pharmacodynamic responses observed in the Phase I trial with normal healthy volunteers.

6:30 Close of Day

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

THURSDAY, SEPTEMBER 28

7:30 am Registration Open

8:00 Interactive Breakout Discussion Groups with Continental Breakfast
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. Details on the topics and moderators are available on the conference website.

AUTOIMMUNE DISEASES: NEW DRUG TARGETS OR NEW DRUG CANDIDATES

9:00 Chairperson's Remarks
John Robinson, Ph.D., Director, Medicinal Chemistry, Array Biopharma

9:05 Report-back from Breakout Discussion Moderators

9:35 BTK Inhibitors for Lupus and Other Autoimmune Diseases
Roland Grenningloh, Ph.D., Director, Preclinical Pharmacology, EMD Serono

10:05 The Cullin Ring Ligase 4-Cereblon (CRL4CRBN) E3 Ubiquitin Ligase Complex and Its Modulation by CC-220 in the Treatment of Systemic Lupus Erythematosus
Garth Ringheim, Ph.D., Director, Translational Development Inflammation and Immunology, Celgene Corporation
CC-220 is a modulator of the CRL4CRBN E3 complex that induces ubiquitination and degradation of the cereblon substrates Aiolos and Ikaros, transcription factors involved in regulating B-cell function and generation of antibody secreting plasma cells. The mechanism of action of CC-220, its impact on B-cell differentiation and function, and results from a Phase IIa dose escalation study in subjects with systemic lupus will be presented.

10:35 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

AUTOIMMUNE DISEASES: NEW DRUG TARGETS OR NEW DRUG CANDIDATES *(Cont.)*

11:20 Targeting E2/E3 Ubiquitin Ligase Activity Is a Novel Strategy to Combat Autoimmunity
Kamyar Hadian, Ph.D., Principal Investigator & Head, Assay Development and Screening Platform, HelmholtzZentrum München
This lecture will give insights into the discovery of a novel E2/E3 protein-protein interaction small molecule inhibitor that we were able to validate and characterize in a variety of biochemical as well as cell-based assays including primary mouse and human cells. More importantly, we can show that this first-in-class inhibitor is effective in preclinical autoimmune mouse models for psoriasis as well as rheumatoid arthritis.

11:50 Structure-Based Design of IL-17A Antagonists
Shenping Liu, Ph.D., Associate Research Fellow, Discovery Sciences Groton, Pfizer
Monoclonal antibodies targeting pathway of pro-inflammatory cytokine IL-17A have shown significant efficacies in treating psoriasis and psoriatic arthritis. To develop non-antibody IL-17A antagonists, we conducted phage display and X-ray screen to identify peptides and fragment leads. We have determined structures of IL-17A in complex with peptide, fragments and small molecule antagonists. These structures enabled us to understand the structural basis of IL-17A signaling and design IL-17A antagonists with much improved potencies.

12:20 pm Targeting the cGAS-STING Pathway Using a Homogenous HTS Compatible Transcreener cGAS Assay
Sponsored by BellBrook Labs
Robert Lowery, Ph.D., President & CEO, BellBrook Labs
Aberrant activation of the DNA sensor cyclic GAMP synthase (cGAS) by self-DNA drives serious autoimmune diseases such as systemic lupus erythematosus. To accelerate discovery of cGAS inhibitors, we developed Transcreener-based assays for detecting cGAMP, which allow sensitive measurement of cGAS enzymatic activity with FP and TR-FRET signals.

12:50 Enjoy Lunch on your Own

1:50 Refreshment Break in the Exhibit Hall with Poster Viewing

INTRACELLULAR KINASE TARGETS FOR INFLAMMATION

2:35 Chairperson's Remarks
Laura Silvian, Ph.D., Principal Scientist and Head, Physical Biochemistry, Biogen

2:40 RIPK1 - A Kinase at the Intersection of Cell Death and Inflammation
Alexei Degterev, Ph.D., Associate Professor, Developmental, Molecular and Chemical Biology Department, Tufts University
RIPK1 kinase has garnered major interest as a key effector of pathologic necrosis in a variety of settings. Significant evidence, however, points to additional and not yet equally appreciated contributions of this

kinase to the cell death-independent regulation of inflammatory responses through the mechanisms that remain largely unknown. My talk will elucidate pathways of cell death-independent regulation of inflammation by RIPK1.

3:10 Targeting RIPK for Autoimmunity
Domagoj Vucic, Ph.D., Senior Scientist, Inflammation, Genentech
Inflammatory form of cell death called necroptosis involves activation of kinases RIP1 and RIP3. We have used genetic (RIP1 Kinase-Dead, RIP3 and MLKL KO mice) and chemical (RIP1 inhibitors) tools to investigate physiological role of necroptosis in inflammatory and ischemia reperfusion injury mediated disease models and find that inhibiting RIP1 kinase activity has a great benefit in a large number of inflammatory diseases.

3:40 Session Break

3:55 ARRY-624: A TYK2-Leaning, JAK Inhibitor: A First-in-Class Small Molecule Selectively Targeting the IL-12/23 Pathways
John Robinson, Ph.D., Director, Medicinal Chemistry, Array Biopharma
Pan JAK inhibitors block signaling of >20 cytokines & growth factors, effect both NK and CD8+ T-cell populations, and exhibit increased risk of infection & malignancy clinically. We hypothesized that a TYK2-targeted kinase inhibitor, such as ARRY-624, which does not engage JAK1/3, may lead to differentiated efficacy and clinical safety vs. currently available treatment options. This profile allows for selective modulation of IL-12 (Th1) and IL-23 (Th17) pathways, while sparing IL-2/IL-7 and IL-15 (g-chain-utilizing cytokines).

4:25 Inhibition of Autoimmune Pathways with Dual Inhibition of JAK1 and TYK2
Andrew Fensome, Ph.D., Associate Research Fellow, Medicinal Chemistry, Pfizer
The Janus (JAK) kinases TYK2 and JAK1 are important signaling molecules in autoimmune diseases such as psoriasis and ulcerative colitis. We will discuss the rationale to pursue dual inhibition of TYK2 and JAK1, our understanding of PK/PD relationships from tofacitinib, property space and insights from structural biology which led to the identification of PF-06700841, which is currently in Phase II clinical trials.

4:55 Close of Conference

Inaugural | September 26-27, 2017

Lead Generation Strategies

Biophysical Techniques Applied to Drug Discovery

A paradigm shift is underway in the biopharma industry due to advances in biophysical techniques and their applications to drug discovery. Typically, early phase drug discovery comprised of hit generation followed by lead optimization. However now the two processes are often combined into one, referred to as lead generation. Traditional hit-finding techniques use high throughput screening coupled to biochemical assays to screen small molecule libraries with a large number of chemical entities. However now, with the improvement in speed and automation of biophysical techniques such as NMR and sensor-based assays that detect the interactions between molecules, more information-revealing biophysical assays can be used to screen smaller but more focused libraries. This work has involved discovery biologists and chemists working together from the start. Cambridge Healthtech Institute's Inaugural Lead Generation Strategies conference will bring together these scientists to delve into which targets are being addressed and how by these new approaches — are some targets more amenable to particular techniques? Updates on biophysical approaches in the context of specific drug discovery projects will also be covered.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Constrained Peptides and Macrocyclics
- September 25 Short Course: Covalent Fragments: Applications in Target-Based and Phenotypic Screens
- September 26-27 Conference: Lead Generation Strategies
- September 27-28 Conference: Autoimmune and Inflammation Drug Targets
- September 27 Short Course: Introduction to Targeted Covalent Inhibitors
- September 28-29 Symposium: Tackling Rare Diseases

TUESDAY, SEPTEMBER 26

7:00 am Registration Open and Morning Coffee

STRATEGIES FOR FINDING AND FUNNELING DRUG LEADS

8:00 Welcome Remarks
Anjani Shah, Ph.D., Conference Director, Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks
Kevin Lumb, Ph.D., Director, Discovery Sciences, Janssen R&D

8:10 KEYNOTE PRESENTATION: Overview of Non-Alcoholic Fatty Liver Disease–Epidemiology, Diagnosis and Management
Jeff Hermes, Ph.D., Director, Chemical Biology, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd.
Nearly two decades ago, a push for screening of millions of compounds drove HTS labs to reduce assay volumes, increase plate densities and simplify assays. Are there still compelling reasons to use enormous, chemically diverse libraries in a "one and done" approach, or are there smarter, more informed ways to screen? This lecture will make the case for integrated and iterative screening with higher quality assays and libraries.

8:40 FEATURED PRESENTATION: FBDD: Part of an Integrated Drug Discovery Platform
Derek Cole, Ph.D., Director, Medicinal Chemistry, Takeda
This presentation will focus on the establishment of an efficient fragment-based drug discovery (FBDD) platform to enable fragment hit identification and FBDD/SBDD-based lead optimization to provide lead series and/or tool compounds to test pharmacological hypothesis. We will also share ongoing efforts to extend FBDD philosophies, strategies and technologies to more challenging targets, including GPCRs and other membrane proteins.

9:10 Knowledge Versus Deception: The Art of Triage
Michael A. Walters, Ph.D., Director, Lead and Probe Discovery, ITDD (Institute for Therapeutics Discovery and Development); Research Associate Professor, Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota
HTS is often the genesis of lead compounds. Given the constrained resources available for hit-to-lead projects, it is imperative that the prioritization of compounds for follow-up (triage) is knowledge-based and holistic. The art of triage incorporates chemistry knowledge, concerns itself with physicochemical properties and not only activity, and recognizes the often-deceptive nature of certain compound classes. Practical guidelines for effective HTS triage will be presented.

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

STRATEGIES FOR FINDING AND FUNNELING DRUG LEADS *(Cont.)*

10:25 A Novel Series of 3-Phosphoglycerate Dehydrogenase Inhibitors and its Cellular Phenotypes
Nello Mainolfi, Ph.D., Senior Director, Head of Drug Discovery, Raze Therapeutics
PHGDH (3-phosphoglycerate dehydrogenase) is the first enzyme branching from glycolysis into the serine synthetic pathway. Increases in PHGDH expression (mRNA and protein levels) have been observed in nearly 70% of estrogen receptor-negative breast cancers. We have been able to successfully identify first in class small molecule inhibitors with nanomolar cellular potency, high degree of selectivity and oral bioavailability

10:55 Delineation of Screening Hits by NMR Spectroscopy: The Good, the Bad and the Ugly
Mary Harner, Ph.D., Research Investigator II, Mechanistic Biochemistry, Bristol-Myers Squibb R&D
While early-phase hits originate from disparate screening approaches, assay formats and libraries, they share one commonality: the need for direct (i.e. biophysical) on-target binding confirmation. As a biophysical tool, NMR spectroscopy is uniquely situated to provide quality control, direct binding, and mechanistic binding assessments on small molecule hits, in addition to its well-documented application as a fragment screening approach. Case studies will be presented that champion NMR's ability to detect direct binding of hits when all else fails.

11:25 CryoEM for Drug Discovery Applications
Sriram Subramaniam, Ph.D., Senior Investigator, Head, Biophysics Section, Laboratory of Cell Biology, National Institutes of Health

11:55 Building on Fragment-Based Drug Design
Sponsored by domainex
Trevor Perrior, Ph.D., CSO, Domainex
The Domainex FragmentBuilder platform is based on our proprietary library, high-throughput microscale thermophoresis for fragment screening, and structure-based optimisation capability. This technology will be illustrated with case studies on the lysine methyltransferase, G9a; and on the work that led to the Domainex TBK1/IKKε inhibitor drug candidate, DMXD-011.

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

FRAGMENT-ASSISTED APPROACHES

1:50 Chairperson's Remarks
Derek Cole, Ph.D., Director, Medicinal Chemistry, Takeda California

1:55 Experiences of X-ray crystallographic screening at Astex
Andrew Woodhead, Ph.D., Director, Chemistry, Astex Pharmaceuticals
X-ray crystallography has been the cornerstone of fragment screening at Astex for the past 15 years. Over that time, information gleaned from thousands of proprietary protein-ligand crystal structures across a wide range of protein families has been highly influential. This presentation will describe how this structural information has led to the evolution of Astex's fragment library, helped to identify novel binding sites and unravel new mechanisms of action, plus most importantly, has provided a platform to develop drugs to provide benefit to patients.

2:25 Integrating Novel Biophysical Approaches in Fragment-Based Lead Discovery Workflow: MST and nDSF for Screening and Validation
Alexey Rak, Ph.D., Head of Bio Structure and Biophysics, Integrated Drug Discovery, Sanofi R&D
The search for optimal combinations of biophysical techniques for fragment-based lead discovery that can correctly and efficiently identify and quantify binding can be challenging due to the physicochemical properties of fragments. Here we present an approach utilizing automated microscale thermophoresis (MST) affinity screening to identify fragments active against human kinase. MST in concert with nDSF identified multiple hits that were confirmed by X-ray crystallography but not detected by orthogonal methods.

2:55 Generating Small Molecule Probes in Target-Agnostic Style
Sponsored by REACTION BIOLOGY CORP
Haiching Ma, Ph.D, CSO, Reaction Biology Corporation
Both epigenetics and human kinome biology are currently major focuses of basic research and drug discovery efforts. However, members of each of these target classes belong to larger protein families, other members of which may have biological functions distinct from those of epigenetic modifiers or kinases while nevertheless having similar protein structures. Reaction Biology Corporation (RBC) brings its extensive working experience in epigenetics and human kinome biology to meeting such challenges to target specificity and selectivity and has served thousands of companies and universities worldwide in their drug discovery efforts. We will present our budget-friendly, rapid turnaround, high-throughput chemical biology strategies and show how we could help your Project Teams to generate chemical probes and lead materials by delivering high quality data and support.

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

FRAGMENT-ASSISTED APPROACHES *(Cont.)*

4:05 Biophysical Fragment Screening Success When HTS Leads Nowhere
Peter Coombs, Ph.D., Senior Scientist, Assay Development & Screening Group, LifeArc (new name for MRC Technology)
Fragment screening at LifeArc (the new name for MRC Technology) has developed into a core lead generation resource. Combining orthogonal biophysical approaches, particularly focusing on SPR and thermal shift assays, with *in silico* fragment docking, site-directed mutagenesis and early medicinal chemistry, has allowed us to successfully prosecute challenging enzyme and PPI targets which have failed to produce leads in HTS. I will present key case studies describing how we have used biophysical approaches on targets for Alzheimer's, immuno-oncology and metastatic breast cancer, including an example where lead fragments have since been progressed into selective nanomolar inhibitors of a novel cancer target in the absence of X-ray crystal structures.

4:35 Bromodomain Candidates Discovered by an Integrated Lead-Generation Platform
Pawel Sledz, Ph.D., Senior Research Associate, Department of Biochemistry, Caflisch Laboratory, University of Zurich
We developed an efficient *in silico* lead generation platform based on a high-throughput fragment-docking engine. The docked poses are used as a starting point to propose single-step chemical modifications of the fragment-hits to generate a library of lead candidates. I discuss its application to the development of high-affinity blockers of non-BET bromodomains, potential candidates for cancer and Alzheimer's disease therapy.

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. Details on the topics and moderators are available on the conference website.

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

RECORD ATTENDANCE EXPECTED:
RESERVE YOUR SPOT TODAY!

Cover
Conference At-A-Glance
Short Courses
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Cambridge 25 YEARS HEALTHTECH Institute
A Division of Cambridge Innovation Institute

7:10 Close of Day

WEDNESDAY, SEPTEMBER 27

7:30 am Registration Open and Morning Coffee

BEYOND BIOPHYSICAL APPROACHES FOR LEAD GENERATION

8:00 Chairperson's Remarks
Mary Harner, Ph.D., Research Investigator II, Mechanistic Biochemistry, Bristol-Myers Squibb R&D

8:05 Never Say Never: Phenotypic Screening Uncovers a Novel Mechanism for Regulation of PCSK9
Paula M. Loria, Ph.D., Associate Research Fellow, Primary Pharmacology Group, Discovery Sciences, Pfizer
The power and challenge of phenotypic screening is that it can be unbiased to the mode of action of test compounds and thus has the capacity to sample new biology. We have identified small molecules that selectively stall PCSK9 translation via direct interaction with the ribosome. I will discuss the screening and hit deconvolution approaches we applied in the discovery of these intriguing drug candidates.

8:35 Discovery of BET Inhibitor Lead Molecules Using DNA-Encoded Library Technologies
Gang Yao, Ph.D., Senior Scientist, Encoded Library Technology Group Drug Design & Selection Boston, GSK
The bromo and extra C-terminal domain (BET) family of bromodomain-containing proteins are important regulators of the epigenome and their dysfunction have been linked to disease. This talk describes the discovery of novel BET inhibitors using the encoded library technology (ELT). Further optimization of the hits led to a high-quality drug-like inhibitor that displayed a high level of target engagement and favourable oral PK properties.

9:05 Network-Driven Drug Discovery (NDD) - A Unique Lead Generation Platform
Sponsored by e-therapeutics
Colin Stubberfield, Head, Drug Discovery, e Therapeutics plc
The majority of drug discovery approaches involve the search for a single binding target in a well-characterised pathway. But while pathways are easy to envisage, they do not reflect the complexity of biological systems. A more realistic way to describe the underlying interactions which occur is as a network. However, to exploit this view of biology in drug discovery a new process must be considered. I will describe our approach and its successful implementation.

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

BIOPHYSICAL APPROACHES FOR MEMBRANE PROTEINS

10:20 NMR Spectroscopy and Integrative Structural Biology of Human GPCRs
Matthew Eddy, Ph.D., Postdoctoral Fellow, Laboratory of Raymond Stevens, The Bridge Institute, University of Southern California
Nuclear magnetic resonance (NMR) spectroscopy complements other structural biology techniques, such as x-ray diffraction, by identifying multiple simultaneously populated conformations in equilibrium. Here, we leverage this advantage to study two human GPCRs. First, we report how a GPCR fusion strategy used for x-ray crystallography influences the protein conformational equilibrium and highlight potential cases where drug-ligand interactions can be affected. Second, we report a novel approach to incorporation of stable isotopic NMR labels into a wild type human GPCR and new insights obtained from this method.

10:50 Next Generation Bio-Sensing: New Opportunities for Challenging Targets
Tim Kaminski, Ph.D., Postdoctoral Fellow, Discovery Sciences, Innovative Medicines and Early Development Biotech Unit, AstraZeneca Gothenburg
Single molecule experiments enable us, next to its unmatched sensitivity, to directly gain a mechanistic insight into biological processes by observing its stochastic behavior. We are developing a toolbox which advances single molecule microscopy from a method primarily used in academia into a versatile tool for drug discovery. By using this method, we are able to address shortcomings of established biophysical methods as e.g. tight binding limit, working with membrane proteins, higher throughput. Additionally, we are able to extract kinetic profiling of inhibition reactions in solution by observing the association and dissociation of thousands of molecules in parallel with a surface-based single molecule platform.

11:20 Enjoy Lunch on Your Own

12:35 pm Plenary Keynote Program
(click here for details)

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

2:45 Close of Conference

Cambridge 25 YEARS HEALTHTECH Institute
A Division of Cambridge Innovation Institute

Inaugural | September 27-28, 2017

Target Identification Strategies

Phenotypic Screening, Functional Genomics and More

Target identification leading to novel, druggable targets for therapeutic intervention remains a top priority for the pharma/biotech industry when it comes to building a robust drug discovery pipeline. It also remains a formidable challenge and companies continue to invest a lot of resources in finding and validating good drug targets. Where are the challenges when it comes to identifying and validating targets? What tools and strategies are being used and how well are they working? What's being done once targets are validated that will lead to better and safer therapies? This conference on Target Identification Strategies will bring together leading experts to highlight the key developments in this field.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Constrained Peptides and Macrocyclics
- September 26-27 Conference: CRISPR for Disease Modeling and Target Discovery
- September 27-28 Conference: Target Identification Strategies
- September 27 Short Course: Practical Phenotypic Screening
- September 28-29 Symposium: Tackling Rare Diseases

WEDNESDAY, SEPTEMBER 27

11:50 am Conference Registration Open

12:35 pm Plenary Keynote Program
(click here for details)

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

USING CRISPR AND RNAi SCREENS FOR TARGET IDENTIFICATION & VALIDATION

2:45 Welcome Remarks
Tanuja Koppal, Ph.D., Conference Director, Cambridge Healthtech Institute

2:50 Chairperson's Opening Remarks
John Feder, Ph.D., Associate Director of Genome Biology and Emerging Technologies, Department of Genetically Defined Diseases and Genomics, Bristol-Myers Squibb

2:55 Development and Optimization of CRISPR Gene Editing for Drug Discovery Applications
John Feder, Ph.D., Associate Director of Genome Biology and Emerging Technologies, Department of Genetically Defined Diseases and Genomics, Bristol-Myers Squibb
The integration of CRISPR genome engineering into the drug discovery process is well underway. Examples will be presented as to how CRISPR is being used to address many of the issues that have traditionally stymied drug development. Data and learnings will also be shared from our recent efforts to improve the methods for CRISPR-based homology directed repair gene editing.

3:25 High-Throughput CRISPR-Based Approaches to Cancer Target Identification
Stephanie Mohr, Ph.D., Lecturer, Genetics & Director, Drosophila RNAi Screening Center at Harvard Medical School
Drosophila research has pioneered advances in cancer-related research, including identification of hedgehog and hippo signaling pathways. A new generation of fly studies seamlessly moves from work in the fly to mammalian systems. We use CRISPR knockout and activation to model cancers and identify new therapeutic strategies. Through this work, we are able to identify synthetic lethal interactions that can be recapitulated in mammalian cancer cells.

3:55 Ultra-Sensitive Targeted RNA Expression Profiling: DriverMap Human Genome-Wide Gene Expression Profiling Assay
Sponsored by CELLECTA
Paul Diehl, Ph.D., COO, Cellecta
The DriverMap assay's unparalleled specificity and sensitivity results in greatly enhanced detection of low- and medium- abundance mRNA transcripts as well as an improved cost-effectiveness for high-throughput research applications.

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

5:00 Combinatorial Omics: Leveraging Genomic-Phenomic Modulation for the Interpretation of Large Scale Screens
Arvind Rao, Ph.D., Assistant Professor, Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center
In this talk, we will draw on studies from drug screening and RNAi to describe data mining workflows to go from phenotypic measurements to biological insight. The availability of modern bioinformatics tools and multiple public databases make for very interesting investigations in multimodal data integration. Our goal will be to present a view of what's possible, using case studies from RNAi screening in triple negative breast cancer, and drug screening in glioblastoma.

5:30 CRISPR vs. RNA Interference for the Discovery of Cancer Genetic Dependencies
Jason Sheltzer, Ph.D., Principal Investigator, Cold Spring Harbor Laboratory
To date, many genetic dependencies in cancer have been discovered using RNAi. While RNAi is modular, reversible, and generally insensitive to gene copy number, it is also susceptible to off-target interactions. In several instances, CRISPR/Cas9-mutagenesis fails to recapitulate genetic dependencies previously discovered using RNAi. For example, MELK a putative breast cancer dependency identified via RNAi screening can be mutated with CRISPR without any apparent fitness defect. We discuss the advantages and disadvantages of both in the light of these results.

6:00 RNAi Screens for Identifying Kinases That Mediate Tumor Resistance to T Cell Attack
Tillmann Michels, Ph.D., Head of Research Group Immune Checkpoint Inhibitors, Laboratory of Prof. Philipp Beckhove, Regensburg Center for Interventional Immunology
Effector molecules of T cell attack against tumors not only fail to induce tumor death at low concentrations (or effector-to-target ratios) but induce tumor proliferation. Using high throughput RNAi screens, we identified kinases that shift effector molecule induced signaling form apoptosis to survival. These kinases are optimal targets to increase the clinical benefits of immunotherapy.

6:30 Close of Day

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

THURSDAY, SEPTEMBER 28

7:30 am Registration Open

8:00 Interactive Breakout Discussion Groups with Continental Breakfast
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. Details on the topics and moderators are available on the conference website.

PHENOTYPIC SCREENING & CHEMICAL BIOLOGY TOOLS

9:00 Chairperson's Remarks
Gregory A. Michaud, Ph.D., Chemical Biology and Therapeutics (CBT), Novartis Institutes for BioMedical Research, Inc.

9:05 Target Identification Using Chemogenomic and Reactivity-Based Screening
Lyn Jones, Ph.D., Vice President, Chemical Biology, Jnana Therapeutics
Target identification continues to be a resource intensive endeavor that often fails. The value of chemogenomic screening as a technology that can expedite the discovery of therapeutically relevant targets from phenotypic assays will be presented. New developments in protein labeling chemistry with applications to chemoproteomic profiling and molecular pathology studies will also be described.

9:35 A Small Molecule Inhibitor of C5 Complement Protein
Gregory A. Michaud, Ph.D., Chemical Biology and Therapeutics (CBT), Novartis Institutes for BioMedical Research, Inc.
The complement pathway is an important part of the immune system, and uncontrolled activation is implicated in many diseases. The human complement component 5 protein (C5) is a validated drug target within the complement pathway, as an anti-C5 antibody (Soliris) is an approved therapy for paroxysmal nocturnal hemoglobinuria (PNH). Compound 7l (Zhang et al, ACS Med. Chem. Lett., 2012), was recently reported as an inhibitor of the complement pathway, but its molecular target was not identified. Here we report that human C5 is the target for Compound 7l.

10:05 Whole-Genome siRNA Screen Identifying Novel Targets of the TGFβ Pathway
Chris Kitson, Ph.D., Principal Scientist, Fibrosis Biology Discovery, Bristol-Myers Squibb
Transfection of a genome-wide siRNA library into normal human lung fibroblasts enabled identification of novel targets from the TGFβ pathway, using high-content analysis to measure the degree of cellular differentiation. Hits were retested in multiple donors, with additional reagents, and triaged through a series of filters. Targets from the screen are supporting our early fibrosis portfolio.

10:35 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

11:20 Functional Annotation of Biological Processes Targeted by Chemical Libraries
Jeff Piotrowski, Ph.D., Principal Scientist, Target Identification, Yumanity Therapeutics
To characterize the functional diversity of large compound libraries, we developed a highly parallel and unbiased yeast chemical-genetic screening system and screened 7 diverse compound libraries. Our analysis shows that we can visualize the functional diversity of each library, prioritize subsets of compounds that target specific biological processes, globally validate targeted processes, and identify compounds targeting multiple processes. With spontaneous mutant analysis, we can link compounds to targets in yeast, and translate to mammalian orthologs.

11:50 Interrogating the Plasma Membrane Proteome for New Targets
Shaun M. McLoughlin, Ph.D., Senior Research Scientist III, Target Identification and Validation Technologies, AbbVie
Surface proteins play an integral role in the progression of cellular pathology. Consequently, these proteins have been exploited for the development of pharmaceutical therapies. Despite its importance, the surface proteome has remained largely uncharacterized owing to significant analytical challenges, low protein copy number and rapid target degradation. This discussion will detail traditional and modern techniques for plasma membrane protein extraction and their application to models of cancer resistance.

12:20 How IBM Watson Health Helps Accelerate Life Sciences Research
Sponsored by IBM
Alix Lacoste, Ph.D., Lead Technical Solution Specialist, Watson Health for Life Sciences, IBM
With millions of scientific research articles published each year, innovation in the life sciences suffers from knowledge waste and lack of knowledge integration. IBM Watson for Drug Discovery addresses this issue by mining large corpuses of literature and data to accelerate biomedical research. Using advanced analytics and machine learning, the platform can also predict novel relationships, as demonstrated through our recent work with Barrow Neurological in ALS disease, and Pfizer in immuno-oncology, among many projects.

12:50 Session Break

1:00 New Approaches to Target Identification
Sponsored by Clarivate Analytics
Richard K. Harrison, Ph.D., CSO, Clarivate Analytics
Discovering new drugs and getting them to market is one of the most challenging endeavors in industrial R&D. Less than 1-in-10 compounds that enter clinical trials becomes a medicine. Target Identification is arguably the most important step in the drug discovery process. This talk will highlight the use of omic and pathway based analysis for identification of new targets and the use of new analytical tools to rapidly triage targets to identify the most promising.

1:50 Refreshment Break in the Exhibit Hall with Poster Viewing

RECORD ATTENDANCE EXPECTED:
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INNOVATIVE APPROACHES FOR FINDING NOVEL TARGETS

2:35 Chairperson's Remarks
Doug Johnson, Ph.D., Research Fellow, Chemical Biology Group, Pfizer Worldwide Research & Development

2:40 Chemoproteomic Profiling with Clickable Photoaffinity Probes for Target ID and Mechanism of Action Studies
Doug Johnson, Ph.D., Research Fellow, Chemical Biology Group, Pfizer Worldwide Research & Development
This talk will describe how we used clickable photoaffinity probes for off-target identification/ validation in live cells for two secretase projects relevant to Alzheimer's Disease. In the first example, we used γ-secretase modulator (GSM) and inhibitor (GSI) photoaffinity probes to determine the target and in one case the binding site within the γ-secretase complex. In the second example, we generated a clickable photoprobe analog of a Pfizer BACE1 inhibitor that exhibited ocular toxicity in rats and found that the photoprobe labeled the off-target Cathepsin D in RPE cells.

3:10 Target Identification Strategies for Dermatological Indications
Deepak Kumar Rajpal, Ph.D., Director, Computational Biology, GlaxoSmithKline
We plan to share a framework for developing new therapeutic intervention strategies for psoriasis by computational approaches and utilizing publicly available clinical transcriptomics data sets. We share a proposed a psoriasis disease signature, present approaches to identify potential drug repurposing opportunities and outline a novel target selection methodology. We anticipate that methologies shared here or similar approaches will aid in target discovery in dermatological indication space, support biomarker discovery and the development of new drugs.

3:40 Session Break

3:55 A Genome Engineering Approach for Drug Target Identification in Malaria Parasites
Sumanta Dey, Ph.D., Postdoctoral Associate, Laboratory of Dr. Jacquin C. Niles, Department of Biological Engineering, Massachusetts Institute of Technology
A strategy for rapidly identifying targets for anti-malarial compounds using phenotypic assays is lacking. To address this, we developed a resource of *Plasmodium falciparum* lines, in which expression of individual target genes can be conditionally modulated. Through implementation of high throughput compound screens on these engineered parasites, we aim to identify novel inhibitors which specifically hit the target proteins to kill the parasites.

4:25 Target Identification and Assay Validation for the Tox21 HTS Program
Menghang Xia, Ph.D., Leader, Systems Toxicology, Division of Pre-Clinical Innovation, National Center for Advancing Translational Sciences, NIH
The toxicology in the 21st century (Tox21) program has developed and utilized a quantitative high throughput screening (qHTS) paradigm that has provided a more efficient and cost-effective alternative to traditional tests for profiling the toxicity of environmental chemicals. In this program, approximately 10K environmental chemicals including clinically used drugs have been screened against a panel of biologically relevant cell-based assays. This talk describes the Tox21 program, selection of qHTS-based assays and the various Tox21 screening assays.

4:55 Close of Conference

Inaugural | September 26-27, 2017

NASH and Fibrosis

Drug Discovery in Fatty Liver Disease, IPF and Other Fibrotic Diseases

Fibrosis is an area of increasing research activity in the drug discovery industry, especially in the context of liver disease. A response to the injury of cells, fibrosis is at the nexus of several biologic processes such as inflammation, cell death and metabolic dysregulation in which our scientific knowledge has significantly increased in the past decade. Liver fibrosis, often occurring at the later stages of fatty liver disease and referred to as non-alcoholic steatohepatitis (NASH), is of special interest because the number of people with NASH has doubled in the past twenty years and no medical treatments exist though promising therapeutics are in late stage clinical trials. Join us at Cambridge Healthtech Institute's Inaugural NASH and Fibrosis meeting to keep abreast of the rapid progress in new therapeutic candidates and share drug discovery strategies in this increasingly important medical field.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Targeting HBV
- September 26-27 Conference: NASH and Fibrosis
- September 27-28 Conference: Autoimmune and Inflammation Drug Targets
- September 27 Short Course: Practical Phenotypic Screening
- September 28-29 Symposium: Tackling Rare Diseases

TUESDAY, SEPTEMBER 26

7:00 am Registration Open and Morning Coffee

NASH DRUG CANDIDATES

8:00 Welcome Remarks
Anjani Shah, Ph.D., Conference Director, Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks
Rebecca Taub, M.D., CMO & Executive Vice President, R&D, Madrigal Pharmaceuticals

8:10 KEYNOTE PRESENTATION: NASH Basic Science Overview and Medical Landscape
Kathleen Elizabeth Corey, M.D., Assistant Professor of Medicine, Massachusetts General Hospital

8:40 Updates on a Dual PPAR Agonist in Clinical Development for Treating NASH
Sophie Megnien, M.D., CMO, Genfit Corp.

9:10 Progress in the Development of FXR Agonists
Yat Sun Or, Ph.D., Senior Vice President, R&D and CSO, Enanta Pharmaceuticals, Inc.
FXR agonism is under investigation as a potential treatment for multiple metabolic and liver conditions, including NASH. A brief overview of FXR agonists in early clinical trials will be presented, as well as the preclinical data illustrating EDP-305 selectivity for FXR, its significant perturbation of FXR-dependent gene expression, and its striking effects on hepatocyte ballooning and liver fibrosis in multiple animal models.

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

NASH DRUG CANDIDATES *(Cont.)*

10:25 FXR Agonists in Phase II Development for NASH
Bryan Laffitte, Ph.D., Director, Discovery Pharmacology, Genomics Institute of the Novartis Research

10:55 Cenicriviroc, a Dual CCR2 and CCR5 Antagonist, for the Treatment of Liver Fibrosis in Adults with Nonalcoholic Steatohepatitis
Eric Lefebvre, M.D., Vice President, Head of Clinical Research and Development – NASH, Allergan
The CENTAUR Phase IIb study evaluated the oral chemokine receptor CCR2/5 antagonist cenicriviroc (CVC) in non-alcoholic steatohepatitis and liver fibrosis in adults at increased risk of progression to cirrhosis. CVC was well tolerated, with twice as many patients achieving ≥1-stage improvement in fibrosis and no steatohepatitis worsening vs. placebo after 1 year. Patients with higher disease activity and fibrosis stage showed greater numerical improvements in fibrosis.

11:25 Thyroid Hormone Receptor Targets
Rebecca Taub, M.D., CMO & Executive Vice President, R&D, Madrigal Pharmaceuticals

11:55 Enjoy Lunch on Your Own

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

LIVER FIBROSIS: EMERGING TARGETS AND TOOLS

1:50 Chairperson's Remarks
Bryan C. Fuchs, Ph.D., Assistant Professor of Surgery, Harvard Medical School

1:55 FEATURED PRESENTATION: Tools for Assessing Fibrosis and Monitoring Response to Treatment in Preclinical Models
Bryan C. Fuchs, Ph.D., Assistant Professor of Surgery, Harvard Medical School
There are a number of anti-fibrotic therapies entering clinical trials in NASH patients, but a major obstacle to their development is the lack of sensitive and noninvasive tools for assessing fibrosis. Here, we discuss our preclinical work to develop molecular imaging as a biomarker that could not only be used to select patients for clinical trials but also provide an early assessment of treatment efficacy.

2:25 Targeting Liver Fibrosis through Modulating the Wnt Pathway
Weilin Xie, Ph.D., Senior Principal Scientist, Biotherapeutics, Celgene

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2:55 Low-risk *in vivo* Diagnosis of Pulmonary Fibrosis with Endobronchial Optical Imaging
Lida Hariri, M.D., Ph.D., Instructor, Pathology Department, Harvard Medical School
Idiopathic pulmonary fibrosis (IPF) is a fatal form of fibrotic interstitial lung disease (ILD). Diagnosis of IPF is essential to determine the most effective therapy for patients, but often requires surgical tissue resection, which has a high-risk profile. We aim to determine whether endobronchial optical imaging can serve as a low-risk method for in-vivo IPF diagnosis. We performed endobronchial optical imaging in ILD patients undergoing diagnostic wedge biopsy. Optical imaging was able to visualize diagnostic IPF features, and differentiate IPF from other ILDs. These findings support the potential of optical imaging as a minimally-invasive method for IPF diagnosis.

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

LIVER FIBROSIS: EMERGING TARGETS AND TOOLS *(Cont.)*

4:05 FAP and FGF21: Complementary Targets for the Treatment of NASH
Travis W. Bainbridge, MS, Senior Scientific Researcher, Department of Protein Chemistry, Genentech, Inc.
Fibroblast activation protein (FAP) is a membrane-bound protease expressed at sites of tissue remodeling, inflammation and fibrosis. FGF21 is a hepatoprotective hormone we identified as an FAP substrate. Cleavage by FAP inactivates FGF21, while FAP inhibition increases endogenous levels of active FGF21, making FAP an attractive target for liver disease. Additionally, a FAP-specific activity assay for monitoring the pharmacodynamics of FAP inhibitors will be described.

4:35 CANCELLED: Targeting Ammonia with OCR-002 Reduces the Progression of Non-Alcoholic Fatty Liver Disease
Rajiv Jalan, M.D., Ph.D., Professor of Hepatology, University College London
NAFLD is characterized by reduced activity of key urea cycle enzymes resulting in hyperammonemia. Pathophysiological concentrations of ammonia produce activation of stellate cells, which can be reversed by administration of the ammonia-lowering drug, OCR-002. Treatment of a rodent model of NAFLD (high-fat high-cholesterol diet) with OCR-002 prevented progression of fibrosis, providing proof of concept for an ammonia lowering therapy in NAFLD that can be readily translated.

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. Details on the topics and moderators are available on the conference website.

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

7:10 Close of Day

WEDNESDAY, SEPTEMBER 27

7:30 am Registration Open and Morning Coffee

NON-LIVER FIBROSIS

8:00 Chairperson's Remarks
H. James Harwood Jr., Ph.D., Founder and CEO, Delphi BioMedical Consultants, LLC

8:05 Roles of LPA and S1P in Lung and Dermal Fibrosis
Rachel Knipe, M.D., Instructor of Medicine, Assistant Physician, Division of Pulmonary and Critical Care Medicine, and Laboratory of Andrew Tager, Massachusetts General Hospital

8:35 Epigenetic Targets for Cardiorenal Fibrosis
Timothy A. McKinsey, Ph.D., Director, Consortium for Fibrosis Research & Translation, Department of Medicine, University of Colorado – Anschutz Medical Campus
Despite the well-accepted roles for fibrosis in the pathogenesis of heart failure and chronic kidney disease, there are no FDA-approved therapies to combat excessive extracellular matrix deposition in cardiac or renal tissue. I will discuss our recent findings suggesting that specific epigenetic regulatory proteins serve crucial pro-fibrotic functions, and the potential for small molecule inhibitors of these factors for the treatment of cardiorenal fibrosis.

9:05 Report-back from Breakout Discussion Moderators

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

NON-LIVER FIBROSIS *(Cont.)*

10:20 Moving from Lung Fibrosis to Liver Fibrosis
Ying Luo, Ph.D., CEO, GNI Group
A new compound targeting liver fibrosis has shown excellent efficacy in liver fibrosis and kidney fibrosis animal models. It also showed significantly improved safety profile over pirfenidone in Phase I studies. Currently, it is in a 240 patient Phase II studies for HBV-associated liver fibrosis in China.

10:50 The Development of PAT-1251, a Small Molecule LOXL2 Inhibitor to Treat Fibrosis
John Hutchinson, Ph.D., President and CSO, PharmAkea
LOXL2 catalyzes oxidation of ε-amines of lysine residues within collagen, generating reactive aldehydes that condense to form collagen cross-linkages. Dysregulation of this process can lead to fibrosis. PAT-1251 was identified as a potent irreversible inhibitor of LOXL2 that is highly selective over LOX and other AOs. PAT-1251 significantly reduced fibrosis in mouse lung bleomycin models and has completed healthy volunteer Phase I trials.

11:20 Enjoy Lunch on Your Own

12:35 pm Plenary Keynote Program
(click here for details)

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

2:45 Close of Conference

Cambridge 25 YEARS HEALTHTECH Institute
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Inaugural | September 27-28, 2017

Emerging Oligonucleotide Therapeutics

New Platforms & Drug Modalities Enabling Better Therapies

Advances in genomics, gene editing, oligonucleotide synthesis, delivery and manufacturing, and an increase in collaborations and licensing opportunities have all contributed to a resurgence in the development of DNA and RNA-based drugs. Although only a handful of oligonucleotide therapeutics are currently approved, more than 125 of them are in various stages of development. This conference on Emerging Oligonucleotide Therapeutics tracks both the scientific and clinical progress being made in developing new molecular entities, improving synthesis and delivery technologies and extending stability and safety profiles for oligonucleotide-based therapies.

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WEDNESDAY, SEPTEMBER 27

11:50 am Conference Registration Open

12:35 pm Plenary Keynote Program
(click here for details)

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

DEVELOPMENT OF NEW OLIGONUCLEOTIDE PLATFORMS AND CHEMISTRIES

2:45 Welcome Remarks
Tanuja Koppal, Ph.D., Conference Director, Cambridge Healthtech Institute

2:50 Chairperson's Opening Remarks
Bruce D. Given, M.D., COO, Arrowhead Pharmaceuticals

2:55 Chemistry Developments and Therapeutic Applications of GalNAc-siRNA Conjugates
Ivan Zlatev, Ph.D., Senior Scientist, Research, Alnylam Pharmaceuticals

3:25 RNAi Based Human Therapy for Chronic Hepatitis B Infection
Amy Lee, Ph.D., Senior Director, In Vivo Pharmacology and Macro-Molecular Discovery, Arbutus Biopharma Corp.
ARB-1467 and ARB-1740 are lipid nanoparticle-delivered RNAi therapeutics currently in Phase II MAD clinical studies. These agents are designed to inhibit viral replication and lower all viral antigens. Reducing HBV proteins, particularly HBsAg, is expected to abrogate viral suppression of immune function and facilitate reinvigoration of the host response/ defense. Clinical results to date are promising, with multi-dosing resulting in stepwise, additive reduction in serum HBsAg.

3:55 Sponsored Presentation *(Opportunity Available)*

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

5:00 Antisense Oligonucleotides: Treating Neurological Disorders at the Level of RNA
Sarah L. DeVos, Ph.D., Postdoctoral Fellow, Laboratory of Dr. Bradley T Hyman, Massachusetts General Hospital
Adequate therapies are lacking for neurological disorders, including Alzheimer's. Antisense oligonucleotides (ASOs) that directly target RNA of disease-associated genes may be therapeutically beneficial. Tau ASOs, for example, have rescued multiple mouse models and show target engagement in non-human primates. These and other data are moving neuro-focused ASOs from "bench to bedside", with one FDA approved ASO and several others in human clinical trials for neurodegeneration.

5:30 Oligonucleotides with Charge-Neutralizing Branched Groups on the Backbones That Enhance Cellular Uptake
David R. Tabatadze, Ph.D., President and CEO, ZATA Pharmaceuticals
Novel phosphoramidite monomers enabling the incorporation of charge-neutralizing branched groups (CNBGs) on internucleoside phosphates of oligonucleotides during the automated synthesis have been developed. BCNSs terminated with amino groups form ion pairs with neighboring phosphate groups. Such oligonucleotides possess good solubility and hybridization properties, are not involved in non-standard intramolecular aggregation, have low cytotoxicity, adequate chemical stability, improved serum stability, and display significantly enhanced cellular uptake.

6:00 Characterization of Novel Conjugated RNAi drugs
Bruno M.D.C. Godinho, PhD., Milton-Safenowitz Post-Doctoral Fellow, Laboratory of Dr. Anastasia Khvorova, RNA Therapeutics Institute, University of Massachusetts Medical School
Clear understanding of the PK/PD behavior is essential for characterizing the performance of RNAi-based drug candidates *in vivo*. As novel conjugated oligonucleotides emerge in the field, simple and reproducible methodologies are required to facilitate and accelerate systematic assessment of these compounds. Strategies for chemical stabilization oligonucleotide constructs, a platform for evaluation of PK and biodistribution, and a high throughput method for assessment of efficacy are three key pillars for characterization of RNAi-based compounds.

6:30 Close of Day

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

THURSDAY, SEPTEMBER 28

7:30 am Registration Open

8:00 Interactive Breakout Discussion Groups with Continental Breakfast
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. Details on the topics and moderators are available on the conference website.

EXPLORING CRISPR AND OTHER INNOVATIVE DRUG MODALITIES

9:00 Chairperson's Remarks
Thomas D. Madden, Ph.D., President and CEO, Acuitas Therapeutics

9:05 Therapeutic Protein Expression *in vivo* Using Messenger RNA-Lipid Nanoparticles
Thomas D. Madden, Ph.D., President and CEO, Acuitas Therapeutics
Messenger RNA (mRNA) is an important new therapeutic modality. However mRNA is labile and requires a delivery system to access cells. New generations of lipid nanoparticle systems (LNP) allow efficient delivery and expression of mRNA via different routes of administration. Key parameters impacting potency and safety will be discussed. In addition preclinical results illustrating the application of mRNA-LNP therapeutics in a several clinical areas will be presented.

9:35 Using Single-Stranded Donor DNA for Homology Directed Repair Catalyzed by CRISPR/Cas9 Activity
Eric. B. Kmiec, Ph.D., Director, Gene Editing Institute and Senior Research Scientist, Center for Translational Cancer Research, Helen F. Graham Cancer Center & Research Institute, Christiana Care Health System
This talk will focus on utilizing the information gathered from studies on the mechanism of action and regulatory circuitry surrounding gene editing using single-stranded oligonucleotides in combination with CRISPR/Cas9. We will examine how genetic lesions often arise during the process of homology directed repair and point mutation resolution. Examples will be provided outlining the strategy for carrying out genetic surgery more precisely and how they may enable productive outcomes in the clinic.

10:05 Efficacy of U1 Adaptor Gene Silencing of the Undruggable KRAS and MYC Oncogenes in Xenograft Mice
Samuel Gunderson, Ph.D., President and Co-Founder, SilaGene Inc.
U1 Adaptors oligonucleotides (U1AOs) interfere with polyadenylation of gene-specific mRNA, causing their selective destruction inside the nucleus. U1AOs can accept extensive covalent modifications for nuclease resistance and conjugation to tumor-targeting peptides without loss of silencing activity, offering important advantages as therapeutic agents. Systemically delivered U1AO-peptide conjugates targeting KRAS and MYC lead to tumor shrinkage in xenograft mice harboring pancreatic cancer with no apparent toxicity.

10:35 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

OLIGONUCLEOTIDES FOR CANCER IMMUNOTHERAPY

11:20 RNAi-Mediated β-Catenin Inhibition Promotes T Cell Infiltration and Potentiates Immune Checkpoint Blockade
Shanthi Ganesh, Ph.D., Associate Director, Pre Clinical Oncology, Dicerna Pharmaceuticals, Inc.
Recent research implicates Wnt/β-catenin signaling as a mechanism of resistance to cancer immunotherapy. DCR-BCAT is an RNAi-based experimental drug targeting β-catenin, formulated in a tumor-selective nanoparticle. In preclinical models, systemic administration of DCR-BCAT induced rapid increases in tumor T cells and dramatically improved responses to immunotherapy agents. In this presentation, we explore the mechanism of synergistic efficacy and suggest clinical evaluation of this first-in-class RNAi agent.

11:50 SB 11285, a Novel STING Agonist for ImmunoTherapy of Cancer
R.P. (Kris) Iyer, Ph.D., Co-Founder & CSO, Spring Bank Pharmaceuticals
Immunotherapy has emerged as a transformative approach for the treatment of cancer. Evidence suggests that the activation of Stimulator of Interferon Genes (STING) pathway in tumor cells and/or immune cells induce type I Interferon production leading to apoptosis of tumor cells, as well as, induction of adaptive immune response thereby providing a powerful anti-cancer strategy. Herein, we describe the discovery and preclinical studies of SB 11285, a novel STING agonist for application in immuno-oncology.

12:20 pm Enjoy Lunch on Your Own

1:50 Refreshment Break in the Exhibit Hall with Poster Viewing

TACKLING CHALLENGES WITH DELIVERY

2:35 Chairperson's Remarks
Dan Peer, Ph.D., Director, Laboratory of Precision NanoMedicine, Tel Aviv University

2:40 Moving from Intravenous to Subcutaneous Delivery in RNAi – Why and How
Bruce D. Given, M.D., COO, Arrowhead Pharmaceuticals
RNA interference (RNAi) occurs in the cytoplasm. RNAi triggers are routed on cell entry through endosomes, which are well equipped to metabolize RNA and to initiate host immune responses. Legacy delivery systems require mechanisms for endosomal escape and intravenous dosing. Advances in RNAi trigger chemistry and targeting allow effective knockdown without requiring active endosomal escape, without toll receptor activation and allowing subcutaneous delivery.

3:10 From Local to Systemic: Delivering Novel siRNA Therapeutics for Multiple Clinical Indications
Patrick Y. Lu, Ph.D., President & CEO, Sirnaomics, Inc.
Sirnaomics is trying to use its proprietary and optimized polypeptide-based delivery technology, to develop the novel anti-fibrotic RNAi therapeutics targeting both TGFβ1 and Cox-2 simultaneously. The initial indication is to treat skin hypertrophic scar and then extend it to liver fibrosis, such as Primary Sclerosing Cholangitis, and liver cancer, such as Cholangicarcinoma, as well as other fibrotic conditions. With INDs approved by both U.S. FDA and China FDA, we have started clinical trials in both countries. I will discuss the unique advantage of this polypeptide nanoparticle technology for efficient siRNA delivery, its pharmaceutical properties for manufacturing and its preclinical safety profile.

3:40 Session Break

RECORD ATTENDANCE EXPECTED:
RESERVE YOUR SPOT TODAY!

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Conference At-A-Glance
Short Courses
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3:55 A Multi-Dimensional RNA-Based Approach to Treat Genetic Disorders
John Androsavich, Ph.D., Senior Scientist, Translate Bio
Many genetic diseases can be treated by restoring defective gene expression. We can activate gene expression by three distinct technology platforms: 1) Targeting repressive cis-acting long noncoding RNA, 2) Enhancing stability of mRNA transcript, or 3) Supplementing *in vitro* transcribed mRNA. With these three different platforms, we can achieve specific gene upregulation and tailor to desired therapeutic profiles. Recent progress in the discovery and preclinical development of all three platforms will be presented.

4:25 Targeted Platform for RNA Therapeutics
Dan Peer, Ph.D., Director, Laboratory of Precision NanoMedicine, Tel Aviv University
The translation of RNA from an effective genomic tool into a novel therapeutic modality has been hindered by the difficulty to deliver RNA molecules into specific target tissues by systemic administration, especially to leukocytes. Here, I will describe some of the challenges and opportunities in modulating leukocytes response using RNA molecules and discuss adverse effects such as immuno-toxicity. In addition, I will detail the challenges of targeting lipid-based nanoparticles directly into specific cells.

4:55 Close of Conference

Cambridge 25 YEARS HEALTHTECH Institute
A Division of Cambridge Innovation Institute

14th Annual | September 26-27, 2017

CRISPR for Disease Modeling and Target Discovery

Building New Tools While Improving Specificity and Efficacy

Gene editing, particularly the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)/Cas9 system, is now being extensively used in drug discovery for disease modeling, functional screening, target identification and more. CRISPR for Disease Modeling and Target Discovery will bring together experts, from target discovery to functional screening, to talk about how CRISPR is being used to unravel cellular pathways in disease and identify potential targets for drug intervention. This is a unique opportunity to hear from experts in pharma/biotech, academic and government labs specifically about their experiences leveraging the utility of CRISPR-based gene editing to create relevant cell lines, knock-outs and *in vivo* tools for modeling diseases, identifying and validating targets, functional screening, epigenome engineering, and more. It's also an opportunity that brings together users and solution providers to talk about ways to overcome some of the inherent challenges in specificity, efficiency, delivery and off-target effects, associated with CRISPR/Cas9.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Targeting HBV
- September 26-27 Conference: CRISPR for Disease Modeling and Target Discovery
- September 27-28 Conference: Target Identification Strategies
- September 28-29 Symposium: Tackling Rare Diseases

TUESDAY, SEPTEMBER 26

7:00 am Registration Open and Morning Coffee

CRISPR-BASED FUNCTIONAL & PHENOTYPIC SCREENS

8:00 Welcome Remarks
Tanuja Koppal, Ph.D., Conference Director, Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks
John Doench, Ph.D., Associate Director, Genetic Perturbation Platform, Broad Institute of Harvard and MIT

8:10 Pooled Screening with CRISPR-Cas9: Where Are We Now?
John Doench, Ph.D., Associate Director, Genetic Perturbation Platform, Broad Institute of Harvard and MIT
The ease of programming Cas9 with an sgRNA presents an abundance of potential target sites, but the on-target activity and off-target effects of individual sgRNAs can vary. We will discuss improved models that allow for increased on-target efficacy, metrics for understanding potential off-target sites, and how the combination of these findings can be used to design optimal libraries for genetic screens.

8:40 Large-Scale CRISPR Screening: Mining for the Deep
Roderick Beijersbergen, Ph.D., Group Leader, Netherlands Cancer Institute and Head, NKI Robotics and Screening Center
Large scale CRISPR/Cas9 screening across many different cell lines provides the opportunity to identify gene-gene correlations based on similar phenotypic profiles. Such analyses not only identify known interactions and biological networks, but also discover novel associations. In particular, these interactions can be explored for novel therapeutic strategies for cancer. The results of such efforts will be discussed.

9:10 Development of New CRISPR/Cas9-Based Tools to Study Drug Interactions through Knockout and Directed Evolution
Michael Bassik, Ph.D., Assistant Professor, Department of Genetics, Stanford University
We have used parallel shRNA and CRISPR screening to explore the biology of essential and non-essential genes, and have identified the target and mechanism of action of a novel host-targeting antiviral drug. More recently, we have used pairwise expression of sgRNAs to identify synergistic combinations of drug targets, and adapted our screening systems for new applications in mutagenesis and directed evolution.

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

10:25 Efficient CRISPR Screen Design and Analysis
Xiaole Shirley Liu, Ph.D., Professor, Department of Biostatistics and Computational Biology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute and Harvard School of Public Health
Genome-wide CRISPR-Cas9 screen has been widely used to interrogate gene functions. However, the analysis remains challenging and rules to design better libraries beg further refinement. I will discuss methods we have developed for the efficient design and analysis of CRISPR screens. I will also discuss our analysis of CRISPR screens comparing cells with and without drug treatment to understand the drug mechanism of action.

10:55 TECHNOLOGY PANEL DISCUSSION: Trends in CRISPR Technology and Applications
Moderator: John Doench, Ph.D., Associate Director, Genetic Perturbation Platform, Broad Institute of Harvard and MIT
Panelists: Roderick Beijersbergen, Ph.D., Group Leader, Netherlands Cancer Institute and Head, NKI Robotics and Screening Center
Michael Bassik, Ph.D., Assistant Professor, Department of Genetics, Stanford University
Xiaole Shirley Liu, Ph.D., Professor, Department of Biostatistics and Computational Biology, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute and Harvard School of Public Health
David Piper, Ph.D., Research & Development Leader, Cell Biology, Thermo Fisher Scientific
Shawn Shafer, Ph.D., Director of Advanced Genomics, MilliporeSigma
Paul Diehl, Ph.D., COO, Cellecta
This panel will bring together 3-5 technical experts from leading technology and service companies to discuss trends and improvements in library design, assay reagents and platforms, and data analysis tools that users can expect to see soon to explore new applications.

11:55 Functional Genomics Screening with Invitrogen™ LentiArray™ CRISPR Libraries
Sponsored by ThermoFisher SCIENTIFIC
David Piper, Ph.D., Research & Development Leader, Cell Biology, Thermo Fisher Scientific
Investigating pathways and validating gene functions and molecular targets that underlie disease relevant biological processes remain to be a challenge in drug discovery. The CRISPR-Cas9 system provides an efficient method for specific, complete, and permanent gene knockout and is a potent tool for making new discoveries and identifying gene function. The Invitrogen™ LentiArray™ CRISPR library collections harnesses this capability and expands it into high throughput applications to create the next generation of tools for functional genomics screening thereby accelerating therapeutic research and biomarker discoveries. Described here are the various ready to use predefined CRISPR library collections and custom service options available through Thermo Fisher Scientific along with example application data to demonstrate gene targeting efficacy and screening workflows. We have demonstrated here a knock-out screening approach that utilizes the Invitrogen™ LentiArray™ CRISPR library to interrogate the impact of individual gene knock-outs on the NFκB pathway as measured by a functional cell-based reporter assay using our CellSensor™ NF-κB-bla ME180 cell line. We describe the library design concepts, assay development, initial screening results and validation of specific identified hits. Together with our CRISPR library and service offering we expect these approaches to be scalable to the entire human genome and portable to multiple cell types and end-point assays including both high-throughput plate-based assays and high-content imaging based assays.

12:25 pm Session Break

12:35 Luncheon Presentation: Going the Extra Mile: Advancing Screening with Lentiviral CRISPR and RNAi Libraries
Sponsored by MilliporeSigma
Suzanne Hibbs, MS, MBA, Study Coordination Manager, Cell Design Studio, MilliporeSigma
CRISPR Cas9 nucleases have revolutionized the field of gene editing and high-throughput screens for target identification. MilliporeSigma seeks to share best approaches utilized and methods learned from our years of genome editing experience. In collaboration with the Wellcome Trust Sanger Institute, we have developed the first commercially available, genome-wide, truly arrayed guide RNA CRISPR-Cas9 lentiviral screening library. We will compare complementary screening technologies, such as RNAi, from small gene pathways to entire genomes.

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

UNRAVELING DISEASE PATHWAYS USING CRISPR/Cas9

1:50 Chairperson's Remarks
James Inglese, Ph.D., Head, Assay Development & Screening Technologies, National Center for Advancing Translational Sciences, NIH

1:55 Pooled CRISPR-Cas9 Screens for Host Factors Modulating AAV and HSV Infection
Patrick Collins, Ph.D., Senior Scientist, Genome Analysis Unit, Amgen
Adeno-associated virus and herpes simplex virus are vectors for two approved, virus-mediated therapies. To identify host factors modulating infection by these two vectors, we performed genome-wide screens using a pooled CRISPR library in U-2 OS Cas9 stable cells. We then infected with AAV or HSV and selected for cells with altered GFP transgene expression or cells resistant to HSV-mediated lysis. We will detail our approach and compare the results of our screens to other efforts aimed at identifying host factors for these vectors.

2:25 CRISPR-Cas9 Editing of Herpes Simplex Virus Genomes during Lytic and Latent Infection
Hyung Suk Oh, Ph. D., Research associate, Department of Microbiology and Immunobiology, Harvard Medical School
There is a great medical need to cure latent viral infections, and CRISPR-Cas9 is a potential approach to edit and inactivate latent viral DNA genomes. We have used CRISPR-Cas9 technology to edit lytic herpes simplex virus genomes and reduce lytic infection. In addition, we have employed CRISPR-Cas9 to edit quiescent viral genomes in cell culture. Studies are underway to target latent infection in murine systems.

2:55 CRISPR/Cas9 Genome-Wide sgRNA Libraries for More Effective Genetic Screens
Sponsored by CELLECTA
Paul Diehl, Ph.D., COO, Cellecta
Genome-wide loss-of-function screening is a fundamental method to identify genes responsible for driving biological processes. Complex pooled lentiviral-based libraries expressing large numbers of genetic disruptors, such as shRNAs (RNAi) or sgRNAs (CRISPR), make large-scale cell screening practical. CRISPR-based technologies offer not only an effective alternative, but distinct advantage.

3:10 Conducting Functional Genomic CRISPR Screens with Arrayed Chemically Modified Synthetic sgRNA Libraries
Sponsored by SYNTHEGO
Abhishek Saharia, Ph.D., Director, Product Management, Synthego
We have developed an arrayed library of chemically modified synthetic sgRNA that enables rapid screening of complex phenotypes in almost all human cells. Using this arrayed and multiplexed library, we demonstrate highly effective gene editing and knockout rates (up to 98%), highlighting the value of this arrayed CRISPR screening tool.

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

4:05 Identification of Genetic Modifiers of Somatic CAG Instability in Huntington's Disease by *in vivo* CRISPR/Cas9 Genome Editing
Vanessa Wheeler, Ph.D., Associate Professor of Neurology, Center for Genomic Medicine, Massachusetts General Hospital and Harvard Medical School
A recent genome-wide association study identified DNA repair genes as modifiers of HD age at onset. These studies implicate the CAG repeat expansion process as a disease driver and highlight the potential therapeutic impact of targeting these genes. To this end, we are using the CRISPR-Cas9 toolbox in HD mouse models, to dissect underlying disease mechanisms by determining if these genes modify CAG repeat expansion and early disease phenotypes in the mouse.

4:35 Application of Genome Editing to Develop HTS Assays for Rare and Neglected Disease Drug Discovery
James Inglese, Ph.D., Head, Assay Development & Screening Technologies, National Center for Advancing Translational Sciences, NIH
Dravet Syndrome is a convulsive disorder caused by heterozygous loss-of-function mutations in the voltage-gated sodium channel alpha-subunit encoded by the SCN1A gene. Here we describe a quantitative high-throughput screening (qHTS) assay engineered from the Neuro2a cell line in which one of the two SCN1A alleles has been replaced by a bioluminescence coincidence reporter using CRISPR/Cas9-medieated homologous recombination. Characterization of the assay and preliminary small molecule screening results will be presented.

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. Details on the topics and moderators are available on the conference website.

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

7:10 Close of Day

WEDNESDAY, SEPTEMBER 27

7:30 am Registration Open and Morning Coffee

CRISPR FOR TARGET IDENTIFICATION

8:00 Chairperson's Remarks
Roderick Beijersbergen, Ph.D., Group Leader, Netherlands Cancer Institute and Head, NKI Robotics and Screening Center

8:05 Validating and Invalidating Cancer Genetic Dependencies with CRISPR/Cas9
Jason Sheltzer, Ph.D., Principal Investigator, Cold Spring Harbor Laboratory
We have investigated putative genetic dependencies in triple-negative breast cancer using CRISPR/Cas9-mediated genome editing. In certain cases, on-target mutagenesis cast doubt on previously-reported cancer cell addictions. We focus on MELK and OTS167, a MELK inhibitor currently in clinical trials, and report that breast cancer cells tolerate the complete loss of MELK with no apparent fitness defect. OTS167 remains active against MELK-knockout clones, demonstrating that it necessarily kills cells through an off-target effect.

8:35 CRISPR/Cas9: A Functional Screening of the Kinome Reveals a New Potential Treatment for an Aggressive Pediatric Brain Tumor
Simone Treiger Sredni, M.D., Ph.D., Associate Professor of Pediatric Neurosurgery, Ann and Robert H. Lurie Children's Hospital of Chicago and Northwestern University, Feinberg School of Medicine
We have used a lentiviral CRISPR library to perform a systematic functional screening of the kinome by editing 160 kinases in a highly malignant pediatric brain tumor called atypical teratoid/rhabdoid tumor (AT/RT). We found that the polo-like kinase 4 (PLK-4) is essential for tumor survival, growth and migration. More importantly, we found that cells respond to PLK-4 small molecule inhibitors. This is the first time PLK-4 has been described in brain or pediatric tumors.

9:05 An IL-17 Signaling Phenotypic Screen Using the Orthogonal Methods of CRISPR and Small Molecule Libraries to Identify New Targets
Peter Slivka, Ph.D., Senior Scientist, Foundational Immunology, AbbVie Bioresearch Center
IL17 plays a critical role in the development and maintenance of autoimmune diseases including psoriasis and psoriatic arthritis. To identify novel targets in the IL17 signaling cascade, we conducted two phenotypic screens in primary keratinocytes using IL17 as a stimulus. The first screen utilized a pooled CRISPR library and the second utilized an annotated small molecule library. This talk will compare the results from the two screens and highlight a novel target of interest identified by both screens.

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

10:20 Nucleic Acid Detection with RNA-Guided RNA Targeting CRISPR Cas13
Jonathan Gootenberg, Ph.D. Student, Laboratory of Dr. Feng Zhang, Broad Institute of MIT and Harvard
Rapid, inexpensive, and sensitive nucleic acid detection may aid point-of-care pathogen detection, genotyping, and disease monitoring. We combine the RNA-targeting CRISPR effector Cas13a with isothermal amplification to establish a CRISPR-based diagnostic (CRISPR-Dx), providing rapid DNA or RNA detection with attomolar sensitivity and single-base mismatch specificity. We use this Cas13a-based molecular detection platform, termed SHERLOCK, to detect specific strains of Zika and Dengue virus, distinguish pathogenic bacteria, genotype human DNA, and identify cell-free tumor DNA mutations.

10:50 Harnessing RNA Targeting CRISPR Systems for Transcriptome Engineering and Human Health
Omar Abudayyeh, M.D., Ph.D. Student, Harvard-MIT Health Sciences and Technology, Laboratory of Dr. Feng Zhang, Broad Institute of MIT and Harvard
RNA plays important and diverse roles in biology, but molecular tools to manipulate and measure RNA are limited. Here, we demonstrate that RNA-targeting CRISPR effector Cas13a can be engineered for mammalian cell RNA knockdown and binding. LwCas13a can be heterologously expressed in mammalian and plant cells for targeted knockdown of either reporter or endogenous transcripts and targeted RNA binding for transcript imaging. Our results establish CRISPR-Cas13a as a flexible platform for RNA targeting with wide applicability for studying RNA in mammalian cells.

11:20 Enjoy Lunch on Your Own

12:35 pm Plenary Keynote Program
(click here for details)

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

2:45 Close of Conference

5th Annual | September 27-28, 2017

Targeting Ocular Disorders

The Latest Targets, Pathways and Drug Delivery Methods

With its complex structure and the breadth of ocular disorders, the eye presents unique challenges to drug discovery. Cambridge Healthtech Institute's Fifth Annual Targeting Ocular Disorders conference provides a platform to discuss novel targets and disease pathways, the latest drug delivery methods, and the most promising emerging therapies for both front and back of eye disorders. A special focus will be on gene therapy, especially optogenetics, and treatments outside of the well-established anti-VEGF monotherapies. Attendees will be able to hear leading experts in ocular drug delivery discuss the pros and cons of various drug delivery methods. The event will cover a broad range of diseases including but not limited to glaucoma, wet and dry age-related and diabetic macular degeneration, and noninfectious uveitis.

RECOMMENDED ALL ACCESS PACKAGE:

- September 26-27 Conference: CRISPR for Disease Modeling and Target Discovery
- September 27-28 Conference: Targeting Ocular Disorders
- September 28-29 Symposium: Tackling Rare Diseases

WEDNESDAY, SEPTEMBER 27

11:50 am Conference Registration Open

12:35 pm Plenary Keynote Program
(click here for details)

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

GENE EDITING & GENE THERAPY BREAKTHROUGHS FOR OCULAR DISORDERS

2:45 Welcome Remarks
Lee Yuan, Conference Director, Cambridge Healthtech Institute

2:50 Chairperson's Opening Remarks
Bo Liang, Ph.D., President, R&D, IVIEW Therapeutics, Inc.

2:55 Lentiviral Gene Therapy for Ocular Disease
Scott Ellis, Ph.D., Head, Early Development, Oxford BioMedica
Oxford BioMedica's gene therapy for Parkinson's disease (ProSavin®) was the first ever lentiviral gene therapy directly administered in man, and its shared LentiVector® gene therapy platform is the basis of three ocular gene therapies currently under clinical evaluation as well as several earlier-stage programs in development. This talk will review our previous experience and current plans using the LentiVector® platform in the development of gene therapies for chronic ocular diseases.

3:25 Intravitreal Gene Therapy for Dry AMD
Jay S. Duker, M.D., Director, New England Eye Center; Professor and Chairman, Department of Ophthalmology, Tufts Medical Center, Tufts University School of Medicine; Founder, Hemera Biosciences
Dry age related macular degeneration (AMD) represents a significant cause of visual loss in the elderly but lacks an approved therapy. Inhibiting the complement system locally within the eye shows promise as a therapeutic intervention. Hemera Biosciences' lead product, HMR59, is an AAV2 based gene therapy delivered intravitreally that blocks membrane attack complex (MAC) through the local production of soluble CD59. HMR59 is currently being tested in a Phase I clinical trial in eyes with severe dry AMD and geographic atrophy (GA).

3:55 Development of Sustain Release Povidone Iodine Ophthalmic Drop through Novel *in situ* Gel Formulation
Bo Liang, Ph.D., President, R&D, IVIEW Therapeutics, Inc.
IVIEW developed a long-acting povidone iodine (PVP-I) ophthalmic drop IVIEW-1201 for the treatment of active infections of the conjunctiva and cornea by bacteria, mycobacteria, virus, fungus, or amoebic causes. There is currently no broadly effective therapy that treats all causes of infection and nothing is approved for the treatment of viral conjunctivitis. This represents a massive unmet need in ophthalmology. The novel in-situ gel formulation IVIEW-1201 where the effective concentration of PVP-I is maintained by the equilibrium between solution PVP-I and the gel bound components results in a long lasting, less toxic pharmacological effect.

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

5:00 Development of an Intravitreal AAV-Based Treatment for Wet Age-Related Macular Degeneration
Mehdi Gasmi, Ph.D., CTO & CSO, Adverum Biotechnologies

5:30 Optogenetic Therapy for Retinal Dystrophies
Anne Douar, Ph.D., Project Director, GenSight Biologics
Optogenetics aims at transferring a gene encoding for a light-sensitive molecule to restore photosensitivity in retinal cells that are still wired into the inner retina layers. The GS030 treatment combines such gene therapy based approach in combination with a photo-stimulating device to potentiate the biologics' activity. Translational research has allowed to demonstrate the proof of concept in rodent and non-human primate models and to establish the safety profile of the product, paving the way to the first in human clinical trial currently in preparation.

6:00 A CRISPR Medicine Approach for Treating Leber Congenital Amaurosis Type 10
Gerald F. Cox, M.D., Ph.D., CMO, Editas Medicine
Leber congenital amaurosis type 10 (LCA10) is a rare infantile-onset retinal dystrophy caused by autosomal recessive mutations in the CEP290 gene. The most common LCA10 mutation, c.2991+1655A>G, creates a cryptic splice acceptor site in intron 26 that causes missplicing and leads to a non-functional protein. CRISPR/Cas9 is being applied to correct the underlying common genetic defect in LCA10, with the goal of providing a durable treatment that restores vision to patients.

6:30 Close of Day

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

THURSDAY, SEPTEMBER 28

7:30 am Registration Open

8:00 Interactive Breakout Discussion Groups with Continental Breakfast
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. Details on the topics and moderators are available on the conference website.

GENE EDITING & GENE THERAPY BREAKTHROUGHS FOR OCULAR DISORDERS

9:00 Chairperson's Remarks
Naj Sharif, Ph.D., FARVO, FBPhS, Executive Director; Head, Global Alliances & External Research, Santen, Inc.

9:05 Investigational Gene Therapy for Inherited Retinal Dystrophies Due to Biallelic Mutations in *RPE65*
Daniel Chung, D.O., Clinical Ophthalmic Lead, Sparks Therapeutics
This presentation is a review of the latest results from a Phase III, open-label, randomized, controlled trial evaluating the safety and efficacy of AAV2-hRPE65v2 (*SPK-RPE65*) to treat inherited retinal dystrophies caused by biallelic mutations in the *RPE65* gene, following adeno-associated virus mediated gene transfer to the retina.

NOVEL TARGETS & DISEASE PATHWAYS

9:35 Novel Glaucoma Drugs and Devices: Paving Paths towards Retinoprotection
Naj Sharif, Ph.D., FARVO, FBPhS, Executive Director; Head, Global Alliances & External Research, Santen, Inc.
Whilst prostaglandin FP-receptor agonists are mainstay current therapeutics used to treat ocular hypertension (OHT) associated with primary open-angle glaucoma (POAG), a number of novel new drugs are on the horizon awaiting FDA approvals. There has also been a recent revolution in the development and clinical utility of minimally-invasive-glaucoma-surgery (MIGS) devices to lower intraocular pressure (IOP) for managing OHT/POAG. However, since reduction of IOP does not always reduce or prevent vision loss from POAG, the holy-grail of neuroprotective therapy, alone or in conjunction with IOP lowering, still represents an achievable goal. These aspects will be addressed in this presentation.

10:05 Plasma Kallikrein Inhibitors for the Treatment of Diabetic Retinopathy/Diabetic Macular Edema
Timothy Shiau, Ph.D., Senior Scientist, Chemistry, Verseon
Topically-applied plasma kallikrein inhibitors are a promising mechanism of slowing, stopping, or reversing diabetic macular edema. We present a series of small molecule, nanomolar inhibitors of plasma kallikrein and progress toward *in vivo* efficacy in a diabetic retinopathy model following topical dosing.

10:35 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

11:20 Plasma Kallikrein Inhibition as a VEGF-Independent Treatment for Diabetic Macular Edema
Edward P. Feener, Ph.D., Co-Founder and CSO, KalVista Pharmaceuticals
This talk will present the scientific and clinical rationale for targeting plasma kallikrein as a novel VEGF-independent treatment for diabetic macular edema (DME). Increased plasma kallikrein levels have been identified in vitreous from DME patients. Preclinical studies have demonstrated that plasma kallikrein induces retinal edema via a VEGF-independent mechanism. KalVista has discovered and developed an intravitreally administered plasma kallikrein inhibitor, KVD001. The Company has successfully completed its first-in-human study in patients with DME and is preparing for Phase II studies.

DRUG DELIVERY METHODS FOR OCULAR DISORDERS

11:50 Late Breaking Presentation

12:20 pm Sponsored Presentation
(Opportunity Available)

12:50 Session Break

1:00 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:50 Refreshment Break in the Exhibit Hall with Poster Viewing

2:35 Chairperson's Remarks
Sharon Klier, Vice President, Ophthalmology, Medical, Quark Pharmaceuticals

2:40 Novel Injectable Products for Treatment of Ocular Diseases
Ming Yang, Ph.D., Director, Research, Graybug Vision
Graybug Vision's lead product, GB-102, consists of an approved receptor tyrosine kinase inhibitor, sunitinib malate, that inhibits multiple pathogenic angiogenesis pathways known to be involved in choroidal neovascularization, the cause of neovascular AMD. Graybug Vision has incorporated sunitinib in its novel delivery system to allow a potential twice per year injection. Graybug Vision has also developed a library of compounds to treat glaucoma by lowering intraocular pressure alone or in combination with neuroprotection when injected twice per year into the subconjunctiva.

3:10 Sustained Micro-Dose Drug Delivery with Injectable Inserts: Current Status and Emerging Applications
Dario A. Paggiarino, M.D., Vice President, CMO, pSivida
Sustained linear-release, micro-dose delivery of antiviral and anti-inflammatory agents has evolved over the years from surgically implanted to injectable miniaturized inserts. The same technology showing long-term clinical benefit in past approved products is now being developed in the delivery of new agents and ocular conditions for which micro-dosing would be key in providing extended control of disease pathophysiology.

3:40 Session Break

3:55 Intracanalicular Inserts for Drug Delivery – Applications in Managing Ophthalmic Diseases
Amar Sawhney, Ph.D., Executive Chairman, Ocular Therapeutix
Intracanalicular inserts may prove to be a promising modality for non-invasive placement of drug products to deliver courses of therapy for several ophthalmic diseases in the anterior segment or on the ocular surface. Dextenza is being developed to deliver an entire 30-day course of preservative-free steroid therapy for pain and inflammation following ocular surgery with a single insertion. Additionally, Ocular

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Therapeutix is evaluating OTX-TP (travoprost insert) for the treatment of glaucoma and ocular hypertension that could provide therapy for up to 3 months. This talk will explore the design, development, and clinical data surrounding these drug product candidates and other sustained release product candidates in the Ocular Therapeutix pipeline.

4:25 PANEL DISCUSSION: Pros and Cons of Ocular Drug Delivery Methods

Moderator: Elias Reichel, M.D., Professor and Vice Chair, Tufts University School of Medicine; Director, Vitreoretinal Diseases and Surgery Service, New England Eye Center; Founder, Hemera Biosciences

Panelists: Ming Yang, Ph.D., Director, Research, Graybug Vision

Amar Sawhney, Ph.D., Executive Chairman, Ocular Therapeutix

Dario A. Paggiarino, M.D., Vice President, CMO, pSivida

The panelists will discuss key considerations when determining the right ocular drug delivery method for their products and challenges that they faced. There will also be general discussion about the pros and cons of different delivery methods for the eye.

4:55 Close of Conference

25 YEARS Cambridge HEALTHTECH Institute
A Division of Cambridge Innovation Institute

2nd Annual | September 26-27, 2017

NK Cell-Based Cancer Immunotherapy

Harnessing NK Cells for the Development of New Cancer Immunotherapies

While a large portion of cancer immunotherapies focus on targeting T cells, there has been a surge of interest in harnessing the relatively underexplored natural killer (NK) cell system for therapeutic intervention. A growing number of studies into pathways elucidating NK cell biology, activating and suppressing NK cell function, the development of pharmacological and genetic methods to enhance NK cell anti-tumor immunity, and the ability to expand NK cells *ex vivo* have set the stage for a new generation of cancer immunotherapies.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Immunomodulatory Small Molecules
- September 26-27 Conference: NK Cell-Based Cancer Immunotherapy
- September 27-28 Conference: Targeting Tumor Myeloid Cells
- September 27 Short Course: Impact of Convergence of Immunotherapy and Epigenetics on Drug Discovery
- September 28-29 Symposium: Tackling Rare Diseases

TUESDAY, SEPTEMBER 26

7:00 am Registration Open and Morning Coffee

ADVANCES IN NK CELL-BASED CANCER IMMUNOTHERAPY

8:00 Welcome Remarks
Kip Harry, Senior Conference Director, Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks
Karl-Johan Malmberg, M.D., Ph.D., Professor, Department of Cancer Immunology, Institute for Cancer Research, Oslo University Hospital

8:10 KEYNOTE PRESENTATION: Novel Ways to Target and Activate NK Cells to Treat Cancer
Sarah A. Cooley, M.D., Associate Professor, Medicine, Division of Hematology, Oncology and Transplantation, University of Minnesota
We have discovered a new subset of NK cells termed adaptive with properties of immunologic memory induced by cytomegalovirus, which we think has potent anti-tumor activity. These cells exhibit enhanced anti-tumor activity *in vitro* and *in vivo*. We have recently developed a method to expand these cells from CMV seropositive donors and are testing this product in clinical trials. Lastly, NK cells can be made antigen specific to target tumors through IL-15 tri-specific killer engagers (TriKEs) to enhance the activity of NK cells in the clinic.

8:40 Update: aNK and haNK for Cancer Treatment
Hans Klingemann, M.D., Ph.D., Vice President, Research & Development, NantKwest, Inc.
I will provide an update on clinical trial activities with aNK haNK cells expressing the high affinity Fc-Receptor for combination therapy with mAbs taNK cells engineered to express CARs for neo-epitopes. I will also discuss augmenting NK activity with IL-15 super-agonist Altor 803, as well as optimizing NK target activity through CRISPR-based gene manipulation.

9:10 hnCD16-NK Cells: Cornerstone Approach for Off-the-Shelf Cancer Immunotherapy
Bahram (Bob) Valamehr, Ph.D., MBA, Vice President, Cancer Immunotherapy, Fate Therapeutics, Inc.
Through targeted transgene integration, we produced a clonal pluripotent cell master cell line to continuously produce NK cells engineered to uniformly express a novel high affinity, non-cleavable version of CD16 Fc receptor (hnCD16-NK). Preclinical data highlight the therapeutic value of hnCD16-NK cells as an ideal ADCC-mediated "off-the-shelf" NK cell-based immunotherapeutic product with augmented persistence, anti-tumor capacity, manufacturing reliability and preclinical efficacy.

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

THERAPEUTICALLY TARGETING NK CELLS

10:25 Tetravalent Bispecific NK Cell-Engaging Technology for the Activation of Innate and Adaptive Immunity in Cancer
Martin Treder, Ph.D., CSO, R&D, Affimed
Affimed has developed a pipeline of clinical & preclinical stage NK cell engagers; they are CD16A-specific tetravalent, bispecific antibodies, characterized by high-affinity, specific binding to CD16A and superior NK cell retention compared to conventional antibodies. Strongly differentiating them from marketed therapeutic antibodies is the virtual lack of interference by circulating IgGs. Our NK cell platform has been shown to be safe and to act synergistically in combination with checkpoint modulators, activating both innate and adaptive immunity.

10:55 NK Cell Activation, Desensitization and Inhibition: Approaches to Mobilize NK Cells for Cancer Immunotherapy
David H. Raulet, Ph.D., C.H. Li Professor of Immunology and Pathogenesis; Co-Chair, Department of Molecular and Cell Biology, University of California, Berkeley
Mechanisms of NK inhibition and desensitization will be discussed. Approaches to reverse inhibition and desensitization for cancer therapy will be presented. Importantly, NK cells must be activated in order to target tumor cells. Activation of NK cells requires engagement of activating receptors on NK cells and cues from the innate immune system. Immunotherapeutic approaches being developed by Dragonfly Therapeutics to activate NK cells and target them to tumors will be discussed.

11:25 Discovery and Validation of Novel NK Cell Checkpoints
Jai Rautela, Ph.D., CSO & Co-Founder, oNKo-innate

11:55 Rapidly Characterizing and Verifying Immunological Cell Populations Using Alpha and LANCE TR-FRET Technology *Sponsored by* PerkinElmer

Jeanine M. Hinterneder, Ph.D., Applications Scientist, PerkinElmer

In the quest to develop new strategies to selectively expand tumor reactive NK cells for cancer immunotherapy, there is a need for more rapid, reliable assays to verify and quantify characteristic biomarkers expressed in these populations. At PerkinElmer, we provide a myriad of tools for rapidly measuring proteins expressed in multiple cell populations, with AlphaLISA and LANCE TR-FRET kits designed to quantify immunotherapy targets like CTLA-4, CD-28, CD-80, PD-1, and PD-L1 as well as cytokines crucial for NK cell development and proliferation, such as IL-15 and IL-21. For examining the mechanisms of action (MOA) of potential therapeutic antibodies, we offer a variety of binding assays, including two kits for probing analyte affinity for the FcγR3A (CD16A) receptor (either high or low affinity isoforms). Downstream signaling pathways can be studied further using our large selection of Alpha SureFire Ultra kits for measuring phosphorylation events, such as our kits for measuring STAT activity (e.g., p-STAT-3 and total STAT-3) and SLP-76 phosphorylation. Additionally, because these assays are highly sensitive, only small sample volumes are required, so multiple targets can be measured from a single well.

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

NK CELL IMMUNO-ONCOLOGY AND CLINICAL STUDIES

1:50 Chairperson's Remarks

Hans Klingemann, M.D., Ph.D., Vice President, Research & Development, NantKwest, Inc.

1:55 Functional Diversification of Human NK Cells - Implications for Cell-Based Cancer Immunotherapy

Karl-Johan Malmberg, M.D., Ph.D., Professor, Department of Cancer Immunology, Institute for Cancer Research, Oslo University Hospital

In this talk, I will discuss new insights into the underlying mechanisms behind the functional diversification of human NK cells, including the dynamic imprints caused by NK cell responses to cytomegalovirus infection. In terms of clinical translation, we are currently exploring new strategies to selectively expand tumor reactive NK cell subsets for cancer immunotherapy.

2:25 Utilizing Immunostimulatory Cytokines to Unleash Natural Killer Cell Anti-Tumor Responses

Todd A. Fehniger, M.D., Ph.D., Associate Professor, Medicine, Division of Oncology, Washington University School of Medicine

Memory-like NK cells exhibit enhanced functional response to leukemia and other malignancies *in vitro* and *in vivo*, and recently have shown promise in a first-in-human early phase clinical study for patients with acute myeloid leukemia. IL-15 receptor super agonist complexes provide *in vivo* endogenous IL-15 receptor trans-presentation, and may be harnessed to support the expansion and functional capacity of NK cell in cancer patients. Thus, cytokine function-enabled NK cells represent an innovative translational immunotherapy approach for cancer patients.

2:55 Profiling How Immune Inhibitors Secreted by Melanoma Affect NK & Other Immune Cells *Sponsored by* ELSEVIER

Anton Yuryev, Ph.D., Consulting Director, Biology, Research & Development, Elsevier

Understanding how cancer cells inhibit the local immune response is fundamental to selecting the best targets for immune-based therapies. A simplified workflow that incorporates disparate information sources and that helps provide connected, integrated data to support target selection will be presented, using immune cells suppressed by secreted melanoma proteins.

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

4:05 Adoptive Immunotherapy with Expanded NK Cells - The Impact of STAT3 Signaling and Crosstalk with Adaptive Immunity

Dean Anthony Lee, M.D., Ph.D., Professor, Pediatrics; Director, Cellular Therapy and Cancer Immunotherapy Program, Nationwide Children's Hospital; James Comprehensive Cancer Center/Solove Research Institute, The Ohio State University

We developed a system for *ex vivo* NK cell expansion based on genetically modified feeder cells expressing IL-21, which through STAT3 signaling induces robust activation and proliferation of NK cells from normal donors, patients, cord blood, and embryonic/pluripotent stem cells. We established the GMP infrastructure to manufacture clinical-grade NK cells using this approach, and infused expanded NK cells into patients as monotherapy, in single or repeated infusions, or in combination with chemotherapy or stem cell transplantation.

4:35 Immune Responses in the Cancer Patients Who Receive the Random Donor-Derived Expanded NK Cell

Sungyoo Cho, Ph.D., CSO, Green Cross LabCell

Ex vivo-expanded and highly activated NK cells from random unrelated healthy donors injected into patients with malignant lymphoma or advanced recurrent solid tumors with or without lymphodepletion. Different from CAR-T treatment, there is no SAE and cytokine storm in multiple high dose injection. NK cell treatment shows different from T cell therapy in GvHD/GvT aspect. NK cell persistency and efficacy can control by pre-treatment regimen, and the rejection and antibody induction from recipients can also be controlled.

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. Details on the topics and moderators are available on the conference website.

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

7:10 Close of Day

WEDNESDAY, SEPTEMBER 27

7:30 am Registration Open and Morning Coffee

NK CELL-BASED DEVELOPMENT PLATFORMS FOR CANCER IMMUNOTHERAPY

8:00 Chairperson's Remarks

Bahram (Bob) Valamehr, Ph.D., MBA, Vice President, Cancer Immunotherapy, Fate Therapeutics, Inc.

8:05 Autologous *ex vivo* Understanding of NK Cell Effector Functions: A Single-Cell Lab-on-a-Chip Perspective
Tania Konry, Ph.D., Assistant Professor, Department of Pharmaceutical Sciences, Northeastern University
Natural Killer (NK) cells are an essential component of innate immunity that actively inhibit tumor development. Here we present a novel single-cell method of analyzing the mechanisms underlying the cellular interactions of NK cells with multiple myeloma cells. The integrated droplet microfluidics device developed by our group permits compartmentalization of cell pairs and secreted products within sub-nanoliter volumes and thereby controls cell-to-cell communication by limiting it to interactions between the co-encapsulated cells. It allows monitoring of both contact-dependent (immune synapse formation, delivery of lytic hits) and contact-independent cellular interactions (release of cytokines, chemokines) simultaneously. This dynamic single-cell experimental model is expected to provide preclinical information particularly relevant to the scenario of NK cell-cancer cell interactions.

8:35 oNKord® – Genetic Update – From Proven Safety to Established Efficacy
Jan Spanholtz, Ph.D., CSO, Glycostem
Glycostem Therapeutics is developing allogeneic cellular immunotherapy to treat various types of cancer. Glycostem's patented industrial applicable production platform technology enables the generation of a multitude of products like expanded stem cells, NK cells, dendritic cells and genetically modified versions of those. The universal allogeneic treatment principle, allowed by the unrestricted use of immune cells in various types of cancer, is enabled by unlimited source of cord blood stem cells.

9:05 Selected Poster Presentation: IL-15 Infusions in Cancer Patients Induce Expansions of Cytotoxic CD56bright NK Cells with Increased Cytokine Release Capabilities
Sigrid P. Dubois, Ph.D., Staff Scientist, Lymphoid Malignancies Branch, Center for Cancer Research National Cancer Institute

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

TECHNOLOGIES ENABLING NK CELL-BASED CANCER IMMUNOTHERAPY

10:20 SPEAKER CANCELLATION: Expansion of NK Cells
Eun Young Choi, Ph.D., Researcher, Laboratory, IMMUNISBIO
With 60 cc of patient's peripheral blood, more than 5 billion immune cells can be cultured. The cultured immune cell would consist of 60% natural Killer cell (NK cell) and NKT cell and 40% T cell. With autologous and cytotoxic characteristics of NK cell, it can be effectively used in treating cancer without side effects.

10:50 Autologous *ex vivo* Expanded NK Cells for Solid Tumor Immunotherapy
Ali Ashkar, D.V.M., Ph.D., Professor, Pathology and Molecular Medicine, McMaster Immunology Research Centre, McMaster University
Recent advances in NK cell expansion and activation have generated renewed interest in adoptive NK cell therapy for cancers. We have expanded NK cells from blood of breast, lung and ovarian cancer patients and have investigated their activities against autologous primary tumor cells. In addition, we have established xenograft models with the primary tumors to study the anti-tumor activities of autologous NK cells against primary tumor cells *in vivo*. *Ex vivo* expanded NK cells survive and proliferate *in vivo* in the presence of autologous PBMCs.

11:20 Enjoy Lunch on Your Own

12:35 pm Plenary Keynote Program
(click here for details)

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

2:45 Close of Conference

Cambridge 25 YEARS HEALTHTECH Institute
A Division of Cambridge Innovation Institute

Inaugural | September 27-28, 2017

Targeting Tumor Myeloid Cells

Reshaping the Tumor Microenvironment (TME)

Recently our understanding of the Tumor Microenvironment (TME) has shed light onto the importance of tumor-infiltrating myeloid cells, such as tumor-associated neutrophils (TANs), myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and tumor-associated dendritic cells (TADCs), as critical contributors to the suppression of innate and adaptive immune responses. Importantly, these cells exist in various states within the TME, producing either immunosuppressive or immunostimulatory responses. Therapeutically targeting tumor myeloid cells to eliminate or convert them to their immunostimulatory state has emerged as a new and complementary strategy in the suite of cancer immunotherapy approaches.

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- September 27 Short Course: Impact of Convergence of Immunotherapy and Epigenetics on Drug Discovery
- September 28-29 Symposium: Tackling Rare Diseases

WEDNESDAY, SEPTEMBER 27

11:50 am Conference Registration Open

12:35 pm Plenary Keynote Program
(click here for details)

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

TUMOR-ASSOCIATED MACROPHAGES (TAMs) AS THERAPEUTIC TARGETS

2:45 Welcome Remarks
Kip Harry, Senior Conference Director, Cambridge Healthtech Institute

2:50 Chairperson's Opening Remarks
Jennifer Guerriero, Ph.D., Instructor of Medicine, Lead Scientist of the Immuno-Oncology Group, Letai Laboratory, Dana-Farber Cancer Institute

2:55 KEYNOTE PRESENTATION: Tumor-Associated Macrophages as a Therapeutic Target
Alberto Mantovani, M.D., Professor, Pathology, Humanitas University; Scientific Director, Istituto Clinico Humanitas
Macrophages are key orchestrators of chronic inflammation. They respond to microenvironmental signals with polarized genetic and functional programmes. M1 and M2 cells represent simplified extremes in a universe of functional states. Available information suggests that some TAM are an M2 population. Polarization of phagocytes sets these cells in a tissue remodeling and repair mode and orchestrate the smoldering and polarized chronic inflammation associated to established neoplasia. Intrinsic metabolic features and orchestration of metabolism are key components of macrophage polarization and function.

3:25 Macrophage-Targeted Cancer Immunotherapy
Carola Ries, Ph.D., Head, Cancer Immunotherapy I, Pharma Research and Early Development (pRED), Roche Innovation Center Munich
To therapeutically target TAMs, we harnessed their dependence on the key survival factor, macrophage colony-stimulating factor 1 (CSF1), and developed a monoclonal antibody (Emactuzumab/RG7155) that blocks dimerization and activation of human CSF1R. Treatment of cancer patients with Emactuzumab substantially reduces the intratumoral TAM infiltrate. We will present data on a cancer immunotherapy combination, which targets TAMs and stimulates an anti-tumoral T cell response leading to tumor remission in preclinical mouse models.

3:55 Selected Poster Presentation: Targeting Tumor-Associated Macrophages by Melittin Suppresses Tumor Progression in a Lewis Lung Carcinoma Mouse Model
Chanju Lee, Research Scientist, Kyung Hee University

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

MODULATING MACROPHAGES IN THE TUMOR MICROENVIRONMENT

5:00 A First-in-Class Selective Class IIa Histone Deacetylase (HDAC) Inhibitor, TMP195
Michael Nolan, Ph.D., Director, GlaxoSmithKline
We recently reported that a first-in-class selective class IIa HDAC inhibitor (TMP195) influenced human monocyte responses to colony stimulating factors CSF-1 and CSF-2 *in vitro*. Here, we utilize a macrophage-dependent autochthonous mouse model of breast cancer to demonstrate that *in vivo* TMP195 treatment alters the tumor microenvironment and reduces tumor burden and pulmonary metastases through macrophage modulation. TMP195 induces recruitment and differentiation of highly phagocytic and stimulatory macrophages within tumors.

5:30 Discovery and Development of DCC-3014, a Highly Specific Inhibitor of CSF1R Kinase
Bryan Smith, Ph.D., Senior Director of Biology, Deciphera Pharmaceuticals
The discovery and development of DCC-3014 will be presented, including the use of Deciphera's switch control platform to identify highly specific inhibitors of CSF1R kinase. DCC-3014 potently inhibits CSF1R, while sparing near neighbor kinases FLT3, KIT, and PDGFRs by >100 to >1,000 fold, and additionally sparing a 300 kinase panel by >1,000 fold. Cellular studies, *in vivo* PK/PD studies, and *in vivo* efficacy

studies in syngeneic cancer models (single agent and in combination with anti-PD1) will also be presented.

6:00 Class IIa HDAC Inhibition Promotes an Anti-Tumor Macrophage Phenotype that Induces Breast Tumor Regression and Inhibits Metastasis
Jennifer Guerriero, Ph.D., Instructor of Medicine, Lead Scientist of the Immuno-Oncology Group, Letai Laboratory, Dana-Farber Cancer Institute
We recently reported that a first-in-class selective class IIa HDAC inhibitor (TMP195) influenced human monocyte responses to colony stimulating factors CSF-1 and CSF-2 *in vitro*. Here, we utilize a macrophage-dependent autochthonous mouse model of breast cancer to demonstrate that *in vivo* TMP195 treatment alters the tumor microenvironment and reduces tumor burden and pulmonary metastases through macrophage modulation. TMP195 induces recruitment and differentiation of highly phagocytic and stimulatory macrophages within tumors.

6:30 Close of Day

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

THURSDAY, SEPTEMBER 28

7:30 am Registration Open

8:00 Interactive Breakout Discussion Groups with Continental Breakfast
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. Details on the topics and moderators are available on the conference website.

TARGETING THE CD47-SIRP(ALPHA) AXIS

9:00 Chairperson's Remarks
Michael M. Goldberg, M.D., President and CEO, Navidea Biopharmaceuticals, Inc. & Macrophage Therapeutics, Inc.

9:05 A Portfolio of Humanized Anti-CD47 Monoclonal Antibodies with Diverse Combinations of Functional Properties and Preclinical Anti-Tumor Activity
Robert W. Karr, M.D., CSO, Tioma Therapeutics
Anti-CD47 antibodies have also been shown to promote an anti-tumor adaptive immune response. Ti-061, Tioma's first generation humanized anti-CD47 antibody, has preclinical anti-tumor activity *in vitro* and *in vivo* and is being studied in a Phase I trial. Tioma's second generation anti-CD47 antibodies have novel combinations of functional properties, including direct killing of tumor cells, minimal RBC binding and increasing phagocytosis of tumor cells, potentially enhancing their anti-tumor activity.

9:35 TTI-621 (SIRPαFc): A Checkpoint Inhibitor of the Innate Immune System that Blocks the CD47 "Do Not Eat" Signal
Lisa Johnson, Ph.D., Research Scientist, Trillium Therapeutics, Inc.
Trillium Therapeutics is developing TTI-621 (SIRPαFc), a fusion protein consisting of the CD47-binding domain of human SIRPα linked to the Fc region of human IgG1. It is designed to block the CD47 "do not eat" signal and engage activating Fc receptors on macrophages to enhance phagocytosis and anti-tumor activity and is currently being evaluated in two Phase I clinical studies. This presentation will discuss the preclinical rationale and emerging clinical data for this novel innate immune system checkpoint inhibitor.

10:05 Selective Targeting of SIRP Alpha Induces Potent Memory Anti-Tumor Immune Responses in Mice and Does Not Prevent SIRP Gamma Dependent Human T Cell Responses
Bernard Vanhove, Ph.D., COO, OSE Immunotherapeutics
Using murine models of TNBC and HCC, we noticed a preclinical efficacy of antagonistic anti-SIRPalpha mAbs in monotherapy or in combination with anti-PDL-1 and 4-1BB mAbs. Combinations elicited anti-tumor T cell responses. In humans, but not in mice, CD47 also interacts with SIRPgamma expressed by T cells, playing a role in human T cell proliferation. We show here that blocking CD47/SIRPgamma interaction is deleterious for T cell responses *in vitro* while specifically targeting SIRPalpha is "T cell friendly".

10:35 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

11:20 Targeting CD47 with High-Affinity SIRPα Fusion Protein to Enhance Both Innate and Adaptive Immunity against Cancer without Hematological Toxicity
Hong I. Wan, Ph.D., Chief Scientific Officer, Alexo Therapeutics, Inc.
CD47 is a widely expressed cell surface protein that functions as a marker of self. Interaction of CD47 with signal regulatory protein-α (SIRPα), its receptor on macrophages, inhibits phagocytosis. CD47 blockade may enhance both innate and adaptive immunity against cancer and is being evaluated as a new immunotherapy. Fusion proteins comprised of the N-terminal D1 domain of SIRPα and inactive Fc domains were engineered to bind CD47 with high affinity and prevent interaction of CD47 with wild type SIRPα. These high-affinity SIRPα fusion proteins enhanced the activity of multiple anti-cancer antibodies and have minimal effect on normal blood cells both *in vitro* and *in vivo*. ALX148, a high-affinity CD47 blocker designed to avoid toxicity on CD47-expressing blood cells, is currently in clinical development in a broad spectrum of malignancies (NCT03013218).

NOVEL AGENTS TARGETING TUMOR-ASSOCIATED MYELOID CELLS

11:50 Targeting the Tumor Microenvironment by Selectively Depleting the Tumor Supporting M_2 Macrophages
Michael M. Goldberg, M.D., President and CEO, Navidea Biopharmaceuticals, Inc. & Macrophage Therapeutics, Inc.
Macrophage Therapeutics has developed a highly targeted agent that can deliver therapeutic payloads with extremely high Kds, on the order of 10^{-11} or higher, targeted to the mannose receptor (CD206). The mannose receptor is only expressed on activated macrophages and internalizes and recycles every 15 minutes. MT1002 targets CD206 and delivers a therapeutic agent linked to the targeted dextran backbone with a pH sensitive linker. Data will be presented that demonstrates that MT1002 depletes the TAMs via apoptosis, without any effect on non-activated macrophages.

12:20 pm Enjoy Lunch on Your Own

1:50 Refreshment Break in the Exhibit Hall with Poster Viewing

NOVEL AGENTS TARGETING TUMOR-ASSOCIATED MYELOID CELLS *(Cont.)*

2:35 Chairperson's Remarks
Bernard Vanhove, Ph.D., COO, OSE Immunotherapeutics

2:40 Overcoming Resistance to Checkpoint Blockade by Selectively Targeting PI3K-Gamma in Tumor Myeloid Cells
Jeffery Kutok, M.D., Ph.D., CSO, Biology and Translational Medicine, Infinity Pharmaceuticals
IPI-549 is an investigational, orally administered immuno-oncology development candidate that selectively inhibits PI3K-gamma which is highly expressed in tumor associated myeloid cells. In preclinical studies, IPI-549 increases anti-tumor immunity by reprogramming tumor-associated myeloid cells from the M2, pro-tumor phenotype to the M1, anti-tumor phenotype and activating anti-tumor T cell responses. IPI-549 also overcomes immune checkpoint blockade resistance in preclinical tumor models.

3:10 EP4 Antagonism in Combination Immuno-Oncology Therapeutic Approaches
Xingfeng Bao, Ph.D., Head, Immuno-Oncology, Integrated Biology Engine, Eisai AiM Institute, Eisai, Inc.
PGE2 in the tumor microenvironment contributes to the accumulation of immunosuppressive myeloid cells by interacting with the EP4 receptor on newly arriving monocytes, skewing their development into MDSCs and TAMs. The EP4 antagonist E7046, now in Phase I/Ib trials, inhibits this interaction and enhances formation of a more favorable anti-tumor immune milieu. This approach combines well preclinically with T cell-directed immunotherapies such as checkpoint inhibitors in boosting anti-tumor immunity.

3:40 Session Break

3:55 Imprime PGG - A Yeast-Derived Pathogen-Associated Molecular Pattern (PAMP) Triggers the Anti-Cancer Immunity Cycle to Potentiate the Efficacy of Immune Checkpoint Inhibitors
Jeremy R. Graff, Ph.D., CSO and Senior Vice President, Research, Biothera Pharmaceuticals, Inc.
Imprime has been safely administered to >400 human subjects. Imprime triggers a cascade of immune activating events that re-polarize the immunosuppressive tumor microenvironment and elicit maturation of antigen presenting cells. Unlike other PAMPs (TLR and STING agonists), Imprime is administered systemically. In preclinical tumor models, Imprime robustly enhances the anti-tumor efficacy of CPIs. Accordingly, Imprime is now being explored in multiple Phase II clinical trials in combination with pembrolizumab.

4:25 Effective Combinatorial Immunotherapy for Castration-Resistant Prostate Cancer
Xin Lu, Ph.D., John M. and Mary Jo Boler Assistant Professor, Department of Biological Sciences, Center for Rare and Neglected Diseases, Harper Cancer Research Institute, University of Notre Dame
Targeted therapy against myeloid-derived suppressor cells (MDSCs), using multikinase inhibitors such as cabozantinib and BEZ235, also showed minimal anti-tumor activities. Strikingly, primary and metastatic CRPC showed robust responses to the synergistic effect when ICB was combined with MDSC-targeted therapy. Mechanistically, the combination efficacy was due to the upregulation of IL-1RA and suppression of MDSC-promoting cytokines secreted by mCRPC cells.

4:55 Close of Conference

Cambridge 25 YEARS HEALTHTECH Institute
A Division of Cambridge Innovation Institute

5th Annual | September 26-27, 2017

Antibodies Against Membrane Protein Targets - PART 1

Technologies to Enable the Advancement of GPCRs, Ion Channels and Transporters as Targets for Biotherapeutics | Part One: The Discovery Workflow

The two-part Antibodies Against Membrane Protein Targets 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 these target families to advance into the clinic and beyond. The first meeting in the set, The Discovery Workflow, offers an examination of state-of-the-art approaches for the expression of high-quality membrane protein antigens and antibody generation, then explores selection and screening strategies that can be applied to discover binders with functional activity against GPCR and ion channel targets.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Immunomodulatory Small Molecules
- September 25 Short Course: Targeting of Ion Channels with Monoclonal Antibodies
- September 26-27 Conference: Antibodies Against Membrane Protein Targets - Part 1: The Discovery Workflow
- September 27-28 Conference: Antibodies Against Membrane Protein Targets - Part 2: Structural Analysis, Characterization and Biopharmaceutical Development
- September 28-29 Symposium: CNS and Neurodegenerative Targets

TUESDAY, SEPTEMBER 26

7:00 am Registration Open and Morning Coffee

8:00 Welcome Remarks
Kent Simmons, Senior Conference Director, Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks
Jonas Lee, Ph.D., Scientist, Membrane Protein Purification, Amgen

8:10 KEYNOTE PRESENTATION: Prospects and Perspectives for Biotherapeutic Discovery against GPCRs, Channels and Transporters
Partha Chowdhury, Ph.D., Senior Director and Head, Antibody Discovery, Sanofi Genzyme
GPCRs, ion channels and transporters are a big part of the human proteome and linked with many diseases. Not counting the anti-infectives, over 35% of approved drugs are targeted to these classes of proteins and are exclusively small molecules. In recent times there has been a precipitous drop in discovery of these drugs. The challenges behind this open an opportunity for biologics development against GPCRs, ion channels, transporters and other MSMs.

GENERATION AND OPTIMIZATION OF MEMBRANE PROTEIN ANTIGENS

8:40 Isolation of Membrane Proteins into SMA Lipid Particles (SMALPs)
Tim Dafforn, Ph.D., Professor, Biotechnology, University of Birmingham, United Kingdom
In 2009, we developed an entirely detergent-free method (SMALPs) that allows the generic extraction and study of membrane proteins without removing them from their native lipid environment. In our current work, we have examined structure and function of SMALP solubilized proteins using techniques that include X-ray crystallography, Cryo-electron microscopy and small angle X-ray and neutron scattering. Together these approaches produce unique insights into the membrane protein function in the presence of the native lipid environment.

9:10 Customized Cell-Free Production of Membrane Proteins
Erik Henrich, Researcher, Institute of Biophysical Chemistry, University of Frankfurt, Germany
Cell-free synthetic biology provides new platforms for the efficient production of pharmaceutically relevant membrane proteins such as enzymes, transporters or GPCRs. Adjusting and refining artificial hydrophobic expression environments is a prerequisite for the functional folding of cell-free synthesized membrane proteins. We demonstrate synergies of nanoparticle technologies and cell-free systems as well as the importance of systematic lipid screening for the generation of high quality samples of even difficult membrane proteins.

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

10:25 Production of Membrane Protein Targets in Yeast *Pichia pastoris* by Auto-Induction
Jonas Lee, Ph.D., Scientist, Membrane Protein Purification, Amgen
Membrane proteins are important therapeutic targets, but they are challenging to produce in large scale. We produced mg scale of human membrane proteins for drug screening and phage display using yeast *Pichia pastoris*. To overcome challenges of low expression level and cumbersome expression protocol in Pichia, we invented an auto-induction method by exploiting the properties of an AOX1 promoter to maximize expression level per cell mass to improve protein purity.

10:55 Nanodiscs for Structural and Functional Studies of Membrane Proteins
Stephen G. Sligar, Ph.D., Swanlund Chair and Director, School of Molecular and Cellular Biology, University of Illinois at Urbana-Champaign
Membrane proteins make up more than half of all currently marketed therapeutic targets. Unfortunately, membrane proteins are inherently recalcitrant to study using the normal toolkit available to scientists. The Nanodisc platform provides a self-assembled system that renders typically insoluble yet biologically and pharmacologically significant targets such as receptors, transporters, enzymes, and viral antigens

soluble in aqueous media. I will present the latest discoveries and applications enabled by Nanodiscs.

11:25 Production of Monoclonal Antibodies against GPCRs Using Cell-Free Synthesized GPCR Antigen
Hiroyuki Takeda, Ph.D., Associate Professor and Principal Investigator, Division of Protea-Drug-Discovery Sciences, Proteo-Science Center, Ehime University, Japan
Production of high quality and large amounts of recombinant GPCR antigen is one of the bottlenecks of antibody development against GPCR. Recently we developed a large-scale GPCR expression method using wheat cell-free system and liposome. Using our bilayer-dialysis method, several mg of GPCRs can be synthesized efficiently in a short time with a high success rate. I will report recent antibody development results demonstrating the performance of cell-free synthesized liposomes as antigens.

11:55 Generation of Antibodies to Difficult Membrane Protein Targets
Sponsored by ANTIBODY SOLUTIONS
John Kenney, Ph.D., President, Antibody Solutions
Multi-pass trans-membrane and multimeric membrane proteins are challenging targets for antibody generation. Results for a multi-pass heteromeric amino acid transporter and other difficult membrane protein targets will be presented to show the key elements of an antibody discovery platform.

12:10 pm AptaAnalyzer™ - A New NGS Analysis Tool for Improved Identification of Peptide and Antibody Ligands
Sponsored by aptaIT
Michael Blank, Ph.D., CSO, AptaIT GmbH
AptaAnalyzer™ is an intuitive software tool enabling the improved identification of ligands from biopanning experiments or of B-cell receptors derived from defined stages of the immune system. AptaAnalyzer™ enables archiving of experiments as well as improved identification and optimization of rare but relevant peptide or antibody ligands.

12:25 Session Break

12:35 Luncheon Presentation: Optimization of Membrane Protein Antigens for Antibody Discovery
Sponsored by integral
Benjamin Doranz, Ph.D., President and CEO, Integral Molecular
Membrane proteins often represent challenging antigens for antibody discovery due to their low expression, structural complexity, and toxicity. We have developed a multi-tiered strategy to improve cell-surface protein expression and conformational stability. In addition to conventional optimization methods to improve protein trafficking, we employ a proprietary high-throughput mutagenesis strategy, using arrays of point mutations, engineered disulfide bonds and chimeras. Case studies will be presented for successfully engineered antigens that yielded high-affinity antibodies against native targets.

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

ANTIBODY GENERATION

1:50 Chairperson's Remarks
Andrew Nixon, Ph.D., Vice President, Biotherapeutics Molecule Discovery, Boehringer Ingelheim

1:55 Generating Functional Antibodies against GPCRs and Ion Channels
Trevor Wilkinson, Ph.D., Associate Director, Antibody Discovery and Protein Engineering, MedImmune, United Kingdom
Structurally complex membrane proteins such as GPCRs and ion channels are acknowledged as challenging targets for monoclonal antibody discovery. Strategies for the discovery of functional antibodies to these target classes are emerging. In this presentation, we will provide an overview of these emerging strategies and provide a number of case studies highlighting the discovery and optimization of antibodies against GPCRs and ion channels.

2:25 Strategies and Technologies for Antibody Discovery without Purified Protein
Jane Seagal, Ph.D., Senior Scientist, Biologics Generation Group, AbbVie Bioresearch Center
Lack of purified antigens is a limiting factor for antibody discovery against multi-spanning proteins. In this talk, enabling approaches (cell lines, membrane extracts, or peptides mimicking extracellular loops and cDNA immunizations) and orthogonal screening assays for the discovery of functional antibodies against challenging targets are discussed.

2:55 HuMab Chickens: The Next-Generation Antibody Discovery Platform
Sponsored by CRYSTAL BIOSCIENCE
Bill Harriman, Ph.D., CSO, Crystal Bioscience
Transgenic rodents producing human sequence antibodies are widely accepted as a reliable source of therapeutic candidates. However, their repertoires are limited by their evolutionary similarity to humans. Crystal Bioscience has expanded the repertoire of transgenic animals by engineering HuMab chickens producing fully human sequence, high affinity mAbs. In addition to revealing novel epitopes and, therefore novel IP, the Crystal Platform yields mAbs recognizing murine orthologs of human antigens that facilitate pre-clinical studies.

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

4:05 Generating Ion Channel Blocking Antibodies by Fusing Cysteine-Knot Miniproteins into Peripheral CDR Loops
John McCafferty, Ph.D., CEO, IONTAS, United Kingdom
Cysteine-knot miniproteins (knottins) have potential as therapeutic agents to block proteases and ion channels but suffer from manufacturing difficulties, short half-lives and a lack of specificity. We demonstrated that functional knottins can be inserted into peripheral antibody CDRs via short linkers while allowing additional contribution of binding from the remaining CDRs. The resulting "knotbody" retains the advantage of blocking activity from the knottin while enjoying extended half-life and additional specificity conferred by the antibody molecule.

4:35 Selection and Design of Agonist Antibodies to Receptor Tyrosine Kinases
Peter S. DiStefano, Ph.D., CSO, Zebra Biologics, Inc.
Recent technologies have allowed the selection of both agonist and antagonist antibodies to a variety of cell surface receptor types using large combinatorial antibody libraries infected into sensitive reporter cells bearing the receptor of interest. We have utilized this strategy to identify agonists to specific members of the receptor tyrosine kinase (RTK) family of cell surface receptors. Agonist antibodies can be identified with potent activity and selectivity.

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. Details on the topics and moderators are available on the conference website.

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

7:10 Close of Day

WEDNESDAY, SEPTEMBER 27

7:30 am Registration Open and Morning Coffee

SELECTION OF TARGET SPECIFIC ANTIBODIES

8:00 Chairperson's Remarks
Andrew Bradbury, Ph.D., Chief Scientific Officer, Specifica Inc.

8:05 Strategies to Identify Rare Functional Antibodies against Membrane Proteins
JT Koerber, Ph.D., Scientist, Antibody Engineering, Genentech
Integral membrane proteins comprise a large untapped target space for therapeutic antibodies, but the discovery of functional antibodies against this class of proteins remains a challenge. Numerous factors including antigen format, immunization or phage panning methods, and complex high-throughput functional screening methods limit the success of antibody discovery. I will discuss a new platform to enable efficient mining of antibodies that bind a membrane protein to identify rare functional clones.

8:35 Antibodies to Challenging Receptor Targets through NGS and Cell-Based Antibody Phage Panning
John Wheeler, Principal Research Scientist, Janssen BioTherapeutics
Several receptor targets cannot be made as soluble proteins and others are problematic for discovery of antibodies that bind to native protein conformations. Cell-based phage panning can identify antibodies to such targets, but is inefficient, often producing low antibody diversity. We utilized next generation sequencing to improve the robustness of cell-based selections. We have thus identified large panels of diverse antibody sequences to several difficult receptor targets.

9:05 Functional Therapeutic Antibody Discovery for Challenging Targets by Single-B-Cell Screening in Nano-Droplets
Sponsored by HiFiBiO
Roshan Kumar, Cambridge Site Head, HiFiBiO, Inc.
We present CelliGO, an integrated process for rapidly identifying functional therapeutic antibodies from immune repertoires, combining phenotypic screening of single B-cells by droplet-based microfluidic cell sorting with genotypic recovery of barcoded antibody sequences. This technology opens up new possibilities for the discovery of functional antibodies modulating challenging targets.

9:20 Antibody Protein *de novo* Sequencing with LC-MS/MS
Sponsored by RAPID NOVOR
Mingjie Xie, MSc, MBA, Co-Founder and CEO, Rapid Novor, Inc.
Many applications in antibody engineering require the direct sequencing of antibody proteins. At Rapid Novor (rapidnovor.com) we have developed a robust workflow and routinely sequenced antibody proteins. Here we share the success experiences, examine common mistakes novices make, and present our practices to ensure the correctness of every amino acid.

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

10:20 A Novel Approach to Overcome Common Binder Selection Biases for Challenging Targets
Pascal Egloff, Ph.D., Postdoctoral Researcher, Markus Seeger Group, Institute of Medical Microbiology, University of Zurich, Switzerland
NestLink is a novel selection technology that enables protein characterization within large pools of candidate molecules in the absence of genetic information. It allows for novel selection pressures beyond binding and for unbiased characterization of thousands of individual pool members in one single experiment. The technology is particularly beneficial for binder development against challenging membrane proteins and it paves the way for a paradigm shift in biopharmaceutical drug delivery testing.

10:50 How Big are Antibody Libraries Really? And Are We Accessing the Full Diversity?
Andrew Bradbury, Ph.D., Chief Scientific Officer, Specifica Inc.
In vitro antibody libraries have been used to generate antibodies against many different therapeutic lead targets. Theoretical and experimental analyses indicate that for a library with a diversity of 1e7, one would expect to select 1-3 antibodies. While this tends to be true for small libraries, or library subsets, this estimate does not appear to scale to larger libraries with diversities estimated to be >1 billion, suggesting that libraries are not as diverse as thought, or selection methods do not tap the full diversity.

11:20 Enjoy Lunch on Your Own

12:35 pm Plenary Keynote Program
(click here for details)

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

2:45 Close of Conference

Cambridge 25 YEARS HEALTHTECH Institute
A Division of Cambridge Innovation Institute

5th Annual | September 27-28, 2017

Antibodies Against Membrane Protein Targets - PART 2

Technologies to Enable the Advancement of GPCRs, Ion Channels and Transporters as Targets for Biotherapeutics | Part Two: Structural Analysis, Characterization and Biopharmaceutical Development

The two-part Antibodies Against Membrane Protein Targets 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 these target families to advance into the clinic and beyond. The second conference, Structural Analysis, Characterization and Biopharmaceutical Development, explores new developments in structural biology and characterization assays used to support research against these targets, then examines progress in biotherapeutic development for GPCR, ion channel and transporter targets.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Immunomodulatory Small Molecules
- September 25 Short Course: Targeting of Ion Channels with Monoclonal Antibodies
- September 26-27 Conference: Antibodies Against Membrane Protein Targets - Part 1: The Discovery Workflow
- September 27-28 Conference: Antibodies Against Membrane Protein Targets - Part 2: Structural Analysis, Characterization and Biopharmaceutical Development
- September 28-29 Symposium: CNS and Neurodegenerative Targets

WEDNESDAY, SEPTEMBER 27

11:50 am Conference Registration Open

12:35 pm Plenary Keynote Program
(click here for details)

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

STRUCTURAL BIOLOGY

2:45 Welcome Remarks
Kent Simmons, Senior Conference Director, Cambridge Healthtech Institute

2:50 Chairperson's Opening Remarks
Dana Lord, Ph.D., Scientist, Sanofi-Genzyme

2:55 KEYNOTE PRESENTATION: State of the Science: Tools for Structural Studies of Membrane Protein Targets
Thomas P. Sakmar, M.D., Richard M. & Isabel P. Furlaud Professor, Laboratory of Chemical Biology & Signal Transduction, The Rockefeller University; Guest Professor, Karolinska Institute, Sweden
Novel methods, including time-resolved X-ray crystallography and high-resolution molecular microscopy, often in combination with computational molecular dynamics simulations, are providing new insights about how membrane proteins really work. Developing biotherapeutics or small molecule drugs increasingly requires a multidisciplinary team effort to apply both new and traditional approaches to enhance pre-clinical drug discovery efforts. My goal is to provide an up-to-date critical summary of some new single-molecule drug discovery tools.

3:25 Large Scale Determination of Previously Unsolved Protein Structures Using Evolutionary Information from Metagenomic Sequence Data
Sergey Ovchinnikov, Biologist, Baker Lab, Institute for Protein Design, University of Washington
Despite decades of work by structural biologists, there are still ~5200 protein families with unknown structure. We show that Rosetta structure prediction guided by residue-residue contacts inferred from evolutionary information can accurately model proteins that belong to large families and that metagenome sequence data more than triple the number of protein families with sufficient sequences for accurate modeling. We generate models for 614 protein families, of which 206 are membrane proteins.

3:55 Computational Approaches to Antibody Engineering: Advances in Modeling Liabilities
Sponsored by SCHRÖDINGER BIOLOGICS
Christopher Negron, Ph.D., Senior Scientist, Schrödinger
Experimental techniques for discovering and optimizing antibodies with high affinity for a target have matured significantly. However, the discovery and optimization of other "drug-like" properties for antibodies remain challenging. Thus we describe computational workflows for identifying and removing liabilities such as aggregation propensity. Beyond this, we will discuss tools such as FEP, that can be used to maintain affinity and stability during the optimization of other "drug-like" properties.

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

5:00 Structure and Function of Chemokine Receptors
Martin Gustavsson, Ph.D., Post-Doctoral Scholar, Handel Lab, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego
Chemokines are small, secreted proteins that interact with G protein coupled chemokine receptors in the cell membrane to drive cell migration and regulate a number of physiological processes. I will present our recent advances in understanding the structure, dynamics and function of chemokine receptors using x-ray crystallography in combination with other biophysical and biochemical methods.

5:30 Implementation and Application of Internal Cryo-EM Lab for Support of Membrane Protein Research
Claudio Ciferri, Ph.D., Senior Scientist, Structural Biology, Genentech
Recent breakthroughs in cryo-EM enabled atomic resolution structure determinations of several proteins including integral membrane proteins. At Genentech,

we are establishing a state-of-the-art cryo-EM group to support small and large molecule drug discovery as well as basic research projects, with a particular focus on membrane proteins. In my talk, I will present the workflow we established to enable structure determination of our membrane protein targets in lipid bi-layer environment.

6:00 **The Peptidisc for Trapping Membrane Proteins in Water-Soluble Nanoparticles**
Franck Duong, Ph.D., Professor, Biochemistry, University of British Columbia, Canada
Purified membrane proteins are insoluble without detergents, adding difficulty to antibody production and protein crystallisation. We present the Peptidisc for their facile capture into water-soluble nanoparticles. Unlike the Nanodisc, which requires scaffold proteins of different lengths and precise amounts of exogenous lipids, the peptidisc just requires a short bi-helical peptide and no lipids. We show the effective reconstitition of 5 different membrane protein systems using 'on-column', 'on-gel', and 'on-beads' methods.

6:30 **Close of Day**

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

THURSDAY, SEPTEMBER 28

7:30 am **Registration Open**

8:00 **Interactive Breakout Discussion Groups with Continental Breakfast**
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. Details on the topics and moderators are available on the conference website.

CHARACTERIZATION

9:00 **Chairperson's Remarks**
Joseph Rucker, Ph.D., Vice President, Research and Development, Integral Molecular, Inc.

9:05 **Biophysical Characterization of Conformational States Accompanying GPCR Activation**
Scott R. Prosser, Ph.D., Professor, Chemistry and Biochemistry, University of Toronto, Canada
The spectroscopic characterization of GPCRs reveals a complex conformational landscape, which responds to ligands, allosteric agents, and environmental factors. This ensemble description allows us to consider mechanistic concepts in light of well-known pharmacological phenomena including basal activation, inverse agonism, efficacy, biased signaling, and pre-coupling. Recent studies of the adenosine A2A receptor, a prototypical class A GPCR, will be presented and discussed in terms of consequences to drug discovery in GPCRs.

9:35 **Mass Spectrometric Analysis of Membrane Proteins and Complexes in Biopharma**
Iain Campuzano, Ph.D., Senior Scientist, Amgen
Membrane proteins make up approximately 50% of possible "druggable" targets, making them very attractive molecules for many research groups. Herein we will demonstrate how native mass spectrometric techniques are currently being used to determine membrane protein molecular weight and subunit stoichiometry. We will also demonstrate how the phospholipid number can be accurately derived for empty nanodisc particles. Finally, a UPLC-MS based method for accurate molecular weight determination will also be discussed.

10:05 **Biophysical and Functional Characterization of GPCR Antagonistic Antibodies Raised in Chicken**
Jennifer Könitzer, Ph.D., Research Investigator, Immuno-Oncology Large Molecule Discovery, Bristol-Myers Squibb
Antagonizing the glucose-dependent insulinotropic polypeptide receptor GPCR (GIPR) may open up new therapeutic modalities in the treatment of diabetes and obesity. The receptor is highly conserved between rodents and humans, which has contributed to previous rodent immunization campaigns generating very few usable antibodies. Switching the immunization host to chicken enabled the generation of a large and diverse panel of monoclonal antibodies containing 172 unique sequences.

10:35 **Coffee Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced**

11:20 **Structure-Based Engineering to Restore High Affinity Binding of an Isoform-Selective Anti-TGFβ1 Antibody**
Dana Lord, Ph.D., Scientist, Sanofi-Genzyme
One problem during antibody generation is the loss of antigen binding affinity during the scFv to IgG conversion. We use binding, potency, and structural biology experiments to show that this can be attributed to decreased conformational flexibility of the IgG elbow region. This study demonstrates the necessity of structural and functional re-examination when converting scFv to IgG molecules and highlights the potential of structure-based engineering to produce fully functional antibodies.

11:50 **Joining Forces: Epitope Mapping and Structural Characterization of a Bispecific Antibody**
Linda Kaldenberg-Hendriks, Scientist, Merus, The Netherlands
MCLA-128 is a human bispecific IgG targeting HER2 and HER3 that potently inhibits HRG-driven proliferation of HER2-amplified cancer cells. We have performed epitope mapping studies and generated high-resolution crystal structures for both arms of this bispecific antibody and their targets, as well as solution-state small-angle X-ray scattering data for the MCLA-128:HER2:HER3 complex. The resulting data were used to create a model for the unique mode of action of MCLA-128.

12:20 pm **Sponsored Presentation**
(Opportunity Available)

12:50 **Session Break**

1:00 **Luncheon Presentation** *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:50 **Refreshment Break in the Exhibit Hall with Poster Viewing**

CASE STUDIES OF BIOTHERAPEUTIC DEVELOPMENT

2:35 **Chairperson's Remarks**
Catherine Hutchings, Ph.D., Independent Consultant, United Kingdom

2:40 **Erenumab, an Anti-CGRP Receptor Antibody for Migraine Prevention**
Cen Xu, Ph.D., Scientific Director, Neuroscience Drug Discovery, Amgen
Generation of antagonist antibodies against the heterodimeric GPCR CGRP receptor is challenging

due to the complex structure of the target. Erenumab (AMG 334) was created using a novel antigen that was designed based on the knowledge of how CGRP interacts with its receptor. This highly potent and selective antagonist antibody has now demonstrated efficacy in clinical studies for the prevention of episodic and chronic migraine.

3:10 **Progress on the Development of Antibody Therapeutics against GPCR Targets**
Catherine Hutchings, Ph.D., Independent Consultant, United Kingdom
G protein-coupled receptors (GPCRs) represent one of the most important target classes for therapeutic drug discovery across a wide range of diseases. The progress made by targeting GPCRs with antibody-based therapeutics will be reviewed outlining the breadth and diversity of antibody molecules and target opportunities in R&D and the clinical pipeline, including recent development to the expansion of opportunities afforded by next-generation modalities.

3:40 **Session Break**

3:55 **Engineered Peptides Targeting Ion Channels in Pain and Immunology**
Ronald Swanson, Ph.D., Senior Director, Janssen
Animal venoms are a rich source of pharmacologically active peptides including ion channel blockers. However, properties such as the affinity, specificity, extended half-life, and manufacturability often must be engineered into the molecules. We have engineered scorpion peptides active against Kv1.3 to address the role of this channel in models of immune disease as well as spider toxin peptides active against Nav1.7, a target of high interest for pain.

4:25 **Structure-Based Strategy to Develop Therapeutic Antibodies against Nav 1.7 for Pain**
Luke Robinson, Ph.D., Principal Scientist, Research, Visterra, Inc.
Ion channels remain a challenging class of targets to generate functional antibodies. Using our Heirotope™ platform, an atomic network-based approach, we have incorporated a structure-guided approach to the discovery of antibodies targeting Nav1.7. We have engineered proteins to represent conformational and functionally relevant target epitopes of this channel. Application of these engineered proteins coupled with high-gain experimental methods, including droplet microfluidics, toward the discovery of therapeutic antibodies will be discussed.

4:55 **Close of Conference**

HOTEL & TRAVEL

The Westin Copley Place
10 Huntington Ave.
Boston, MA 02116
T: 617-262-9600

Discounted Room Rate: $305
Reservation Cutoff: August 28, 2017

For more information, visit **DiscoveryOnTarget.com**

Cambridge 25 YEARS HEALTHTECH Institute
A Division of Cambridge Innovation Institute

12th Annual | September 26-27, 2017

GPCR-Based Drug Discovery

New Target-Class Approaches, New Drug Candidates

G protein-coupled receptors (GPCRs) are targeted by approximately 25-30% of the drugs on the market today which is a testament to the important physiological roles GPCRs play in transducing signals from outside of cells to the inside. However many of the therapeutics now known to act upon GPCRs were actually discovered decades ago before knowledge about their target. This meeting covers the newer era of target-driven drug discovery where the aim is to apply knowledge about GPCR structure and conformation to tailor new drug candidates that bias receptor signaling towards the 'good' pathways and away from undesired signaling pathways. Join us at Cambridge Healthtech Institute's 12th Annual GPCR-Based Drug Discovery conference to discuss and track R&D progress of tackling this complex, membrane-embedded protein class and judge how the significant strides in structural knowledge of various GPCRs, and applications of biophysical techniques, have impacted GPCR-based drug discovery.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Constrained Peptides and Macrocyclics
- September 25 Short Course: GPCR Structure-Based Drug Discovery
- September 26-27 Conference: GPCR-Based Drug Discovery
- September 27-28 Conference: Antibodies Against Membrane Protein Targets - Part 2: Structural Analysis, Characterization and Biopharmaceutical Development
- September 27 Short Course: Introduction to Allosteric Modulators and Biased Ligands of GPCRs
- September 28-29 Symposium: CNS and Neurodegenerative Targets

TUESDAY, SEPTEMBER 26

7:00 am Registration Open and Morning Coffee

GPCR PHARMACOLOGY AND BIASED SIGNALING

8:00 Welcome Remarks
Anjani Shah, Ph.D., Conference Director, Cambridge Healthtech Institute

8:05 Chairperson's Opening Remarks
Andrew Alt, Ph.D., Associate Director, Biology, Arvinas

8:10 FEATURED PRESENTATION: Mechanistic Insights into Opioid Receptor Function from Molecular Dynamics Simulations
Marta Filizola, Ph.D., Professor, Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai
Understanding at the molecular level how to fine-tune opioid receptor signaling toward the analgesic pathway and away from those mediating adverse effects is essential for the future discovery of improved opioid-based painkillers for the management of acute and/or chronic pain. I will provide an overview of studies we are carrying out to address this problem using enhanced molecular dynamics simulation strategies and cutting-edge statistical analyses.

8:40 Biased Signaling at μ Opioid Receptor Splice Variants
Ying-Xian Pan, M.D., Ph.D., Laboratory Head, Department of Neurology, Memorial Sloan Kettering Cancer Center
Extensive 3' alternative splicing of the μ opioid receptor gene (OPRM1) creates multiple C-terminal splice variants that are potentially subjected to biased signaling. We now demonstrate *in vitro* that several μ agonists display differential β-arrestin 2 or G protein bias against a number of Oprm1 C-terminal splice variants, which correlates with *in vivo* data using targeted mouse models, providing new insights on GPCR-biased signaling.

9:10 High Resolution Crystal Structure of the Apelin Receptor
Liaoyuan Hu, Ph.D., Scientific Director, Head of Pharmacology, Amgen Asia R&D Center
The apelin receptor (APJ) plays an important role in a wide range of physiological functions and is a potential target for the treatment of a variety diseases. Here we report the high resolution co-crystal structure of APJ in complex with a surrogate peptide agonist. Overall structural features of the complex and detailed peptide/receptor interactions will be discussed.

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

GPCR PHARMACOLOGY AND BIASED SIGNALING *(Cont.)*

10:25 Ozanimod: An S1P1,5R Modulator that Causes Receptor Internalization Resulting in Altered Lymphocyte Trafficking and Amelioration of Inflammation
Julie Selkirk, Ph.D., Associate Director of Cellular & Molecular Biology, Receptos/Celgene
S1P1R is a GPCR expressed on lymphocytes mediating migration out of secondary lymphoid tissues. S1P1R modulators internalize the receptor, sequestering lymphocytes and preventing their migration to inflammation sites. The S1P1,5R modulator ozanimod is in clinical development to treat Multiple Sclerosis and Inflammatory Bowel Disease. This presentation will cover the pharmacological tools we used to identify a safe and effective S1P1,5R modulator and evidence that ozanimod utilizes different residues than FTY720-p in the orthosteric ligand binding pocket.

10:55 Structure of a Family A GPCR with Synthetic Ligands Bound
Adam Weinglass, Ph.D., Director, Screening & Compound Profiling, Merck & Co.
Agonists of GPR40 enhance glucose-dependent insulin secretion and represent a potential mechanism for the treatment of type 2 diabetes mellitus. Pharmacologic studies indicate that partial and full allosteric agonists (AgoPAMs) bind distinct sites on GPR40 eliciting differentiated preclinical efficacy. Here, we present the path to a ternary complex structure with partial and full allosteric agonists bound, and evidence supporting an identified novel, lipid-facing AgoPAM binding pocket.

11:25 Biased and Cell-Specific Agonists of the Heart Disease Target, RXFP1, a Peptide-Targeted GPCR
Ross Bathgate, Ph.D., Head, Neuropeptides Division, Florey Institute of Neuroscience and Mental Health, University of Melbourne
This presentation will discuss peptide mimetic and small molecule development at a complex peptide GPCR, the heart disease target, RXFP1. We have developed a relaxin peptide mimetic with a cell-specific signaling profile and demonstrated that an RXFP1 small molecule agonist is an allosteric biased agonist. This highlights the need to screen GPCR targeted small molecules or biologics in relevant native cell systems for biased and cell-specific signaling.

11:55 Imipridones: A New Class of Anti-Cancer Small Molecules that Selectively Engage GPCRs
Sponsored by DiscoverX
Varun Prabhu, Ph.D., Associate Director, Research & Development, Oncoceutics, Inc.
GPCRs are the most commonly exploited target in modern medicine; however, efforts in oncology have been limited. We describe imipridone small molecules with a unique tri-heterocyclic core structure that selectively target GPCRs. Lead candidates were profiled using the DiscoverX GPCR platform and characterized for mechanism of action and anti-cancer efficacy.

12:10 pm Sponsored Presentation
(Opportunity Available)

12:25 Session Break

12:35 Luncheon Presentation: Reaching Beyond Developing Stable GPCR Cell Lines
Sponsored by MULTISPAN
Lisa Minor, Ph.D., Scientific Consultant, Multispan, Inc.
Developing high quality assays is paramount for lead discovery and optimization screening. Multispan is well known for our deep foundation in generating quality stable GPCR cell lines and conducting functional assays. Our portfolio has expanded by tackling other related topics. We have devoted significant effort in developing signaling and phenotypic assays using endogenous targets such as RXFP1 in THP-1, CGRP receptor (CLR+RAMP1) in SK-N-MC, AMPK in C2C12, and DNA-PK in HELA cell lines. For cross-reactivity counter screens, we have developed specific cell lines and assays for CGRP, AM, and Amylin receptors by studying and overcoming endogenous RAMP expression and designed a 32-GPCR assay panel comprising the most well-characterized CNS and cardiovascular liability targets. In addition to quantifying GPCR expression by radioligand binding, we have also established a FACS-based quantification of surface expression to rank order recombinant clones and benchmark target expression against physiological level in native cells. In this presentation, we will share our recent work and details of these advances.

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

GPCRs IN CANCER AND OTHER DISEASES

1:50 Chairperson's Remarks
Sid Topiol, Ph.D., CSO, 3D-2drug, LLC; Professor and Director, Structural and Computational Drug Discovery, Stevens Institute of Technology

1:55 GPCRs in Immune Evasion of Cancer
Tillmann Michels, Ph.D., Head of Research Group Immune Checkpoint Inhibitors, Laboratory of Phillipp Beckhove, Interventional Immunology, Regensburg Center for Interventional Immunology
Checkpoint blockade has become an important pillar of cancer therapy. We identified GPCRs and their associated signaling as immune inhibitory pathways using high throughput RNAi screening. GPCRs could either affect T cell activity directly by binding or indirectly by altering the balance of tumor-intrinsic Gα signaling. For example, cAMP can be transported into TILs and induce an inhibitory pathway resulting in TCR-associated Lck inhibition.

2:25 Phenotypic Discovery of ONC201 as the First Selective DRD2 Antagonist for Clinical Oncology
Joshua Allen, Ph.D., Vice President, R&D, Oncoceutics
Imipridones are a new class of anti-cancer small molecules that share a unique tri-heterocyclic core structure and selectively engage GPCRs. Experimental GPCR profiling revealed imipridone ONC212 selectively targets orphan GPCR GPR132/G2A at nanomolar concentrations. GPR132 is a stress-inducible orphan GPCR with highest expression in leukemia and shown to be a tumor suppressor in the context of lymphoid leukemogenesis. ONC212 was non-toxic to normal cells at therapeutic concentrations and demonstrated robust *in vivo* safety/efficacy in leukemia xenograft

2:55 Present and Future Collaborative Innovations within Drug Discovery Informatics
Sponsored by CDD VAULT
Luke Fisher, Ph.D., Principal Consultant, Collaborative Informatics, Collaborative Drug Discovery
The CDD Vault platform (Activity & Registration, Visualization, Inventory, & ELN) provides an easy, secure way for the collaborative sharing of research data and workflows. Web-based platforms are a natural fit for collaborations due to the economic and design benefits of a single platform that transcends any one organization's requirements.

3:10 3DM Protein-Family Analysis Platform Applied to the GPCR Protein-Family
Sponsored by bio-prodict
Henk-Jan Joosten, Ph.D., CEO, Bio-Prodict
Vast amounts of data are available for protein-families (e.g., sequences, literature, structural-, alignment-, SNP-, mutation-, patent-, binding data). 3DM, a protein-superfamily analysis platform, automatically collects and integrates all data and contains many state-of-the-art analysis tools. 3DM is used by many companies, including large pharma, to guide structure-based drug design.

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

GPCRs IN CANCER AND OTHER DISEASES *(Cont.)*

4:05 The Apelin Receptor: Modulating Ligand Structure to Bias Signaling and Impacts on Acute Cardiac Dysfunction
Eric Marsault, Ph.D., Professor, Dept of Pharmacology-Physiology, Université de Sherbrooke

4:35 Development of GIP Receptor Antagonists to Reveal the Role of GIP in Physiology and Pathophysiological Conditions Like Obesity and T2D
Mette M. Rosenkilde, M.D., Ph.D., Professor, Department of Biomedical Sciences, University of Copenhagen
I will discuss the incretins (that bind to class B GPCRs) and novel data for the production of a GIPR (glucose-dependent insulinotropic polypeptide receptor) antagonist for the treatment of T2D and obesity. I will also compare the action of GIP with that of the other famous incretin hormone, GLP1, for which several therapies have been launched recently.

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. Details on the topics and moderators are available on the conference website.

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

7:10 Close of Day

WEDNESDAY, SEPTEMBER 27

7:30 am Registration Open and Morning Coffee

STRUCTURAL AND BIOPHYSICAL APPROACHES FOR GPCRs

8:00 Chairperson's Remarks
Annette Gilchrist, Ph.D., Professor, Pharmacology, Midwestern University

8:05 Crystal Structure of the GLP-1 Receptor Extracellular Domain in Complex with Exendin-4 and a Nanobody
Xiaomin Chen, Ph.D., Senior Principal Scientist, Structural & Molecular Sciences, Worldwide Research & Development, Pfizer
Glucagon-like peptide 1 receptor is one of the class B GPCR and an important drug target. It has an extracellular domain (ECD) in addition to the seven-transmembrane helices and the primary role of the ECD is to bind to a peptide ligand to position it so that its N-terminus binds to the transmembrane region for its activation. Here we report the crystal structure of the receptor ECD bound to exendin-4 and a nanobody.

8:35 Picking the High-Hanging Fruit: Measuring Biomolecular Interactions of GPCRs Using a Variety of Biophysical Techniques
Phillip Schwartz, Ph.D., Senior Scientist, Structural Biology and Biophysics, Takeda California
Drug discovery efforts are undergoing a renaissance in GPCR-related research as orphan receptors become de-masked and our understanding of how to study these difficult targets improves. Identifying preparations amenable to biophysical characterization is a critical step in pursuing GPCR drug development.

9:05 Improved Candidate Identification & Optimization Using Advanced, Non-viral Cell Engineering
Sponsored by MaxCyte®
James Brady, Vice President, Technical Applications & Customer Support, MaxCyte, Inc.
Whether developing small molecule drugs or therapeutic antibodies against membrane receptors, cell-based assays play a critical role in identifying and optimizing candidates. This presentation discusses how high-performance cell engineering can significantly improve the relevance and throughput of cell-based assays leading to advancement of higher quality candidates, faster and more cost-effectively.

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

STRUCTURAL AND BIOPHYSICAL APPROACHES FOR GPCRs *(Cont.)*

10:20 NMR Spectroscopy and Integrative Structural Biology of Human GPCRs
Matthew Eddy, Ph.D., Postdoctoral Fellow, Laboratory of Raymond Stevens, The Bridge Institute, University of Southern California
Nuclear magnetic resonance (NMR) spectroscopy complements other structural biology techniques, such as x-ray diffraction, by identifying multiple simultaneously populated conformations in equilibrium. Here, we leverage this advantage to study two human GPCRs. First, we report how a GPCR fusion strategy used for x-ray crystallography influences the protein conformational equilibrium and highlight potential cases where drug-ligand interactions can be affected. Second, we report a novel approach to incorporation of stable isotopic NMR labels into a wild type human GPCR and new insights obtained from this method.

10:50 Next Generation Bio-Sensing: New Opportunities for Challenging Targets
Tim Kaminski, Ph.D., Postdoctoral Fellow, Discovery Sciences, Innovative Medicines and Early Development Biotech Unit, AstraZeneca Gothenburg
Single molecule experiments enable us, next to its unmatched sensitivity, to directly gain a mechanistic insight into biological processes by observing its stochastic behavior. We are developing a toolbox which advances single molecule microscopy from a method primarily used in academia into a versatile tool for drug discovery. By using this method, we are able to address shortcomings of established biophysical methods as e.g. tight binding limit, working with membrane proteins, higher throughput. Additionally, we are able to extract kinetic profiling of inhibition reactions in solution by observing the association and dissociation of thousands of molecules in parallel with a surface-based single molecule platform.

11:20 Enjoy Lunch on Your Own

12:35 pm Plenary Keynote Program
(click here for details)

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

2:45 Close of Conference

Inaugural | September 28-29, 2017

CNS and Neurodegenerative Targets

Tools and Targets in Neuroscience

The identification of therapeutic targets based on novel mechanistic approaches is urgently needed for CNS and neurodegenerative diseases, particularly for conditions such as Alzheimer's which represent extensive unmet medical need and blockbuster potential for the right therapy. Driven by an improving understanding of CNS disease biology and the emergence of new mechanisms and targets, Cambridge Healthtech Institute's CNS and Neurodegenerative Targets symposium profiles the latest tools, targets and platforms driving today's CNS drug discovery strategies, with critical updates and findings in key areas such as new targets for misfolded proteins, tau, GCPRs, kinase inhibitors, genetics, gene therapy, neuroinflammation and exosomes.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Targeting Autophagy
- September 25 Short Course: Targeting of Ion Channels with Monoclonal Antibodies
- September 26-27 Conference: Lead Generation Strategies
- September 27-28 Conference: Kinase Inhibitor Discovery
- September 27 Short Course: Practical Phenotypic Screening
- September 28-29 Symposium: CNS and Neurodegenerative Targets

THURSDAY, SEPTEMBER 28

4:00 pm Registration

CNS DISCOVERY STRATEGIES AND EMERGING TARGETS

5:25 Welcome Remarks
Daniel Barry, Senior Conference Director, Cambridge Healthtech Institute

5:30 Chairperson's Opening Remarks
Gerry Higgins, Ph.D., M.D., Research Professor, Computational Medicine and Bioinformatics, University of Michigan Medical School

5:40 Developing a Novel Drug Discovery Platform for Identifying Potential Therapeutic Agents and Targets for the Treatment of Neurodegenerative Disease
Robert H. Scannevin, Ph.D., Vice President, Discovery Biology, Yumanity Therapeutics
Typical approaches for identifying drug targets, such as human genetics, often fail to provide an appropriate cellular or pathological context, which is essential for the drug discovery process. Yumanity employs a yeast-based phenotypic discovery platform which is sensitive to neurodegenerative disease proteins. This platform allows for high throughput screening and target identification, and facilitates validation in other cell systems (e.g. iPSC).

6:10 Mining the Topography and Dynamics of the 4D Nucleome to Identify Novel CNS Drug Pathways
Gerry Higgins, Ph.D., M.D., Research Professor, Computational Medicine and Bioinformatics, University of Michigan Medical School
The regulatory non-coding genome contains the majority of genomic variants that are significantly associated with inter-individual variation in drug response. We developed a pharmacoepigenomic informatics pipeline that uses pharmacogenomic GWAS variants as inputs, which disrupt the functional topology of transcription as the primary defining characteristic of pharmacoepigenomic networks. Using this method, we have used network analysis which outputs significantly interconnected pharmacodynamic pathways for lithium and valproate in the human CNS.

6:40 Close of Day

FRIDAY, SEPTEMBER 29

8:00 am Registration and Morning Coffee

TARGETS FOR ALZHEIMER'S DISEASE - BACE, TAU

8:30 Chairperson's Remarks
Matthew E. Kennedy, Ph.D., Director, Neuroscience, Merck Research Labs

8:40 The Promise and Challenge of BACE1 as a Therapeutic Target for Alzheimer's Disease
Robert Vassar, Ph.D., Professor, Cell and Molecular Biology, The Feinberg School of Medicine, Northwestern University
The β-secretase, β-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1), is required to generate the β-amyloid peptide (Aβ) that plays an early critical role in Alzheimer's disease (AD). Thus, BACE1 is a prime AD therapeutic target and several small molecule BACE1 inhibitor drugs are in AD clinical trials. However, the safety and efficacy of BACE1 inhibitors for AD are unknown. Moreover, BACE1 levels are elevated in AD brain, suggesting that the enzyme initiates a vicious cycle of Aβ production. My talk will discuss our results with BACE1 conditional knockout mice to model the safety of BACE1 inhibition *in vivo*. Additionally, I will discuss our efforts to understand the mechanism of BACE1 elevation in AD as a therapeutic target. Finally, I will summarize the current BACE1 inhibitor clinical trials and the prospects for BACE1 inhibition as a therapeutic approach for AD.

**Separate registration is required for short courses and symposia.*

9:10 Targeting Ab and Tau Spreading for Disease Modification in Alzheimer's Disease
Matthew E. Kennedy, Ph.D., Director, Neuroscience, Merck Research Labs
I will discuss the discovery and clinical translation of the BACE inhibitor, verubecestat and review emerging strategies to target tau pathology in AD. How combination therapies targeting amyloid and tau pathology could improve chances of achieving efficacy across stages of AD will also be discussed.

9:40 Novel Therapeutic Targets against Tau Pathology: A Phenotypic Approach
Marija Usenovic, Ph.D., Senior Scientist, Department of Neuroscience, Merck Research Laboratories, Merck & Co., Inc.
Increasing evidence suggests that tau pathology spreads throughout the brain via interconnected neurons. However, the molecular and cellular mechanisms of pathogenic tau transmission are not well established. We performed a phenotypic screen in hiPSC-neurons to identify molecular targets within cell-surface heparan sulfate proteoglycans that block tau oligomer uptake. Here we present the hits and novel therapeutic strategies that would inhibit tau pathology-spread and its consequences on neurodegeneration.

10:10 Networking Coffee Break

TARGETS FOR ALZHEIMER'S DISEASE - BACE, TAU *(Cont.)*

10:40 Development of Antibody against Early Disease Driver cis P-tau for Treating Alzheimer's Disease and Brain Injury
Xiao Zhen Zhou, Ph.D., Assistant Professor, Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School
Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE) share a common risk factor, traumatic brain injury (TBI) and neuropathological hallmark, neurofibrillary tangles. By developing tau conformation-specific antibodies, we have discovered that cis P-tau antibody can effectively eliminate cis P-tau, a precursor of tau pathology and early driver of neurodegeneration linking TBI to Alzheimer's disease. Thus, cis P-tau antibody may be useful for treating Alzheimer's disease and TBI at early stages.

11:30 Chemogenomic Screen Identifies Druggable Modulators of Axonal Transport of Mitochondria
Evgeny Shlevkov, Ph.D., Research Fellow, Neurology, Childrens Hospital Boston

11:40 Sponsored Presentation *(Opportunity Available)*

12:10 pm Enjoy Lunch on Your Own

NEUROINFLAMMATION, RARE DISEASES

1:40 Chairperson's Remarks
S. Pablo Sardi, Ph.D., Pharm.D., R&D Director, Neuroscience, Sanofi

1:50 The Microglial ATP-Gated Ion Channel P2X7, as a CNS Drug Target
Anindya Bhattacharya, Ph.D., Scientific Director, Neuroscience Drug Discovery, Janssen R&D
P2X7 is an ion channel, abundantly expressed in microglia of the CNS. Activation of P2X7 by ATP causes release of pro-inflammatory IL-1β and IL-18 cytokines, resulting in neuroinflammation which in turn can contribute towards a host of CNS disorders. As such, therapeutic intervention of central P2X7 ion channels ought to be an attractive strategy to dampen CNS disorders driven by augmented IL-1β/IL-18 signaling. This talk will focus on Janssen neuroscience team's discovery efforts on P2X7 antagonists leading to a few molecules progressing to early clinical development. These compounds demonstrate robust target engagement, functionally antagonize IL-1β release in the brain, and have demonstrated efficacy in models of neuroinflammation, depression and epilepsy.

2:20 Targeting Lysosomal Defects in the Treatment of Parkinson's Disease: From Genetics to Precision Medicine Trials
S. Pablo Sardi, Ph.D., Pharm.D., R&D Director, Neuroscience, Sanofi
Clinical, genetic and experimental evidence underlies the relevance of lysosomal dysfunction in Parkinson's disease. Stimulation of the lysosomal GBA pathway in the CNS can ameliorate the pathological and behavioral abnormalities in animal models of disease. Modulation of this lysosomal pathway may represent a new disease-modifying treatment for Parkinson's disease patients carrying GBA mutations. This research underscores the study of rare diseases as a new paradigm for drug discovery.

2:50 Modeling C9ORF72 Disease: A Crucial Step for Therapeutic Development in Amyotrophic Lateral Sclerosis and Dementia
Clotilde Lagier-Tourenne, M.D., Ph.D., Assistant Professor, Neurology, Massachusetts General Hospital and Harvard Medical School; Associate Member, Broad Institute
Repeat expansions in the C9ORF72 gene are the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Expression of expanded repeats caused age-dependent accumulation of RNA foci and dipeptide repeat proteins, accompanied by loss of hippocampal neurons and impaired cognitive function in transgenic mice. This model has been an essential tool to develop novel therapeutic approaches, including RNA-targeting antisense oligonucleotides and immunotherapies for patients with ALS/FTD.

3:20 Small Molecule Transforming Growth Factor (TGF-β) Enhancers Are Novel Therapeutic Agents to Prevent and Treat Progressive Neurodegenerative Diseases
Jung S. Huang, Ph.D., Professor, Department of Biochemistry and Molecular Biology, Saint Louis University School of Medicine
Pathogenic peptides/proteins, which are responsible for neurodegenerative diseases, are produced in plasma membrane lipid rafts in brain tissue. Promising agents for neurodegenerative diseases are predicted to possess activities to inhibit production of these peptides/proteins and enhance TGF-β activity which protects neurons and glial cells from injury/death. We discover novel TGF-β enhancers. They enhance TGF-β activity by disrupting lipid rafts. We predict that they are effective agents to prevent/treat neurodegenerative diseases.

3:50 Close of Symposium

**Separate registration is required for short courses and symposia.*

Cambridge 25 YEARS HEALTHTECH Institute
A Division of Cambridge Innovation Institute

3rd Annual | September 28-29, 2017

Tackling Rare Diseases

New Drug Modalities. New Assays & Models. New Therapeutic Strategies.

Rare diseases, or diseases that affect only a small percentage of the population, are growing in significance and prominence in recent years. According to the National Institutes of Health, there are more than 25 million Americans suffering from one of nearly 7000 rare diseases identified, yet there are only about 250 specific or appropriate treatments available. Approximately 80% of these rare diseases are genetic in origin. This symposium on Tackling Rare Diseases will highlight the development of new therapeutic modalities and the use of innovative technologies and approaches to overcome translational challenges.

RECOMMENDED ALL ACCESS PACKAGE:

- September 25 Symposium: Constrained Peptides and Macrocyclics
- September 26-27 Conference: CRISPR for Disease Modeling and Target Discovery
- September 27-28 Conference: Emerging Oligonucleotide Therapeutics
- September 28-29 Symposium: Tackling Rare Diseases

THURSDAY, SEPTEMBER 28

4:00 pm Registration

REGULATORY PERSPECTIVES & INNOVATIVE STRATEGIES

5:25 Welcome Remarks
Tanuja Koppal, Ph.D., Conference Director, Cambridge Healthtech Institute

5:30 Chairperson's Remarks
Adam Hutchings, Director, Dolon Ltd.

5:40 FEATURED PRESENTATION: Rare Disease Landscape: Fact Sheets in Research and Service Delivery
Ségolène Aymé, Emeritus Director of Research, French Institute of Health and Medical Research (INSERM); Expert in Residence for Rare Diseases, Brain and Spine Institute, Paris; and Editor-in-Chief, Orphanet Journal of Rare Diseases
The importance of rare diseases, as a driver for innovation in science and in healthcare organization, is now established and many indicators demonstrate that incentives have been instrumental in shaping the current situation. However, clouds are accumulating as many stakeholders question the affordability of the new diagnostic and therapeutic options. Joined efforts of the various stakeholders are necessary to keep this sector alive.

6:10 Overview of Key Recommendations from the European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL)
Adam Hutchings, Director, Dolon Ltd.
To help improve the speed and consistency of patient access to orphan medicines, a European multi-stakeholder group of rare disease experts, ORPH-VAL, has proposed a set of common principles to improve the consistency of decision making for orphan drugs and balance the needs of innovators and payers. Policymakers and rare disease stakeholders should engage with these recommendations, explore areas where local P&R systems diverge from the principles, and identify and enact potential reforms, all with the goal of improving overall access to medicines for patients with rare diseases.

6:40 Close of Day

FRIDAY, SEPTEMBER 29

8:00 am Registration and Morning Coffee

EXPLORING PHENOTYPIC SCREENING, STEM CELL MODELS AND MORE

8:30 Chairperson's Remarks
Ronald Alfa, M.D., Ph.D., Vice President, Discovery & Product, Recursion Pharmaceuticals

8:40 Development of Multi-Modal Small Molecule Therapeutics for the Neuronal Ceroid Lipofuscinoses
Paul Trippier, Ph.D., Assistant Professor, Department of Pharmaceutical Sciences, School of Pharmacy, Texas Tech University Health Sciences Center
The neuronal ceroid lipofuscinoses (NCLs), although rare, are the most common neurodegenerative disorders of childhood. We have developed a patient-specific induced pluripotent stem cell (iPSC) model of CLN3 disease (Batten disease) in which we have screened a library of proprietary small molecules. This phenotypic screen has identified neuroprotective small molecules with translational activity in patient specific cells. Our mechanism of action studies reveal a novel multi-modal mechanism of action suitable for treating other neurodegenerative disorders.

9:10 Disease Modeling: Even Rare Diseases Are Complex
Michael Liebman, Ph.D., Managing Director, IPQ Analytics, LLC; Adjunct Professor of Pharmacology and Physiology, Drexel College of Medicine
Pediatric ARDS, a rare disease, presents challenges in diagnosis and treatment because it is a syndrome and exhibits significant heterogeneity in patients and their symptoms in spite of the specific diagnosis. The Nathaniel Adamczyk Foundation has been involved in developing a clinical research and decision support platform to catalyze the formation of a community that focuses on these challenges and enables hypothesis development and testing with unique analytic tools.

9:40 Massive Parallelization of Rare Disease Drug Discovery
Ronald Alfa, M.D., Ph.D., Vice President, Discovery & Product, Recursion Pharmaceuticals
Recursion has developed a target agnostic discovery platform that combines artificial intelligence with automated biology for massive parallelization of high-throughput drug screening. In this session, I will

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describe our platform and provide a case study of drugs identified for a rare genetic disease.

10:10 Networking Coffee Break

NEW THERAPEUTIC MODALITIES

10:40 A New Approach to Block ERAD and Reduce the Degradation of Partially Misfolded Mutant Proteins
Clifford Lingwood, Ph.D., Senior Scientist, Molecular Structure and Function, Hospital for Sick Children
Many genetic diseases result from the ER associated degradation (ERAD) of the partiallly misfolded mutant protein. Several bacterial/plant subunit toxins (e.g. cholera, Shiga toxin) hijack this pathway to achieve A subunit cytosolic access by using the same ER translocon. By A subunit mutagenesis we generate a benign toxoid which remains an ER translocon substrate, and as such is a temporary, competitive inhibitor of the ER translocon which partially rescues the deficiency disease phenotype in cell culture (e.g. F508delta CFTR of CF, N370S GCC of Gaucher's).

11:10 The Potential of RNAi in Orphan Diseases – The Alpha 1 Anti-Trypsin Liver Disease Example
Dawn Christianson, Ph.D., Senior Program Manager, Arrowhead Research Corporation
Alpha 1 anti-trypsin deficiency is named a deficiency state because it is usually caused by a gene mutation which prevents the synthesized protein from exiting the liver, resulting in emphysema. However, in the liver it is a storage disease and with better pulmonary care and survival, patients are dying from liver disease or requiring transplant. RNAi is an apt approach to treating the liver disease, as evidenced by studies in animals and humans.

11:40 Sponsored Presentation *(Opportunity Available)*

12:10 pm Enjoy Lunch on Your Own

EXPLOITING TARGETED GENOMICS & DELIVERY TOOLS

1:45 Chairperson's Remarks
Ryan Hartmaier, Ph.D., Senior Scientist, Cancer Genomics, Foundation Medicine, Inc.

1:50 Engineering Tissue-Specific Delivery of Enzymes for Treatment of Lysosomal Diseases
Katherine Cygnar, Ph.D., Staff Scientist, Genome Engineering Tech, Regeneron Pharmaceuticals

2:20 Gene Discovery Efforts in Pediatric Patients with Undiagnosed Conditions
Pankaj B. Agrawal, M.D., MMSC, Geneticist and Medical Director, Gene Discovery Core, Manton Center for Orphan Disease Research, Boston Children's Hospital; Assistant Professor, Pediatrics, Harvard Medical School
Gene discovery core of the Manton Center at Boston Children's Hospital is focused on identifying genes for rare disease patients with unexplained conditions. We have identified several novel genes using latest sequencing technologies and confirmed pathogenicity using cellular and animal models thereby advancing science and helping those families. This needs collaboration between clinicians, genetic counselors, bioinformaticians and basic scientists, long-term goals being to find appropriate therapies.

2:50 Leveraging Cancer Genomics to Identify Targetable Mutations in Rare Cancer Types
Ryan Hartmaier, Ph.D., Senior Scientist, Cancer Genomics, Foundation Medicine, Inc.
The scarcity of genomic data in rare cancer types is a challenge for identifying and developing effective therapeutics. Here we explore the genomics of rare cancer types for novel, potentially druggable genomic alterations. Further, we surveyed the spectrum of known clinically relevant genomic changes to identify potential opportunities for broader utility of approved targeted agents in novel cancer types.

3:20 Familial Amyloid Polyneuropathy: How a Genetic Disease Informs Drug Discovery
Christine Bulawa, Ph.D., Senior Director, Rare Disease Research Unit, Pfizer
This talk will present a case study of drug development for familial amyloid polyneuropathy (FAP), a disease caused by mutations in the circulating protein transthyretin. Insights gleaned from biophysical studies of transthyretin and clinical observations of FAP patients led to the therapeutic strategy of native state stabilization and ultimately to development of tafamidis, the first and only disease modifying therapy for an amyloid disease.

3:50 Close of Symposium

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Cambridge 25 YEARS HEALTHTECH Institute
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CONFERENCE PROGRAMS

CANCER IMMUNOTHERAPY

September 25
S1: Immunomodulatory Small Molecules
S3: Microbiome in Immuno-Oncology

September 26–27
T7A: NK Cell-Based Cancer Immunotherapy

September 27–28
T7B: Targeting Tumor Myeloid Cells

TARGET-BASED DISCOVERY & VALIDATION

September 26–27
T1A: Targeting Histone Methyltransferases & Demethylases
T2A: Targeting the Ubiquitin Proteasome System
T4A: Lead Generation Strategies
T6A: CRISPR for Disease Modeling & Target Discovery
T9A: GPCR-Based Drug Discovery

September 27–28
T1B: Next-Generation Histone Deacetylase Inhibitors
T2B: Kinase Inhibitor Discovery
T4B: Target Identification Strategies

HOT & EMERGING

September 25
S2: Targeting Autophagy
S5: Targeting HBV

September 26–27
T3A: Targeting the Microbiome
T5A: NASH & Fibrosis

September 27–28
T3B: Autoimmune & Inflammation Drug Targets
T6B: Targeting Ocular Disorders

September 28–29
S6: CNS & Neurodegenerative Targets
S7: Tackling Rare Diseases

BIOLOGICS & BEYOND

September 25
S4: Constrained Peptides & Macrocyclics

September 26–27
T8A: Antibodies Against Membrane Protein Targets - Part 1

September 27–28
T8B: Antibodies Against Membrane Protein Targets - Part 2
T5B: Emerging Oligonucleotide Therapeutics

SYMPOSIA

September 25
S1: Immunomodulatory Small Molecules
S2: Targeting Autophagy
S3: Microbiome in Immuno-Oncology
S4: Constrained Peptides & Macrocyclics
S5: Targeting HBV

September 28–29
S6: CNS & Neurodegenerative Targets
S7: Tackling Rare Diseases

SHORT COURSES

September 25, 6:30-9:00 pm
SC2: GPCR Structure-Based Drug Discovery
SC5: Targeting of Ion Channels with Monoclonal Antibodies
SC6: Covalent Fragments: Applications in Target-Based & Phenotypic Screens

September 27, 7:00-9:30 pm
SC9: Impact of Convergence of Immunotherapy & Epigenetics on Drug Discovery
SC10: Introduction to Allosteric Modulators & Biased Ligands of GPCRs
SC12: Practical Phenotypic Screening
SC13: Introduction to Targeted Covalent Inhibitors

TRAINING SEMINARS

September 27, 3:30-6:30 pm & September 28, 9:00 am-5:00 pm
TS1: Data Visualization for Effective Drug Discovery Decisions
TS2: Introduction to Small Molecule Drug Discovery & Development

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