September 21-24, 2015 | Westin Boston Waterfront | Boston, MA

The Industry's Preeminent Event on Novel Drug Targets

Plenary Session Speakers

PLENARY KEYNOTE INTRODUCTION: Comprehensive Kinase and Epigenetic Compound Profiling
Kelvin Lam, Ph.D.
Director, Strategic Partnerships, Reaction Biology Corporation

iPS Cell Technology, Gene Editing and Disease Research
Rudolf Jaenisch, M.D.
Founding Member, Whitehead Institute for Biomedical Research; Professor, Department of Biology, Massachusetts Institute of Technology

The Evolutionary Dynamics and Treatment of Cancer
Martin Nowak, Ph.D., M.Sc.
Professor, Biology and Mathematics and Director, Program for Evolutionary Dynamics, Harvard University

Event Features

15 Conferences
13 Short Courses
3 Symposia
65 Exhibitors
130+ Posters
3 Plenary Keynote Speakers
40+ Interactive Breakout Discussion Groups

Sponsors

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Molecular Sensing
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13th Annual Discovery on Target

Cover
Short Courses
September 22 - 23
Targeting Epigenetic Readers and Chromatin Remodelers
Targeting the Ubiquitin Proteasome System
Targeting the Microbiome
GPCR-Based Drug Discovery - Part 1
Antibodies Against Membrane Protein Targets - Part 1
RNAi for Functional Genomics Screening
Gene Therapy Breakthroughs
Targeting Ocular Disorders

September 23 - 24
Targeting Histone Methyltransferases and Demethylases
Targeting the Unfolded Protein Response
Kinase Inhibitor Discovery
GPCR-Based Drug Discovery - Part 2
Antibodies Against Membrane Protein Targets - Part 2
New Frontiers in Gene Editing
Quantitative Systems Pharmacology

Symposia

Next-Generation Histone Deacetylase Inhibitors
Strategies for Rare Diseases
Developing CRISPR-Based Therapies

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Hotel & Travel Information
Registration Information

Register

DiscoveryOnTarget.com
### CONFERENCE-AT-A-GLANCE

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### PLENARY KEYNOTE PROGRAM

**PLENARY KEYNOTE INTRODUCTION:**
Comprehensive Kinase and Epigenetic Compound Profiling

**Kelvin Lam, Ph.D., Director, Strategic Partnerships, Reaction Biology Corporation**

Kinase inhibitors can be used as chemical probes to understand signal transduction pathways. Since the majority of kinase probes inhibit multiple kinases, understanding the off-target effects will allow scientists to design better poly-pharmacologic compounds to meet specific therapeutic needs. Profiling a compound against the entire kinase gene family will allow us to understand the compound’s full enzymatic activities. Unexpected activities could lead to different chemical design and possibly novel therapeutic opportunities. Reaction Biology offers large-scale in vitro kinase and epigenetic profiling services for (1) compound prioritizing and (2) elucidating novel activities for kinase and epigenetic inhibitors.

**iPS Cell Technology, Gene Editing and Disease Research**

**Rudolf Jaenisch, M.D., Founding Member, Whitehead Institute for Biomedical Research; Professor, Department of Biology, Massachusetts Institute of Technology**

The development of the iPS cell technology has revolutionized our ability to study human diseases in defined in vitro cell culture systems. A major problem of using iPS cells for this “disease in the dish” approach is the choice of control cells because the unpredictable variability between different iPS / ES cells to differentiate into a given lineage. Recently developed efficient gene editing methods such as the CRISPR/Cas system allow the creation of genetically defined models of monogenic as well as polygenic human disorders.

**The Evolutionary Dynamics and Treatment of Cancer**

**Martin Nowak, Ph.D., M.Sc., Professor, Biology and Mathematics and Director, Program for Evolutionary Dynamics, Harvard University**

Cancer is an evolutionary process. Cancer initiation and progression are caused by somatic mutation and selection of dividing cells. The mathematical theory of evolution can therefore provide quantitative insights into human cancer.

### HOTEL & TRAVEL INFORMATION

**CONFERENCE VENUE AND HOST HOTEL:**
Westin Boston Waterfront
425 Summer St. | Boston, MA 02210 | T: 617-532-4600

**Discount Room Rate:** $279 s/d

**Discount Reservation Cut-off Date:** August 25, 2015

**Reservations:** Please visit the travel page of www.DiscoveryOnTarget.com

**Top Reasons to Stay at the Westin Boston Waterfront Hotel**

- Take advantage of the deeply discounted $279 group rate!
- No Commute, since meeting takes place at hotel.
- Lots of new restaurants within walking distances. Waterfront is Boston’s hot new neighborhood!
- Complimentary wireless internet access in guest rooms.
ABOUT THE CONFERENCE

Cambridge Healthtech Institute will host its 13th Annual Discovery on Target event showcasing current and emerging “hot” targets for the pharmaceutical industry September 21-24, 2015 in Boston, MA. Spanning five days, the event attracts 1,000+ attendees (from 21 countries), composed of scientists/technologists, executives, directors, and managers from biopharma, academic, and healthcare organizations. In 2015 the event is comprised of 15 conference tracks, 3 Symposia, 13 short courses, 35+ interactive breakout discussion groups, an exhibit hall of 65 companies, and dedicated poster viewing and networking sessions. The 13th Annual Discovery on Target event assembles an impressive group of 200+ distinguished speakers who look forward to sharing their knowledge, best practices, and expertise with all attendees.

Kendall Square in Cambridge is the Boston area’s biotech hub

The Intro-Net offers you the opportunity to set up meetings with selected attendees before, during and after this conference, allowing you to connect to the key people you want to meet. This online system was designed with your privacy in mind and is available only to registered session attendees of this event. Registered conference attendees will receive more information on accessing the Intro-Net in the weeks leading up to the event.
PRESENT A POSTER AND SAVE $50!
Cambridge Healthtech Institute encourages attendees to gain further exposure by presenting their work in the poster sessions. To secure a poster board and inclusion in the conference materials, your abstract must be submitted, approved and your registration paid in full by August 7, 2015.

- Your poster will be available to 1,000+ delegates
- You'll automatically be entered into our poster competition where two winners each will receive an American Express Gift Certificate
- $50 off your registration fee
- Your research will be seen by leaders from pharmaceutical, biotech, academic and government institutes

Discovery on Target Student Fellowship
Full time graduate students and PhD Candidates are encouraged to apply for the Discovery on Target Student Fellowship. Interested students must complete an online application for the 2015 Student Fellowship. Applications are due by July 10, 2015.

How Students Benefit from Presenting a Poster:
1. Showcase Your Research to 1,000+ Attendees: Within the expansive Exhibit Hall stand by your poster and network with attendees. Distribute copies of journal articles or papers you have authored or contributed to.
2. Start a Future Collaboration and Meet a Potential Employer: Collect business cards and meet prospective collaborators who may be actively pursuing work in your field. Put together a short outline of the field(s) in which you seek collaborators or new professional challenges, and distribute those to the people you meet.
3. Expand Your Network: When you return to school/lab, add each person you meet to your LinkedIn connections. Keep in touch to share new ideas that may advance your own research or stature in the scientific community.

PREMIER SPONSORS

CORPORATE SPONSORS
SPONSORSHIP, EXHIBIT & LEAD GENERATION OPPORTUNITIES

CHI offers comprehensive packages that can be customized to your budget and objectives. Sponsorship allows you to achieve your goals before, during, and long after the event. Packages may include presentations, exhibit space and branding, as well as the use of delegate lists. Signing on early will maximize your exposure to qualified decision-makers and drive traffic to your website in the coming months.

Podium Presentations — Available within Main Agenda!
Showcase your solutions to a guaranteed, targeted audience through a 15- or 30-minute presentation during a specific conference program, breakfast, lunch, or separate from the main agenda within a pre-conference workshop. Package includes exhibit space, on-site branding, and access to cooperative marketing efforts by CHI. Presentations will sell out quickly, so sign on early to secure your talk!

Breakfast & Luncheon Podium Presentations
Opportunity includes a 30-minute podium presentation. Boxed lunches are delivered into the main session room, which guarantees audience attendance and participation. A limited number of these presentations are available for sponsorship.

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

User Group Meeting/Custom Event
Co-locate your user group meeting or custom event. CHI will help market the event, manage logistical operations, develop the agenda, and more. CHI can handle the entirety of the meeting or select aspects.

For additional sponsorship & exhibit information, please contact:
Jon Stroup  |  Sr. Business Development Manager
781-972-9483 | jstroup@healthtech.com
**SC1: Cancer Metabolism: Pathways, Targets and Clinical Updates**

Cancer cells, to fuel their growth, rely on what for normal cells is the ‘side’ metabolic pathway. Therefore inhibiting the metabolic enzymes that are ‘activated’ in the cancer cells offers a more precise and targeted therapeutic approach for cancer. This strategy has started to gain traction in the drug discovery industry over the past few years with the first ‘cancer metabolic’ inhibitors recently progressing into clinical trials. In this course we will review the complex metabolic pathways that are exploited by cancer cells and provide an update of the status of the cancer metabolic inhibitors in development.

**Instructors:**
- Raju Pusapati, Ph.D., Postdoctoral Research Fellow, Discovery Oncology (Jeff Settleman Lab), Genentech, Inc.
- Vipin Suri, Ph.D., Head of Biology, Raze Therapeutics

**SC2: Leveraging Data and Analytics for Drug Discovery**

Effectively using data can help biopharma companies 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; and identifying multiple drug targets (not just single drug targets) to work together as a network. This workshop will explore these issues and the role that data has on drug design to identify biomarkers and discover targets for potential therapies.

**Instructor:** Mark Borovsky, Ph.D., Executive Director, Data Analysis, Novartis

**SC3: Setting Up Effective RNAi Screens: From Design to Data to Validation**

The course is designed to provide in-depth information on how to go about setting up RNAi screening experiments and how to design assays for getting optimal results. The challenges working with siRNAs and shRNAs and the delivery reagents needed to get them into the appropriate cells and tissues will be discussed. The instructors will also provide their input on best practices for the execution of experiments and interpretation of results when dealing with complex biology and informatics.

**Instructors:**
- Caroline Shamu, Ph.D., Director, ICCB-Longwood Screening Facility, Harvard Medical School
- Eugene Buehler, Ph.D., Group Leader, Informatics, National Center for Advancing Translational Sciences, National Institutes of Health
- John Doench, Ph.D., Research Scientist, Broad Institute of Harvard and MIT
- Scott Martin, Ph.D., Group Lead, Functional Genomics, Genentech, Inc.

**SC4: Phenotypic Screening and Chemical Probe Development**

This short course will discuss the development of cellular and model organism-based assays for high-throughput small molecule screening. We will share best practices for target deconvolution, and how the results of these screens (probes) can be used to further interrogate protein/cell functions, and biological processes relevant to physiology and disease. Case studies from various projects will be used to exemplify these approaches.

**Instructor:** Samarjit Patnaik, Ph.D., Research Scientist, Probe Development Center, NCATS, NIH

**SC5: 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, University of Southern California
- Wei Liu, Ph.D., Assistant Professor, Department of Chemistry and Biochemistry, Arizona State University
- Huixian Wu, Ph.D., Postdoctoral Associate, Center for the Science of Therapeutics, The Broad Institute
**SC6: Targeting of GPCR with Monoclonal Antibodies**

While GPCRs (G protein-coupled receptors) are important therapeutic targets, it has been challenging to discover therapeutically relevant antibodies against them. This course will examine different steps along the anti-GPCR antibody discovery pathway and highlight various approaches to accomplishing each step. The topics to be covered include: 1) antibody discovery, including methods to generate antibodies and antigen preparation; 2) assays to measure antibody binding, such as an EC50 using cells expressing the GPCR; 3) in vitro assays to measure functional activity of the antibody, including antagonism (IC50) or agonism using chemotaxis, calcium, cAMP or other cell-based assays; and 4) review of promising GPCR targets and antibodies in the clinic.

**Instructor:** Barbara Swanson, Ph.D., Director, Research, Sorrento Therapeutics, Inc.

**SC7: Setting Up Effective Functional Screens Using 3D Cell Cultures**

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

**Instructors:**
Arvind Rao, Ph.D., Assistant Professor, Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center
Geoffrey A. Bartholomeusz, Ph.D., Assistant Professor and Director, siRNA Core Facility, Department of Experimental Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center
Madhu Lal-Nag, Ph.D., Team Leader, RNAi Screening, National Center for Advancing Translational Sciences, National Institutes of Health

**SC8: Targeting Protein-Protein Interactions: Biophysical Approaches**

Protein-protein interactions (PPIs) represent a large but largely untapped class of biological targets covering virtually every therapeutic area. Despite several success stories, many researchers still consider PPIs to be “undruggable.” This course will provide attendees with an overview of how to discover small-molecule inhibitors of PPIs. Attendees will also learn about potential pitfalls and what not to do. Other topics covered will include how to evaluate the feasibility of PPIs, what biophysical techniques to use, and how fragment-based lead discovery can tackle particularly challenging PPIs.

**Instructors:**
Daniel A. Erlanson, Ph.D., Co-Founder and President, Carnot Therapeutics, Inc.
Edward R. Zartler, Ph.D., President & CSO, Quantum Teasera Consulting

**SC9: Preclinical Animal Models for Ocular Indications**

The goal of the workshop is to provide an introductory overview of current preclinical animal models for ocular indications. The presentations will focus on models for Age-Related Macular Degeneration, Ocular Inflammation and Glaucoma. An overview of the characteristics of different animal models, their pros and cons and potential uses will be discussed.

**Instructors:**
Andy Whitlock, Ph.D., Director, Preclinical Development, Ophthalmology, Ora, Inc.
Goldis Malet, Ph.D., Associate Professor, Ophthalmology, Duke University School of Medicine
Maria B. Grant, M.D., FARVO, Professor, Ophthalmology, Eugene and Marilyn Glick Eye Institute, Indiana University

**SC10: Introduction to Allosteric Modulators and Biased Ligands of GPCRs**

Allosteric modulators, pathway-biased ligands, and heteromer-biased ligands represent novel therapeutic approaches for achieving more selective actions with regards to G protein-coupled receptors (GPCRs). However the identification and characterization of such compounds can be challenging due to context-dependent phenomena. Aimed at scientists working on GPCRs this course will provide information on the identification and validation of allosteric, pathway-biased, and heteromer-biased drugs including emerging screening approaches, practical tips and tools for identification and validation, and the structural basis underlying such drugs.

**Instructors:**
Annette Gilchrist, Ph.D., Assistant Professor, Pharmaceutical Sciences, Midwestern University
Karen Gregory, Ph.D., Postdoctoral Fellow, Laboratory of Arthur Christopolous, Department of Drug Discovery Biology, Monash University, Australia
Kevin Pfleger, Ph.D., Associate Professor, Molecular Endocrinology & Pharmacology, Harry Perkins Institute of Medical Research, University of Western Australia

**SC11: Introduction to Targeted Covalent Inhibitors**

Covalent inhibitors of kinases have re-emerged as a drug design strategy due to the 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:**
Mark Schnute, Ph.D., Associate Research Fellow, Biotherapeutics Chemistry & Immunoscience Research, Pfizer Global R&D
Christoph Zapf, Ph.D., Principal Scientist, Worldwide Medicinal Chemistry, Pfizer Research Labs
**SHORT COURSES**

**SC14: A Primer to Gene Editing:**
**Tools and Applications**

The course will help the novice understand the basics of how gene editing works, what tools are available for use and how those tools differ from each other. For the expert, this course will offer details on the CRISPR technology, how to set up CRISPR-based screens and complement it with existing RNAi-based screens using proper analysis and follow-up studies. The instructors will also cover the use of gene editing in drug discovery and disease modeling and best practices for design and workflows when working with other model systems, besides mammalian cells.

**Instructors:**
John Doench, Ph.D., Research Scientist, Broad Institute of Harvard and MIT
Michael Bassik, Ph.D., Assistant Professor, Department of Genetics, Stanford University
Mi Cai, Ph.D., Senior Scientist, Neuroscience & Pain Research Unit, Pfizer, Inc.
Stephanie Mohr, Ph.D., Department of Genetics, Harvard Medical School

* Separate registration required for Short Courses


In this workshop, you will learn what mechanistic physiological QSP models are, how they are built, and how they can be applied. You will also be introduced to Rosa’s Model Qualification Method (MQM), a systematic approach for ensuring that a model is fit for the purpose for which it is intended. Concepts will be illustrated with examples and case studies. Interactive discussions will cover topics including:
- Criteria for mechanistic physiological QSP modeling projects to ensure impact
- Planning and scoping the model
- Incorporating multiple types of evidence and data sources
- Using “Virtual Patients” to explore uncertainty and variability
- Relevant qualitative and quantitative model testing
- Identifying opportunities for mechanistic physiological QSP modeling

**Instructor:** Christina Freidrich, Ph.D., Chief Engineer, Rosa & Co.

* Separate registration required for Short Courses

**INTERACTIVE BREAKOUT DISCUSSION GROUPS**

This interactive session provides conference delegates and speakers an opportunity to choose a specific roundtable discussion group to join. Each group has a moderator to ensure focused discussions around key issues within the topic. This format allows participants to meet potential collaborators, share examples from their work, vet ideas with peers, and be part of a group problem-solving endeavor. The discussions provide an informal exchange of ideas and are not meant to be a corporate or specific product discussion. The Interactive Breakout Discussion Groups take place across all programs and will be held either on Tuesday, September 22 at 5:10 pm or Thursday, September 24 at 8:00 am. See website for updated topics.
Suggested Event Package:
- September 21 Symposium: Next Generation Histone Deacetylase Inhibitors
- September 23 Short Course: Assays and High-Throughput Screening for Novel Epigenetic Inhibitors
- September 22-23 Conference: Targeting Epigenetic Readers and Chromatin Remodelers
- September 23-24 Conference: Targeting Histone Methyltransferases and Demethylases

MONDAY, SEPTEMBER 21

7:00 am Registration and Morning Coffee

UNDERSTANDING CELLULAR CROSS-TALK

8:30 Chairperson’s Opening Remarks
Wayne W. Hancock, M.D., Ph.D., Children’s Hospital of Philadelphia

8:40 KEYNOTE: Low Dosing of HDAC Inhibitors for Treating Inflammatory Diseases
Charles Dinarello, M.D., Professor of Medicine and Immunology, University of Colorado School of Medicine; Professor of Experimental Medicine at Radboud University, Netherlands

HDAC’s are studied in a broad spectrum of diseases, for the most part due to the anti-inflammatory and immunomodulatory properties of HDAC’s, often observed in vitro and also in animal models. The reduction in inflammation by HDAC’s is consistently observed at low concentrations compared with the higher concentrations required for killing tumor cells. This characteristic makes HDAC’s attractive and safe candidates for treating chronic diseases.

9:10 Similarities and Differences between the Effects of Isoform-Selective HDAC Inhibition and HDAC Gene Deletion
Wayne W. Hancock, M.D., Ph.D., Professor of Pathology; Chief, Transplant Immunology, Children’s Hospital of Philadelphia and University of Pennsylvania

The data generated when an HDAC gene is knocked down or out altogether is typically considered the gold standard for understanding the biologic importance of a given HDAC. We have examples of major differences arising between gene deletion during embryogenesis and gene deletion in the same cell type using conditional approaches in adult mice. Which data set to believe, and how does HDAC inhibition pharmacologically match or differ from gene targeting? The answers are relevant to all efforts to develop pharmaco logical HDACi.

9:40 Design and Development of Novel, Selective Orally-Active HDAC6 Inhibitors
Stephen Shuttleworth, Ph.D., CSO, Karus Therapeutics Ltd.

10:10 Networking Coffee Break

EXPLORING BIOLOGY FOR EFFECTIVE THERAPIES

10:40 HDAC Inhibitors for Cardiovascular Disease
Timothy A. McKinsey, Ph.D., Associate Professor, Associate Head, Translational Research, Medicine, Cardiology, University of Colorado Denver

11:10 Targeting Immunologic and Epigenetic Resistance in Solid Tumors Using HDAC1 Selective Inhibitor Entinostat
Peter Ordentlich, Ph.D., CTO and Founder, Syndax Pharmaceuticals

11:40 Luncheon Presentation (Sponsorship Opportunity Available) or Lunch on Your Own

PROBING NEW HDAC CHEMISTRIES & FUNCTION

1:10 pm Chairperson’s Remarks
Alan P. Kozikowski, Ph.D., Professor, University of Illinois, Chicago

1:20 Imaging HDAC Density and Drug Inhibition in the Human Brain
Jacob Hooker, Ph.D., Assistant Professor, Department of Radiology, Harvard Medical School

We have developed an imaging agent, [11C]Martinostat, to quantify HDAC isoforms non-invasively in humans and are using quantitative imaging to determine the relationships between HDAC and disease in the brain and in peripheral organ systems.

1:50 Exploration of Some New HDAC Inhibitors for Cancer and CNS Diseases
Alan P. Kozikowski, Ph.D., Professor, College of Pharmacy Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago

I will discuss several new chemical scaffolds for HDACi that have been designed and found to be highly selective for HDAC6 inhibition. These new inhibitors have been examined using both thiol and hydroxamate based zinc binding groups. Some of the compounds have the ability to penetrate the BBB, and are being studied for effects in CMT, Rett syndrome, Alzheimer’s, and cancer as well as immune responses through control of Treg populations.

2:20 Defining the HDAC Independent Effects of Hydroxamate-Based Inhibitors in Neuroprotection
Edward Holson, Ph.D., Director, Medicinal Chemistry, Stanley Center for Psychiatric Research and Director, Chemistry, Chemical Biology Platform, Broad Institute HDAC have demonstrated an ability to protect neuronal loss from multiple forms of oxidative insult. We discovered that several hydroxamate based inhibitors derive their neuroprotective effects through HDAC independent mechanisms driven primarily through their ability to chelate metal ions.

2:50 Refreshment Break

HDACI FOR CANCER IMMUNOTHERAPY

3:15 Chairperson’s Opening Remarks
Simon Jones, Ph.D., Vice President Biology and Preclinical Development, Acetylyon Pharmaceuticals

3:20 Epigenetic Priming for Immunotherapy in Breast Cancer
Pamela Munster, M.D., Professor of Medicine, Program Leader Development Therapeutics and Director of Early Phase Clinical Trials’ Program, Helen Diller Cancer Center, University of California, San Francisco

3:50 HDAC Inhibitors for Immuno-combination Therapy of Cancer
Gosse Adema, Ph.D., Professor and Chair in Molecular Immunology, Department of Tumor Immunology, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, The Netherlands

4:20 FEATURED PRESENTATION:
Role of Selective HDAC6 Inhibitors in Cancer Immunotherapy
Eduardo M. Sotomayor, M.D., Director, GW Cancer Center, Professor, Medicine, Division of Hematology/Oncology, George Washington University

4:50 Close of Symposium
Monday, September 21
7:00 am Registration and Morning Coffee

NEW SCREENING, EDITING & DELIVERY TECHNOLOGIES

8:30 Chairperson’s Opening Remarks
Philip Murphy, M.D., National Institutes of Health

8:40 Massive Parallelization of Rare Disease Drug Discovery
Christopher Gibson, Ph.D., Co-Founder and CEO, Recursion Pharmaceuticals
A number of target-agnostic approaches will be discussed, along with a detailed discussion of work being done at Recursion Pharmaceuticals to use complex and subtle phenotypic signatures at the level of individual cells as the basis for broad drug discovery approaches.

9:10 Cell and Gene Therapy for Cystic Fibrosis and Sickle Cell Disease: Modification of iPSCs with CRISPRs and TALENs
Dieter Gruenert, Ph.D., Professor, Department of Otolaryngology-Head and Neck Surgery, Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research, University of California, San Francisco
Through the application of the CRISPR/Cas9 and TALEN platforms it was possible to enhance the correction of both cystic fibrosis (CF) and sickle cell disease (SCD) associated pathogenic mutations with small/short DNA fragment (SDF) polyadenylation. Phenotypic functional and/or genotypic correction was observed for both diseases suggesting potential therapeutic applications.

9:40 A Cure Strategy for WHIM Syndrome Immunodeficiency
Philip Murphy, M.D., Chief, Laboratory of Molecular Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health

10:10 Networking Coffee Break

10:40 Treating Oral Cancer Locally
Manijeh Goldberg, Founder and CEO, Privo Technologies
Privo Technologies, with roots at MIT’s Langer lab, is developing a nanoeengineered platform to deliver a more targeted and higher concentration of Active Pharmaceutical Ingredient (API) directly to the epithelium mucosa. This delivery is being tested for treating some rare diseases such as oral cancer, neuroblastoma and rectal cancer.

11:10 KEYNOTE: Pursuing Rare Diseases through Genome Sequencing
Robert Green, M.D., MPH, Director, Genomes2People Research Program, Associate Professor, Division of Genetics, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School
Whole exome and whole genome sequencing has now entered the clinical practice of medicine, particularly as a tool for pursuing the molecular etiology of undiagnosed diseases. The increasingly broad application of sequencing is not only allowing us to better diagnose well-established Mendelian syndromes, but also to discover new syndromes and broaden the phenotypic profile of many established conditions. Case histories of several undiagnosed diseases, along with new data on population-based sequencing, will be presented.

11:55 Luncheon Presentation (Sponsorship Opportunity Available) or Lunch on Your Own

REPLACEMENT & COMBINATION THERAPIES

1:10 pm Chairperson’s Remarks
Bruce Bloom, J.D., DDS, President and Chief Science Officer, Cures Within Reach

1:20 Targeted Peptide Therapy in Combination With HDAC Inhibitors to Treat Small Cell Lung Cancer and Other Neuroendocrine Carcinomas
Christopher Adams, CEO, Research & Development, Andax Pharmaceuticals

1:50 Prevention of Anti-Drug Antibodies in the Treatment with Protein Replacement Therapies for Rare Diseases
Takashi Kashimoto, Ph.D., CSO, Selecta Biosciences
The development of anti-drug antibodies (ADAs) is a common cause for treatment failure and adverse events associated with protein replacement therapy. Selecta Biosciences has developed Synthetic Vaccine Particles (SVP) to induce durable antigen-specific immune tolerance for the prevention of ADAs.

2:20 ddRNAi and Gene Replacement for Oculopharyngeal Muscular Dystrophy (OPMD)
Peter French, Ph.D., CEO and Managing Director, Benitec Biopharma Ltd.
OPMD is a late-onset degenerative muscle disorder caused by a mutation in the FABP5 gene. Our approach is a combination gene therapy designed to both silence the mutant gene with a ddRNAi construct and simultaneously to insert the wild type gene.

2:50 Refreshment Break

PURSUE DRUG REPURPOSING & OTHER STRATEGIES

3:20 Repurposing “Failed” Drugs to Treat Pediatric Sarcomas
Andrew Napper, Ph.D., Head, High-Throughput Screening and Drug Discovery Lab, Biomedical Research, Nemours
This presentation will review recent success stories, describe current initiatives, and hypothesize about what the future will bring for drug repurposing for rare diseases.

4:20 Development of Effective Prevention and Treatment of Skin Cancer In Xeroderma Pigmentosum
W. Clark Lambert, M.D., Ph.D., Professor and Associate Head, Dermatology and Director, Dermatopathology, Rutgers University Medical School

4:50 Creating an Accelerated Research Environment for Rare Diseases
Franz Eichler, M.D., Associate Professor of Neurology, Massachusetts General Hospital and Harvard Medical School
The Massachusetts General Hospital (MGH) Rare Disease Think Tank has assembled leaders in the rare disease field. This unique platform provides access to the best possible medical evidence for known and emerging rare diseases. It creates opportunities for clinical trial design and informed clinical decision making, repurposing known drugs, and implementing pilot research studies.

5:20 Close of Symposium
After its rapid rise to fame as an efficient, easy-to-use research tool, the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)/Cas system, is now being scrutinized for its therapeutic applications. This inaugural one-day symposium on Designing CRISPR-based Therapies will bring together experts from the lab and the clinic to talk about the future of CRISPR-based therapies. Scientists and clinicians will share their experiences leveraging this technology and discuss potential opportunities and obvious pitfalls.

Suggested Event Package:
- September 21 Short Course: Setting Up Effective RNAi Screens: From Design to Data to Validation
- September 21 Short Course: Setting Up Effective Functional Screens Using 3D Cell Cultures
- September 22 Symposium: Developing CRISPR-Based Therapies
- September 23 Short Course: A Primer to Gene Editing: Tools and Applications
- September 23-24 Conference: New Frontiers in Gene Editing

TUESDAY, SEPTEMBER 22
7:00 am Registration and Morning Coffee

EVALUATING THERAPEUTIC APPLICATIONS

8:30 Chairperson’s Opening Remarks
Alexandra Glucksmann., Ph.D., Chief Operating Officer, Editas Medicine

8:40 Advancing the CRISPR/Cas9 Technology Platform for Therapeutic Applications
Alexandra Glucksmann., Ph.D., COO, Editas Medicine

8:50 Genome editing technologies, including the CRISPR/Cas9 system, allow for precise and corrective molecular modifications to treat the underlying cause of genetic diseases. Editas Medicine is developing CRISPR/Cas9-based therapeutics across a broad range of indications. This presentation will focus on Editas’ approach to CRISPR technology optimization within the context of specific therapeutic applications.

9:10 Design of CRISPR/Cas9 Nickase Pairs for DNA Polynucleotide-Mediated Genomic DNA Modification
Dieter Gruenert, Ph.D., Professor, Department of Otolaryngology - Head and Neck Surgery, Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research, University of California, San Francisco

Due to the relative short “guide RNA” (gRNA) sequence (~20 bases) of the CRISPR/Cas9 system, there is likely an increased probability that this gRNA binds to other genomic sites, enhancing the potential of multiple Cas9 cuts. CRISPR/Cas9n largely circumvents this by creating a CRISPR/Cas9n pair that nicks opposing DNA strands in close enough proximity to facilitate a double strand break. This system was optimized for gene-editing with small/short DNA fragments in iPSCs expressing mutant genes.

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

10:25 Use of CRISPR/Cas9-Based Gene Editing to Model and Treat Retinal Degenerative Disease
Donald Zack, M.D., Ph.D., Guerrieri Professor of Genetic Engineering and Molecular Ophthalmology, Johns Hopkins University

We have used CRISPR/Cas9-based gene editing to generate ES/iPS reporter lines and used them to develop retinal eyecups in vitro, both to model normal development and to generate models for retinal disease. Using these cells we are screening for differentiation and cell survival promoting molecules. We are also developing CRISPR/Cas9 reagents for the treatment of autosomal dominent retinitis pigmenta, a blinding form of retinal degenerative disease.

10:55 Engineering Sequence-Specific Diagnostics for Antibiotic-Resistant Bacteria
Timothy K. Lu, M.D., Ph.D., Associate Professor, Synthetic Biology Group, Department of Electrical Engineering and Computer Science and Department of Biological Engineering, Synthetic Biology Center, Massachusetts Institute of Technology

Current antimicrobials are broad spectrum, leading to indiscriminate bacterial targeting and rapid drug-resistance evolution. We demonstrate Programmable-Spectrum AntiMicrobial (PSAM) agents whose activity can be customized against specific DNA sequences using CRISPR-Cas9 technology delivered via bacteriophage and conjugate vectors. PSAMs are a novel class of highly discriminative antimicrobials that exact selective pressure at the level of DNA to enable programmable remodeling of microbiota and reduce off-target effects.

11:25 Chairperson’s Remarks
Myung Shin, Ph.D., Senior Principal Scientist, Biology-Discovery, Genetics and Pharmacogenomics, Merck Research Laboratories

2:00 Application of Genome Editing Tools to Model Human Genetic Findings in Preclinical Animals
Myung Shin, Ph.D., Senior Principal Scientist, Biology-Discovery, Genetics and Pharmacogenomics, Merck Research Laboratories

2:30 CRISPR-mediated Direct Mutation of Cancer Genes in the Mouse Liver
Wen Xue, Ph.D., Assistant Professor, Program in Molecular Medicine,RNA Therapeutics Institute, University of Massachusetts Medical School

3:00 Discovery of Cancer Drug Targets by CRISPR-Cas9 Screening of Protein Domains
Junwei Shi, Ph.D. Student, Laboratory of Dr. Christopher Vakoc, Cold Spring Harbor Laboratory

3:30 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Winner Announced

BUILDING RELEVANT MODELS FOR DRUG DISCOVERY

1:50 Chairperson’s Remarks
Myung Shin, Ph.D., Senior Principal Scientist, Biology-Discovery, Genetics and Pharmacogenomics, Merck Research Laboratories

2:00 Application of Genome Editing Tools to Model Human Genetic Findings in Preclinical Animals
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3:30 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Winner Announced

* Separate Registration Required for CRISPR-Based Therapies Symposium
Inaugural

**Symposium: Developing CRISPR-Based Therapies**
*From How It Works to Where It Can Be Successfully Applied*

**4:10 Nucleic Acid Delivery Systems for RNA Therapy and Gene Editing**
Daniel Anderson, Ph.D., Professor, Department of Chemical Engineering, Institute for Medical Engineering & Science, Harvard-MIT Division of Health Sciences & Technology and David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology

We describe our work on high throughput methods for developing and characterizing RNA delivery and gene editing systems. Libraries of degradable polymers and lipid-like materials have been synthesized, formulated and screened for their ability to deliver RNA, both in vitro and in vivo. Formulations have shown utility in higher animals, and are now in clinical development. The potential of these delivery systems for the treatment of the disease, and in vivo application of therapeutic genetic editing will be discussed.

**4:40 Next-Generation Gene Therapy: Genome Editing**
Matthew Porteus, M.D., Ph.D., Associate Professor, Pediatrics, Stanford University School of Medicine

There are now estimated to be 10,000 diseases caused by mutations in single genes (monogenic diseases). Curative therapy for these diseases would be based on treating these diseases at their foundation-by genetically modifying the genome. Genome editing provides a powerful mechanism to precisely engineer the genome with nucleotide precision, true precision therapy, and this talk will focus on both the various tools available for genome editing and ways that the genome can be edited for therapeutic purposes.

**5:10 Close of Symposium**
Cambridge Healthtech Institute's third annual Targeting Epigenetic Readers and Chromatin Remodelers meeting will once again unite academic and industry researchers for the development of chemical probes, to discuss advances in preclinical and clinical programs, and ultimately to further our understanding of the therapeutic opportunities associated with targeting reader domains and chromatin remodelers.

Suggested Event Package:
- September 21 Symposium: Next Generation Histone Deacetylase Inhibitors
- September 21 Short Course: Cancer Metabolism: Pathways, Targets and Clinical Updates
- September 23 Short Course: Assays and High-Throughput Screening for Novel Epigenetic Inhibitors
- September 22-23 Conference: Targeting Epigenetic Readers and Chromatin Remodelers
- September 23-24 Conference: Targeting Histone Methyltransferases and Demethylases

TUESDAY, SEPTEMBER 22

7:00 am Registration and Morning Coffee

DEVELOPING NOVEL BROMODomain INHIBITORS

8:00 Chairperson’s Opening Remarks
Dafydd Owen, Ph.D., Associate Research Fellow, Medicinal Chemistry, Biotherapeutics Worldwide R&D, Pfizer

8:10 New Chemical Tools Targeting BET Bromodomains and Advances in the Bump and Hole Approach
Alessio Ciulli, Ph.D., Associate Professor & Principal Investigator, Chemical & Structural Biology, College of Life Sciences, University of Dundee
In my talk I will present recent developments from our lab at targeting BET bromodomain proteins using chemical tools, including advances and optimization of our bump and hole approach to introduce controlled selectivity of BET bromodomain chemical probes.

8:40 Specific BET Bromodomain Inhibitors to Treat Disease
Chris Burns, Ph.D., Laboratory Head, Chemical Biology Division, Walter and Eliza Hall Institute, Australia
We have identified chemically novel scaffolds that bind to bromodomain proteins. We prepared a series of compounds based on these chemical scaffolds and profile the compounds for both bromodomain inhibition and activity against AML, to generate compounds with improved selectivity compared to known inhibitors.

9:10 Targeting Epigenetic Readers for Cancer Therapy
Jin Qi, Ph.D., Lead Scientist, Medical Oncology, Dana-Farber Cancer Institute
Epigenetic proteins are promising and intensely studied targets for therapeutic drug discovery in cancer. Among the chromatin modifying enzymes, so-called epigenetic “writers,” “reader” and “erasers,” chromatin binding modules or epigenetic “readers” are more difficult targets perhaps owing to perceptions regarding the difficulty of targeting protein-protein interactions. We have recently developed first-in-class, drug-like inhibitors of “bromodomain and extraterminal domain” epigenetic readers (BETs) for mechanistic study and therapeutic application in cancer and other diseases. We are continuously integrating the transcriptional consequences of BETi with changes in the epigenomic landscapes of cancer cells to elucidate the mechanisms underlying response to BETi using chemical and genetic perturbations.

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

10:25 In silico Discovery and Experimental Validation of Selective Bromodomain Inhibitors
Amedeo Calfisch, Ph.D., Professor and Chair, Computational Structural Biology, Department of Biochemistry, University of Zurich
We have discovered in silico, validated by X-ray crystallography, and optimized by chemical synthesis a series of N4 potent and selective ligands of the CREBBP bromodomain. Fragment-based, high-throughput docking was employed for the identification of novel scaffolds whose affinity was enhanced in a straightforward manner by incorporating interactions within the ZA channel.

10:55 Design and Development of Novel BET Bromodomain Inhibitors
Shaomeng Wang, Ph.D., Director, Center for Discovery of New Medicines; Warner-Lambert/Parke-Davis Professor, Medicine, Pharmacology and Medicinal Chemistry, University of Michigan Comprehensive Cancer Center
I will discuss the design, synthesis, characterization and development of novel small molecule drugs targeting bromodomain-containing proteins for the treatment of human cancer.

11:25 Novel Chemical Probes Targeting Bromodomains
Dafydd Owen, Ph.D., Associate Research Fellow, Medicinal Chemistry, Biotherapeutics Worldwide R&D, Pfizer
During this lecture I will discuss how a small molecule, PFI-3, dissected knock down studies and truly identify the target required for efficacy drugging SWI/SNF mediated cancers. I will also discuss PFI-4, which is a new probe for the Bromodomain BRPF1. Finally I will share the development of a new probe, PFI-5, an extension to our PFI-3 story.

11:55 Proteomics & Patients
Yingming Zhao, Ph.D., Professor, University of Chicago
12:25 pm Session Break
12:35 Luncheon Presentation (Sponsorship Opportunity Available) or Lunch on Your Own
1:15 Refreshment Break in the Exhibit Hall with Poster Viewing

EMERGING PRE-CLINICAL PROGRAMS

1:50 Chairperson’s Remarks
Claes Wahlestedt, M.D., Ph.D., Leonard M. Miller Professor & Associate Dean, Therapeutic Innovation, Miller School of Medicine, University of Miami

2:00 CNS Effects of BET Bromodomain Inhibitors
Claes Wahlestedt, M.D., Ph.D., Leonard M. Miller Professor & Associate Dean, Therapeutic Innovation, Miller School of Medicine, University of Miami
We have developed novel small molecules, such as EP11313, with characteristics of CNS active drugs. These compounds have to date primarily been tested in various models of glioblastoma. However, they have also been useful in demonstrating a role for BET bromodomain proteins as novel epigenetic regulators of cocaine-induced behavioral plasticity.

2:30 Discovery of Scaffold/Platform for the Development of Dual PI3K/BRD4 Inhibitors
Donald Durden, M.D., Ph.D., Professor, Vice Chair, Pediatrics, University of California, San Diego School of Medicine; CEO and President, SignalRx Pharmaceuticals

Key in vitro and animal proof-of-concept efficacy studies will be presented for the lead compound SF2523. Moreover, the recently described epigenetic kinome adaptation response which encodes targeted therapeutic resistance in cancer is blocked by Brd4 BET inhibitors and represents a novel strategy to augment antitumor effects of targeted therapies including PI-3 kinase inhibitors in vitro and in vivo.

3:00 Sponsored Presentation (Opportunity Available)

3:30 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Winner Announced

SWI/SNF MOLECULAR MECHANISMS IN DISEASE

4:10 Synthetic Lethal Approaches to ARID1A-Mutated Ovarian Cancers
Rugang Zhang, Ph.D., Associate Professor, The Wistar Institute

The Zhang laboratory strives to uncover novel epigenetic strategies for developing cancer therapeutics. Recent work from his laboratory will be presented that investigates the molecular basis and therapeutic opportunities for human cancers with mutations in the components of the SWI/SNF chromatin-remodeling complex.

4:40 Role of BRD4 and SWI/SNF in the Maintenance of Acute Myeloid Leukemia
Chris Vakoc, M.D., Ph.D., Assistant Professor, Cold Spring Harbor Laboratory

Our lab has employed negative-selection shRNA screening to identify chromatin regulator dependencies in a mouse model of acute myeloid leukemia. We have identified Brd4 and SWI/SNF as among the top dependencies in this disease, which exhibit several desirable properties for therapeutic targeting. Recent work will be presented that seeks to understand the molecular mechanism of these chromatin regulators in cancer maintenance.

5:10 Interactive Breakout Discussion Groups (see website for details)

6:10 Welcome Reception in the Exhibit Hall with Poster Viewing

7:15 Close of Day

WEDNESDAY, SEPTEMBER 23

7:30 am Registration and Morning Coffee

EVALUATING THERAPEUTIC POTENTIAL

8:00 Chairperson’s Remarks
Robert J. Sims III, Ph.D., Executive Director, Biology, Constellation Pharmaceuticals, Inc.
Cambridge Healthtech Institute will once again convene leaders in epigenetic drug development to further our understanding of the role aberrant histone methylation plays in disease, to evaluate lead and clinical compounds by developers, and to introduce novel chemical matter for further development.

**Suggested Event Package:**
- September 21 Symposium: Next Generation Histone Deacetylase Inhibitors
- September 23 Short Course: Assays and High-Throughput Screening for Novel Epigenetic Inhibitors
- September 22-23 Conference: Targeting Epigenetic Readers and Chromatin Remodelers
- September 23-24 Conference: Targeting Histone Methyltransferases and Demethylases

**WEDNESDAY, SEPTEMBER 23**

11:30 am Registration
12:55 pm Plenary Keynote Program (see page 2 for details)
2:40 Refreshment Break in the Exhibit Hall with Poster Viewing

**TARGETING THE HISTONE DEMETHYLOME**

**3:25 Chairperson’s Opening Remarks**
Tamara Maes, Ph.D., Co-Founder, Vice President & CSO, Oryzon Genomics

**3:35 FEATURED PRESENTATION: Targeting the Histone Demethylome**
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

Recent data suggest that histone demethylases are chemically tractable targets, and furthermore, that demethylase selective small molecules may be useful tools to dissect chromatin driven biological processes. Data will be presented to illustrate the usefulness of these tool compounds to understand demethylase involvement in oncology and stem cell biology.

**4:05 JARID1/KDM5 Demethylases as Cancer Targets**
Qin Yan, Ph.D., Associate Professor, Department of Pathology, Yale School of Medicine

My laboratory focuses on the roles and regulatory mechanisms of the JARID1/KDM5 histone demethylases. The JARID1A/B demethylases play critical roles in tumor formation, metastasis and drug resistance, and therefore are novel targets for cancer treatment. We have identified novel mechanisms by which the JARID1 enzymes regulate gene expression and promote tumorigenesis. The implications of these results in cancer treatment will be discussed.

**4:35 The Interaction of Marketed Drugs on a Panel of Epigenetic Targets**
Jacques C. Migeon, Ph.D., Principal Scientist, Eurofins Pharma Discovery Services

In an effort to better understand the interaction of marketed pharmaceuticals with the growing number of epigenetics targets available, we ran 1000 drugs on a panel of 16 epigenetic targets. The result of this screening will be presented and discussed.

**5:05 Refreshment Break in the Exhibit Hall with Poster Viewing**

**5:40 Inhibition of LSD1 as a Therapeutic Strategy for the Treatment of AML and SCLC**
Ryan Kruger, Ph.D., Director, Discovery Biology, GlaxoSmithKline

Lysine specific demethylase 1 (LSD1) is a H3K4me1/2 demethylase found in various transcriptional co-repressor complexes. Pre-clinical data demonstrate that pharmacological inhibition of LSD1 causes differentiation of AML cells *in vitro* and *in vivo*. In SCLC cell line and primary sample xenograft studies LSD1 inhibition resulted in potent tumor growth inhibition. The current study describes the anti-tumor effects of GSK2879552, a novel, potent, selective, irreversible LSD1 inhibitor currently in clinical development.

**6:10 Development of Histone Demethylase Inhibitors for Oncological and Neurodegenerative Disease**
Tamara Maes, Ph.D., Co-Founder, Vice President & CSO, Oryzon Genomics

ORY-2001 is a dual LSD1/MAO-B inhibitor with near equipotential activity in both targets but selective over MAO-A and other FAD dependent aminooxidases. The compound effectively protects mice from MPTP insult, demonstrating its brain MAOi capacity, and restores the memory loss of SAMP-8 mice, a non transgenic model for accelerated aging and Alzheimer disease. The mechanisms by which ORY-2001 acts on the mouse hippocampus will be discussed.

**6:40 Close of Day**
THURSDAY, SEPTEMBER 24

7:30 am Registration

8:00 Interactive Breakfast Breakout Discussion Groups (see website for details)

DISSCOVERY AND DEVELOPMENT OF NOVEL METHYTRANSFERASE INHIBITORS

8:45 Chairperson’s Remarks
Karen Maegley, Ph.D., Associate Research Fellow, Biochemistry and Primary Screening, Pfizer Oncology

8:55 Chemical Tractability of Protein Methyltransferases: Lessons Learned from Protein Structures and Screening Campaigns
Matthieu Schapira, Ph.D., Principal Investigator, Computational Chemistry, Structural Genomics Consortium; Associate Professor, Department of Pharmacology & Toxicology, University of Toronto

The Structural Genomics Consortium is screening multiple chemical libraries from academic and industry partners against a large panel of protein methyltransferases. I will review hit rates observed so far, highlight resulting chemical probes and complex structures, and discuss the chemical tractability of the cofactor and substrate binding sites.

9:25 Discovery of Chemical Probes for Histone Methyltransferases
Aiping Ma, Ph.D., Senior Research Scientist, Jian Jin Laboratory, Medicinal Chemistry, Chemical Biology & Drug Discovery, Icahn School of Medicine at Mount Sinai

However, only a limited number of chemical probes of HMTs have been discovered. Our laboratory has been pursuing a multifaceted structure-based probe discovery strategy. Progress on discovering selective, substrate-competitive inhibitors of SETD8, a PRMT3 chemical probe which occupies a novel allosteric binding site, and a cofactor-competitive EZH2 and EZH1 chemical probe which effectively blocks proliferation of MLL-AF9 transformed murine progenitors will be presented.

9:55 Discovery of a Novel Smyd3 Inhibitor That Bridges the SAM-and MEKK2-Binding Pockets
Qin Yan, Ph.D., Associate Professor, Department of Pathology, Yale School of Medicine

Our laboratory has cloned a number of PKMT SET domains, and has identified novel classes as fragment-based drug design, is applicable to a wide-range of enzyme and protein-protein interaction targets nominated by Domainex or its collaborators.

10:25 Coffee Break in the Exhibit Hall with Poster Viewing

11:00 Development of Potent Inhibitors of Menin-MLL Interaction with Strong Efficacy in Animal Models of Leukemia
Jolanta Grembecka, Ph.D., Assistant Professor, Department of Pathology, University of Michigan

Here we report the development of highly potent and orally bioavailable small-molecule inhibitors of the menin-MLL interaction, MI-463 and MI-503, and show their profound effects in MLL leukemia cells and substantial survival benefit in mouse models of MLL leukemia. Finally, we demonstrate the efficacy of these compounds in primary samples derived from MLL leukemia patients.

11:40 Mechanistic Characterization of PRMT5 Enzyme Complexes
Karen Maegley, Ph.D., Associate Research Fellow, Biochemistry and Primary Screening, Pfizer Oncology

PRMT5 methylates arginine residues on protein substrates. Many different PRMT5 complexes have been described and different complexes are suggested to have different substrate preferences. We have enzymatically characterized PRMT5 complexes and will compare and contrast mechanism of action and inhibition and suggest a potential regulation mechanism.

12:10 pm Is it Real, Or is it Virtual?
Using the Domainex Technology Platform to Identify Novel Inhibitors of Lysine Methyltransferases
Trevor Pernier, Ph.D., Director, Research, Domainex Limited

Using its Combinatorial Domain Hunting and LeadBuilder platform technologies, Domainex has cloned a number of PKMT SET domains, and has identified novel classes of drug-like inhibitors. This powerful combination of virtual and library screening, as well as fragment-based drug design, is applicable to a wide-range of enzyme and protein-protein interaction targets nominated by Domainex or its collaborators.

12:40 Session Break

12:50 Luncheon Presentation (Sponsorship Opportunity Available) or Lunch on Your Own

1:30 Refreshment Break

MOLEcular MECHANISMS IN CANCER

2:15 Chairperson’s Remarks

2:20 Chromatin Modulators Provide a New Insight into Cancer Genomes
Johnathan R. Whetstone, Ph.D., Tepper Family MGH Research Scholar, Associate Professor of Medicine, Harvard Medical School and Massachusetts General Hospital Cancer Center

To date, enzymes that are capable of promoting site-specific copy number changes have yet to be identified. We have recently been able to demonstrate that H3K9/36me3 lysine demethylase KDM4A overexpression leads to localized copy gains without global chromosome instability. The copy gain occurs within a single cell cycle, requires S-phase and is not stable but regenerated each cell division.

2:50 Nitric Oxide is an Epigenetic Regulator of Gene Expression via Inhibition of JmjC-Domain Containing Histone Demethylases
Douglas Thomas, Ph.D., Associate Professor, Department of Medicinal Chemistry & Pharmacognosy, University of Illinois at Chicago

Nitric oxide (NO, nitrogen monoxide) is an endogenously produced free radical signaling molecule with numerous purported roles in health and disease. Our recent findings provide a direct mechanistic link between cell-surface-derived NO and significant changes.
in histone posttranslational modifications (PTMs) by demonstrating its ability to inhibit the catalytic activity of JmJ-C-domain containing histone demethylases. These results reveal a novel signaling mechanism of NO and demonstrate that a significant proportion of NO-driven transcriptional responses arise from changes in histone PTMs.

3:20 Session Break

EVALUATING THERAPEUTIC POTENTIAL

3:30 Targeting Arginine Methyltransferases in Cancer Therapy
Robert A. Baiocchi, M.D., Ph.D., Associate Professor, Division of Hematology, Department of Internal Medicine, The Ohio State University
We developed a first-in-class, small molecule PRMT5 inhibitor that blocked EBV-driven B lymphocyte transformation and survival while leaving normal B cells unaffected. Inhibition of PRMT5 led to lost recruitment of a PRMT5/p65/HDAC3 repressive complex on the miR96 promoter, restored miR96 expression and PRMT5 down-regulation.

4:00 EZH2 Inhibitors and Their Application in Cancer
Patrick Trojer, Ph.D., Executive Director, Head, Biology, Constellation Pharmaceuticals
Constellation has identified potent, selective small molecule inhibitors of the histone H3 lysine 27 (H3K27)-specific methyltransferase Enhancer of Zeste Homolog 2 (EZH2). These compounds cause selective cell killing of Non Hodgkin Lymphoma cell lines and regression in subcutaneous NHL models in vivo. The impact on tumor growth is correlated with global reduction of H3K27me3 levels and the induction of EZH2 target gene expression. We have identified Multiple Myeloma as an additional potential application for EZH2 inhibitors.

4:30 FEATURED PRESENTATION: Discovery of EPZ015666: A First-in-Class PRMT5 Inhibitor with Potent in vitro and in vivo Activity
Jesse Smith, Ph.D., Executive Director, Biological Sciences, Epizyme
We describe the identification and characterization of EPZ015666 (GSK3235025), a potent, selective and orally available inhibitor of Protein Arginine Methyltransferase-5 (PRMT5). This novel inhibitor is SAM-uncompetitive, peptide-competitive and interacts with the PRMT5:MEP50 complex through a unique inhibition mode. Treatment with EPZ015666 on Mantle Cell Lymphoma (MCL) cells leads to inhibition of PRMT5 mediated methylation and cell killing.

5:00 Close of Conference
Third Annual Targeting the Ubiquitin Proteasome System

Cambridge Healthtech Institute’s third annual Targeting the Ubiquitin Proteasome System will once again gather an interdisciplinary collection of leaders working to advance the rapidly expanding field of UPS drug discovery.

Cover

September 22-23
Targeting Epigenetic Readers and Chromatin Remodelers
Targeting the Ubiquitin Proteasome System
Targeting the Microbiome
GPCR-Based Drug Discovery - Part 1
Antibodies Against Membrane Protein Targets - Part 1
RNAi for Functional Genomics Screening
Gene Therapy Breakthroughs
Targeting Ocular Disorders
SEPTEMBER 23 - 24
Targeting Histone Methyltransferases and Demethylases
Targeting the Unfolded Protein Response
Kinase Inhibitor Discovery
GPCR-Based Drug Discovery - Part 2
Antibodies Against Membrane Protein Targets - Part 2
New Frontiers in Gene Editing
Quantitative Systems Pharmacology

SYMPOSIA

Next-Generation Histone Deacetylase Inhibitors
Strategies for Rare Diseases
Developing CRISPR-Based Therapies

Sponsor & Exhibit Opportunities
Hotels & Travel Information
Registration Information

DiscoveryonTarget.com

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

DESIGN AND DEVELOPMENT OF NOVEL DEUBIQUITINASE (DUB) INHIBITORS

10:25 Selective De-Ubiquitylase Inhibitors for Cancer Immunotherapy
Tauseef R. Butt, Ph.D., President and CEO, Progena, Inc
Progena has discovered selective USP7 inhibitors that demonstrate efficacy in a number of p53-positive and p53-negative animal tumor models. USP7 inhibitors block cancer growth in immunocompetent mice; these molecules impair Treg functions, thereby promoting T effector-mediated anti-tumor activity. In addition these USP7 inhibitors have also demonstrated direct anti-tumor activity in several models. Molecular mechanisms of these dual-acting USP7 inhibitors will be discussed.

10:55 Proteasome-Associated DUBs: Molecular Targets for Cancer Treatment
Martina Bazzaro, Ph.D., Associate Professor, Masonic Cancer Center, University of Minnesota Pharmacological inhibition of the proteasome-associated USP14 and UCHL5 has preclinical efficacy in preclinical models without toxicity in the host. Furthermore, we have shown that primary ovarian cancer cells derived from patients with recurrent ovarian cancer are particularly sensitive to USP14/UCHL5 inhibition. Pharmacological and genetic inhibition of autophagy, potentiate the cell killing effects of USP14/UCHL5 inhibitors in cancer cell lines.

11:25 Characterization of the Biochemical and Biological Activities of Proteasome Deubiquitinating Inhibitors
Padaig D’Arcy, Ph.D., Associate Professor, Cancer Pharmacology, Department of Oncology and Pathology, Karolinska Institute
We previously identified the small molecule b-AP15 as a novel class of proteasome inhibitor that functions by abrogating the deubiquitinating (DUB) activity of the proteasome. An optimized lead of this compound, named VLX1570, has subsequently been developed. VLX1570 shows in vivo activity in models of multiple myeloma and has recently been improved for clinical studies.

11:55 Sponsored Presentation (Opportunity Available)

12:10 pm Enabling and Supporting Ubiquitin System Drug Discovery
Jason Brown, Ph.D., Scientific Director, Ubiquigent Limited
Targets across the ubiquitin system offer a significant opportunity for the development of novel therapeutics. Ubiquigent’s mission is to facilitate and support such drug discovery programmes. This is enabled through our provision of a wide array of tools and services (including our industry leading DUB inhibitor profiling service) whose applications will be reviewed in this presentation along with our future plans.

12:25 pm Session Break

12:35 Luncheon Presentation (Sponsorship Opportunity Available)

or Lunch on Your Own

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

Suggested Event Package:
- September 21 Short Course: Targeting Protein-Protein Interactions: Biophysical Approaches
- September 22 Short Course: Assays and High-Throughput Screening for Novel Epigenetic Inhibitors
- September 22-23 Conference: Targeting the Ubiquitin Proteasome System
- September 23-24 Conference: Targeting the Unfolded Protein Response

TUESDAY, SEPTEMBER 22

7:00 am Registration and Morning Coffee

STRUCTURAL AND MECHANISTIC INSIGHTS INTO DEUBIQUITINASE ENZYMES

8:00 Chairperson’s Opening Remarks
Xavier Jacq, Ph.D., Head of Biology, MISSION Therapeutics

8:10 FEATURED PRESENTATION: Diverse Mechanisms of Allosteric Activation in DUB Enzymes
Titia Sixma, Ph.D., Professor, Head of Division and Group Leader, Biochemistry, Netherlands Cancer Institute

For a number of different DUBs, allosteric mechanisms of regulation have been identified and these present interesting new opportunities for targeting. We study the enzymology of different DUBs structurally and biophysically. Here we discuss how USP4 and USP7 have different regulatory mechanisms with a common catalytic switch. We also discuss how UCH-L5 can be switched on and off by structurally related regulators.

8:40 Parkin and USP30 Signaling in Parkinson’s Disease
Christian Cunningham, Ph.D., Scientist, Early Discovery Biochemistry Department, Genentech

Using mass spectrometry, we show that recombinant USP30 preferentially removes these linkage types from intact ubiquitylated mitochondria and counteracts parkin-mediated ubiquitin chain formation in cells. These results, combined with a series of chimaera and localization studies, afford insights into the mechanism by which a balance of ubiquitylation and deubiquitylation regulates mitochondrial homeostasis, and suggest a general mechanism for organelle autophagy.

9:10 Investigating Deubiquitination with Small Molecule and Ubiquitin-Based Probes
Zhihao Zhuang, Ph.D., Associate Professor, Department of Chemistry & Biochemistry, University of Delaware

In cells individual DUBs are linked to specific cellular pathways, making them attractive targets for small molecule modulation. DUBs are also known to possess different types of ubiquitin chain linkage specificities. Understanding the DUB chain linkage specificity requires new probes to be developed. The probes can also be used to understand the different modes of ubiquitin chain binding and cleavage by DUBs.
NOVEL STRATEGIES & TOOLS MODULATING THE UPS (CONT.)

4:10 New Strategies for the Identification of Chemical Inhibitors of E2 Enzymes: The Problem with Ubc9
John ‘Jay’ Schneckloth Jr., Ph.D., Investigator, Chemical Biology Laboratory; Head, Chemical Genetics Section, Center for Cancer Research, National Cancer Institute, NIH
I will discuss my group’s recent efforts to target E2 ubiquitin and ubiquitin-like conjugating enzymes. In addition I will describe the development and application of a high throughput electrophoretic mobility shift assay to screen for natural product inhibitors of sumoylation. Additionally, I will describe my group’s use of fragment-based inhibitor discovery techniques to develop inhibitors of Ubc9.

4:40 Pharmacological Activators of Tumor Suppressor PTEN
Alexander Statsyuk, Ph.D., Assistant Professor, Department of Chemistry, Northwestern University
We developed a novel fragment-based drug discovery platform, and used it to discover first in class mechanism based covalent inhibitor of Nedd4-1 ubiquitin ligase, which degrades tumor suppressor PTEN. The developed drug discovery platform is generally applicable to discover covalent drug leads for E1, E2, E3 enzymes and DUBs (~800 known enzymes).

5:10 Interactive Breakout Discussion Groups (see website for details)

6:10 Welcome Reception in the Exhibit Hall with Poster Viewing

7:15 Close of Day

WEDNESDAY, SEPTEMBER 23

7:30 am Registration and Morning Coffee

NOVEL STRATEGIES & TOOLS MODULATING THE UPS

8:00 Chairperson’s Remarks
John ‘Jay’ Schneckloth Jr., Ph.D., Investigator, Chemical Biology Laboratory; Head, Chemical Genetics Section, Center for Cancer Research, National Cancer Institute, NIH

8:10 Strategies for Enhancing Proteasome Inhibitor Efficacy
Jonathan Blank, Ph.D., Senior Scientist, Biochemistry, Takeda Oncology
The 20S proteasome core particle contains two copies of three catalytic subunits, each with differing proteolytic specificity. We describe a novel class of non-covalent dipeptide inhibitors possessing nano-molar potency for the β2 site in vitro with high selectivity over the β1 and β5 sites that can potentiate the effect of β5 inhibition with bortezomib or ixazomib.

8:40 In situ Generated Activity-Based Probes for Ub/Ubl E1-E2-E3 Enzymes: Structure, Activity and Biological Sensing
Farid El Oualid, Ph.D., CSO & COO, R&D, UbiQ
I will present the design and characterization of the first full-length Ub/Ubl-based activity-based probes (ABPs) for the E1-E2-E3 cascade. The ABPs are processed as native Ub/Ubl and at the same time allow covalent trapping of the active site cysteine of E1-E2-E3 enzymes (HECT and RBR type). I will discuss how these new ABPs can be used for activity-based protein profiling (of cell lysates and live cells) and structural biology experiments (of HECT, RBR and RING type ligases).

9:10 An E2/E3 Protein-Protein Interaction Inhibitor
Hamyar Hadian, Ph.D., Head, Assay Development and Screening Platform, Institute of Molecular Toxicology and Pharmacology, German Research Center for Environmental Health (GmbH)
Here we discuss the identification of an E2/E3 protein-protein interaction inhibitor that we validated in a variety of biochemical as well as cell-based assays. More importantly, we show that this compound is also effective in vivo mouse experiments.

9:40 Coffee Break in the Exhibit Hall with Poster Viewing
TARGETING PPIS OF RING DOMAIN E3 LIGASES

10:25 FEATURED PRESENTATION: Targeting Protein-Protein Interactions and Surfaces of Cullin RING E3 Ubiquitin Ligases (CRLs) with Chemical Probes
Alessio Ciulli, Ph.D., Associate Professor & Principal Investigator, Chemical & Structural Biology, College of Life Sciences, University of Dundee
The talk will describe current progress from the lab with developing and characterising small molecules targeting Cullin RING E3 Ubiquitin Ligases (CRLs). CRL-targeting chemical tools can be used alone as E3 ligase inhibitors or modulators of the biological pathway in which the specific CRL is involved. In addition, CRL-targeting ligands can be suitably tethered with a ligand for a given protein of interest.

10:55 Targeting Ubiquitination Activity of RING Domain in Cancer with Small Molecules
Tomasz Cierpicki, Ph.D., Assistant Professor, Pathology, University of Michigan
Targeting the Ring E3 ligases with small molecules is a very challenging task due to the lack of well-defined substrate binding pockets and a complex biochemical assays required for enzymatic activity studies. To identify small molecule inhibitors of Ring1B-Bmi1 we performed fragment-based screening using NMR spectroscopy. We identified a class of compounds that directly bind to Ring1B-Bmi1 and block its ubiquitination activity on H2A.

11:25 Enjoy Lunch on Your Own

12:55 pm Plenary Keynote Program (see page 2 for details)

2:40 Refreshment Break in the Exhibit Hall with Poster Viewing

3:25 Close of Conference
Recently, a number of strategies, chemical tools, and disease models have greatly enhanced our understanding of the underlying molecular machinery controlling the UPR, enabling small-molecule and gene targeting of specific UPR components. Modulating protein folding and homeostasis is emerging as a new and innovative therapeutic strategy. Cambridge Healthtech Institute’s Inaugural Targeting the Unfolded Protein Response will again gather an interdisciplinary collection of leaders working to advance the rapidly expanding field of UPR drug discovery.

Suggested Event Package:
- September 21 Short Course: Phenotypic Screening and Chemical Probe Development
- September 22 Short Course: Assays and High-Throughput Screening for Novel Epigenetic Inhibitors
- September 22-23 Conference: Targeting the Ubiquitin Proteasome System
- September 23-24 Conference: Targeting the Unfolded Protein Response

**WEDNESDAY, SEPTEMBER 23**

11:30 am Registration
12:55 pm Plenary Keynote Program (see page 2 for details)
2:40 Refreshment Break in the Exhibit Hall with Poster Viewing

**MECHANISMS REGULATING THE UNFOLDED PROTEIN RESPONSE (UPR)**

3:25 Chairperson’s Opening Remarks
Claudio Hetz, Ph.D., Professor, Institute of Biomedical Sciences, University of Chile; Principal Investigator, Laboratory of Cellular Stress and Biomedicine, Adjunct Professor, School of Public Health, Harvard University

3:35 FEATURED PRESENTATION: Targeting the Unfolded Protein Response
Randal J. Kaufman, Ph.D., Director, Degenerative Disease Research, Sanford Burnham Medical Research Medical Institute; Professor, Department of Pharmacology, University of California, San Diego; President and CEO, Kaufman Genetics, Inc.

The major portion of our research is aimed at elucidating fundamental mechanisms that regulate protein folding and the cellular responses to the accumulation of unfolded protein within the endoplasmic reticulum (ER). Research into the fundamental processes that regulate protein synthesis and folding within the ER provides key insights for understanding genetic diseases that result from protein folding defects.

4:05 Inhibiting the Terminal Unfolded Protein Response to Prevent Cell Degeneration
Scott André Oakes, M.D., Associate Professor, Pathology, University of California, San Francisco

We have designed rigorous in vitro assays and mouse models to identify and monitor the pro-survival and pro-death signals sent from the master UPR regulator IRE1α—an ER transmembrane kinase/RNase. Through building and testing a series of chemical-genetic IRE1α tools, our labs discovered that mammalian IRE1α has binary outputs that determine either homeostasis or apoptosis dependent on the strength of upstream ER stress.

5:05 Refreshment Break in the Exhibit Hall with Poster Viewing

**PROBING UPR PATHWAYS FOR THERAPEUTIC RESPONSE**

5:40 Gene Therapy Strategies to Target the UPR in Brain Diseases
Claudio Hetz, Ph.D., Professor, Institute of Biomedical Sciences, University of Chile; Principal Investigator, Laboratory of Cellular Stress and Biomedicine, Adjunct Professor, School of Public Health, Harvard University

Here we discuss our efforts to assess the role of the UPR in brain diseases, and develop gene therapy strategies to alleviate ER stress in specific brain regions. Examples in ALS, Alzheimer’s disease and Parkinson’s disease will be provided. A new concept is emerging where targeting specific components of the UPR provides distinct and even opposite effects.

6:10 IRE1 Signaling in Glioblastoma
Eric Chevet, Ph.D., Senior Principal Scientist, French National Institute for Health Research (INSERM)

IRE1 signaling has been shown to contribute to the progression of solid tumors through pro-angiogenic mechanisms. Herein, we expose the methodologies for investigating IRE1 signaling in tumor cells and in tumors. Moreover, we show that selective pharmacological inhibition of IRE1 RNase activity sensitizes tumor cells to ER stress.

6:40 Close of Day

**THURSDAY, SEPTEMBER 24**

7:30 am Registration
8:00 Interactive Breakfast Breakout Discussion Groups (see website for details)

**DESIGN AND DEVELOPMENT OF NOVEL INHIBITORS TARGETING UPR SENSORS: IRE1α AND PERK**

8:45 Chairperson’s Remarks
Randal J. Kaufman, Ph.D., Director, Degenerative Disease Research, Sanford Burnham Medical Research Medical Institute; Professor, Department of Pharmacology, University of California, San Diego; President and CEO, Kaufman Genetics, Inc.

8:55 Discovery of Novel Allosteric IRE1α Inhibitors
Dai-Shi Su, Ph.D., Manager, Medicinal Chemistry, Oncology, GlaxoSmithKline

I will report the discovery of diazospirodecanes as potent and selective allosteric IRE1α inhibitors. Elucidation of the structure-activity relationship of the structurally novel high-throughput screening (HTS) lead provided potent and selective IRE1α inhibitors. The SAR optimization, first co-crystal structure of a small molecule inhibitor, GSK2850163A, with human IRE1α, and mode of inhibition (MOI) characterization of compounds will also be discussed in the presentation.
9:25 Small Molecule Inhibitors Targeting IRE1
Dustin Maly, Ph.D., Associate Professor and Raymon E. and Rosellen M. Lavtron Distinguished Scholar in Chemistry, Department of Chemistry, University of Washington
I will discuss the development of a ATP-competitive IRE1 Kinase-Inhibiting RNase Attenuators-KIRAs-that allosterically inhibit IRE1’s RNase by breaking oligomers. One optimized KIRA, KIRA6, inhibits IRE1 in vivo and promotes cell survival under ER stress.

9:55 Discovery and Development of IRE1 inhibitors
Heather P. Harding, Ph.D., Scientist, Metabolic Research Laboratories and NHRI Cambridge Biomedical Research Centre, University of Cambridge
We report on the identification of a small molecule inhibitor that attains its selectivity by forming an unusually stable Schiff base with lysine 907 in the IRE1 endonuclease domain, explained by solvent inaccessibility of the imine bond in the enzyme-inhibitor complex.

10:25 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Winner Announced

11:10 PERK Inhibitors and Translational Control in Neurodegeneration
Jeffrey M. Axten, Ph.D., Director, Medicinal Chemistry, Virtual Proof of Concept (VPoC) DPU, Alternative Discovery & Development, GlaxoSmithKline
Evaluation of PERK inhibitors in various disease models is building a strong case for potential broad use to treat many neurodegenerative disorders. This talk will discuss the efficacy of PERK inhibitors in disease models, advances in our understanding of PERK inhibitor toxicity, as well as challenges and opportunities for future development.

11:40 Partial Restoration of Protein Synthesis Rates by the Small Molecule ISRIB Prevents Neurodegeneration
Julie Moreno, Ph.D., Research Scientist, Department of Microbiology, Immunology & Pathology, Colorado State University
Here we show that pharmacological modulation of eIF2-P-mediated translational inhibition can be achieved to produce neuroprotection without pancreatic toxicity. We found that treatment with the small molecule ISRIB, which restores translation downstream of eIF2, conferred neuroprotection in prion-diseased mice without adverse effects on the pancreas.

12:00 pm Sponsored Presentation (Opportunity Available)

12:40 Session Break

12:50 Luncheon Presentation (Sponsorship Opportunity Available) or Lunch on Your Own

1:30 Refreshment Break in the Exhibit Hall with Poster Viewing

NEXT GENERATION CHAPERONE-BASED THERAPIES

2:15 Chairperson’s Remarks
Eric Chevet, Ph.D., Senior Principal Scientist, French National Institute for Health Research (INSERM)

2:20 Antibody-Targeted Induction of UPR-Mediated Cell Death
Ulrich Brinkmann, Ph.D., Expert Scientist, Pharma Research & Early Development, Roche
We applied antibody-based targeting systems to deliver UPR-inducing compounds to tumor cells. This leads to specific induction of UPR in target cells and subsequent induction of apoptosis. We present these ADC-like entities with novel mode of cytotoxicity for cancer therapy. Preclinical work on this novel concept will be discussed.

2:50 Hsp90 Inhibitor Drug Conjugates (HDCs) with Proteasome Inhibitors: Proof-of-Concept in Preclinical Studies
Weiwen Ying, Ph.D., Synta Fellow and Vice President, Discovery Chemistry, Synta Pharmaceuticals
We have developed a small-molecule drug conjugate platform technology using these unique properties of Hsp90 proteins and Hsp90 inhibitors. Here we will discuss strategies in designing HDCs with carfilzomib and bortezomib and present preliminary biological data. Conjugates with proteasome inhibitors like bortezomib and carfilzomib have been advanced into preclinical studies.

3:20 Session Break

3:30 Targeting Intrinsic Molecular Chaperones in Ultrarare, Protein Misfolding Diseases
Thomas Kirkgaard Jensen, Ph.D., CSO, Orphazyme
Intrinsic molecular chaperones form a tightly regulated, key homeostatic system, which is induced in response to a number of physiological and pathological stresses. In this presentation, I will describe the system and the translational and developmental considerations that has gone into the development of drugs targeting it, with a particular focus on a clinical-stage class of compounds known as chaperone co-inducers.

4:00 HSP70 as a Novel Therapeutic Target for Cancer
Maureen Murphy, Ph.D., Professor and Program Leader, Molecular and Cellular Oncogenesis Program, The Wistar Institute
In this presentation we will focus on the next two most pertinent questions in the HSP70 field: the identification of key HSP70 client proteins, and the pre-clinical efficacy of these inhibitors as anti-cancer agents. We have used proteomics to identify several novel HSP70 clients. We also show that PET-16 is a potent and efficacious inhibitor of melanoma progression and metastasis.

4:30 TAS-116, a Highly Selective Inhibitor of Heat Shock Protein 90: and j, Demonstrates Potent Antitumor Activity and Minimal Ocular Toxicity in Preclinical Models
Shuichi Ohkubo, Ph.D., TAS-116 Early Development Team Chair, Taiho Pharmaceutical Co., Ltd.
Here, we will review the development of HSP90 inhibitors and discuss the issues that have hampered their clinical development. We will then present our recent discovery of TAS-116, which is an orally available, highly selective inhibitor of HSP90 and HSP90 that is currently undergoing clinical trial, and discuss the therapeutic potential of TAS-116.

5:00 Close of Conference
The microbiome R&D is an emerging area of science that is starting to prove its importance. Basic and applied biomedical research from the Human Microbiome Project and other independent studies prove that a disruption of a stable microbiome ecosystem results in dysbioses. This imbalance leads to chronic disease and health conditions. Cambridge Healthtech Institute's inaugural conference, Targeting the Microbiome, tracks the scientific and clinical research and applications being made in microbial targeted therapies for inflammation, metabolic disorders, immune disorders and other indications. There is great promise in correlating the microbiome compositions with these diseases and using the microbiome as a tool for therapeutic development.

Suggested Event Package:
- September 21 Short Course: Leveraging Data and Analytics for Drug Discovery
- September 21 Short Course: GPCR Structure-Based Drug Discovery
- September 21 Short Course: Targeting of GPCRs with Monoclonal Antibodies
- September 22-23 Conference: Targeting the Microbiome
- September 23-24 Conference: GPCR-Based Drug Discovery Part 2
- September 23 Short Course: Using Mechanistic Physiological Models in Drug Development: A Proven Quantitative Systems Pharmacology (QSP) Approach

DYNAMICS OF THE MICROBIOME ON HEALTH AND DISEASE – COMPUTATIONAL APPROACHES, ECOLOGICAL PERSPECTIVES & CLINICAL TRIALS

8:40 Computational and Synthetic Biology Approaches for Discovering Microbiome Interactions and Functions
Georg K. Gerber, M.D., Ph.D., MPH, Assistant Professor of Pathology, Harvard Medical School; Co-Director, Center for Clinical and Translation Metagenomics, Director, Computational Unit, Associate Pathologist, Department of Pathology, Brigham and Women's Hospital

I will describe: (1) a new computational approach for accurately predicting microbiota patterns, with applications to finding networks of bacteria that protect against a human enteric pathogen, and (2) a synthetic biology platform to functionally mine bacterial genomes for genes that contribute to fitness, with applications to finding genes important for colonizing the mammalian gut over time.
11:55 Re-engineering the Microbiome through Targeted Elimination of Specific Pathogens
Brian Varnum, Ph.D., Chief Development Officer, C3 Jan, Inc.
Treatment of microbiome-associated diseases is best approached with use of pathogen-specific antimicrobials. Our platform technology creates targeted antimicrobial peptides to treat and prevent microbial dysbiosis. C16G2, our lead molecule for dental caries, has demonstrated clinical efficacy, as measured by microbiome reengineering. A targeted treatment for Clostridium difficile infection is progressing towards the clinic. Updates for both programs will be presented.

12:25 pm Session Break

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

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

1:50 Chairperson’s Remarks
Willy Valdivia, CEO, Orion Integrated Biosciences, Inc.

2:00 Innovative Microbiome Therapeutics: Understanding the Ecologies of Disease Associated with CDI
David Cook, Ph.D., Executive Vice President of R&D and CSO, Seres Health
SER-109, a first-in-field oral microbiome drug, is in advanced clinical development for the prevention of recurrent Clostridium difficile infection. Clinical outcomes, effects on the gastrointestinal microbiome of patients, and lessons for drug development will be presented.

2:30 Therapy for Gastrointestinal Microbiome-Associated Diseases Requires Dietary Diversity
Mark L. Heiman, Ph.D., FTOS, Vice President, Research and CSO, MicroBiome Therapeutics
Diet is the principal regulator of the gastrointestinal (GI) microbiome, an ecosystem in our GI tract, especially the colon, comprised of trillions of bacteria (microbiota) in a solution of unabsorbed macro- and micro-nutrients. Loss of dietary diversity shifts the microbiome to unhealthy states. I will present 2 strategies to improve dietary diversity by supplementing the habitual uniform diets with GI microbiome modulators (GIMMs).

3:00 Metagenomic Approaches for Drug Discovery
Laurent Chene, Ph.D., Head, Drug Discovery Platform, Discovery, Enterome Bioscience
Using Enterome’s expertise on metagenomic, we identify commensal bacteria associated with diseases and use specific meta/genomics libraries to screen bacterial components regulating biological functions. This approach is used to identify compounds regulating cytokine secretion from IEC and is extended to identification of compounds that modulate gut hormones secretion or could improve immune anti-tumoral responses.

3:15 Role of Commensal Bacteroidetes in Defense against Clostridium difficile Infection
David Haslam, M.D., Associate Professor of Pediatrics, Cincinnati Children’s Hospital
Alteration of the commensal microbiome is the major risk factor for Clostridium difficile infection (CDI). I will describe our studies using a mouse model of CDI that identified members of the commensal microbiota that confer protection from CDI and the mechanisms involved in protection.

3:30 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Winner Announced

4:10 Engineered Probiotics: The Next Frontier for Microbiome Therapeutics
Bernard Mafroy-Camine, Ph.D., President & CEO, ViThera Pharmaceuticals
ViThera Pharmaceuticals with its collaborators at Inserm and Inra in France is a pioneer in the concept of using genetically engineered probiotic bacteria as vectors for delivery of therapeutic proteins targeting the intestinal epithelium for inflammatory bowel disease.

4:40 Micro Biome Restorative Therapy in Dogs and Cats using Ozone Therapy to Reduce the Biofilm
Margo Roman, DVM, Main St Animal Services of Hopkinton (MASH)

5:10 Interactive Breakout Discussion Groups (see website for details)

6:10 Welcome Reception in the Exhibit Hall with Poster Viewing

7:15 Close of Day

WEDNESDAY, SEPTEMBER 23

7:30 am Registration and Morning Coffee

DYNAMICS OF THE MICROBIOME ON HEALTH AND DISEASE – MICROBIOTA-TARGETED THERAPIES AND INTERVENTIONS

8:00 Chairperson’s Remarks
Jennifer Russow Wortman, Director of Bioinformatics, Seres Health, Inc.

8:10 Probiotic Skin Microbiome against S. aureus Infection
Jennifer Russo Wortman, Director of Bioinformatics, Seres Health, Inc.

8:40 The Lung Microbiome in Respiratory Diseases
James R. Brown, Ph.D., Director, Computational Biology, GlaxoSmithKline, Collegeville, PA
Increasing evidence suggests that the lungs microbiome plays an important role in chronic obstructive pulmonary disease (COPD). We will present an overview of lung microbiome clinical studies which potentially suggest novel precision medicine approaches for the future treatment of COPD patients.
Inaugural

Targeting the Microbiome

Microbial Targeted Therapies and Applications for Inflammation, Metabolic Disorders, Immune Disorders, and Other Indications

9:10 Microbiome, Microbial Metabolites, and Metabolic Diseases
Deepak K. Rajpal, Ph.D., Director, Computational Biology, GlaxoSmithKline, King of Prussia, PA
We present a case study of gut microbial modulation resulting in metabolic improvements, which are important for developing novel therapeutic intervention strategies for metabolic diseases. Additionally, we share our initial observations on utilizing the microbial metabolites for developing hypotheses for drug discovery programs.

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

10:25 Metagenome Analysis of the Microbiome to Assess Survival To Disease
Willy Valdivia, CEO, Orion Integrated Biosciences, Inc.
uBiome is a venture-backed startup working to understand the greatest enigma in medicine today - the microbiome. We help consumers, organizations, and healthcare professionals learn about the microbiome and collaborate on research to develop valuable products based on the microbiome. Citizen scientists work together on our platform to try experiments and learn about their microbiomes.

10:55 KEYNOTE PRESENTATION: Exploring the Medical Microbiome
George M. Weinstock, Ph.D., Professor and Associate Director, Jackson Laboratory for Genomic Medicine, Farmington CT
The Human Microbiome, the collection of microbes colonizing the human body, is coming under increasingly sophisticated scrutiny as genomic technologies and analytic tools advance. Microbiome research continues to find correlations between the microbial ecology of the human body and diseases, lifestyles, and other factors. The most recent projects bring together studies of the host with that of the microbes and involve large multidisciplinary datasets that present complex profiles to be mined for diagnostic and mechanistic clues to health and disease. The fruits of this research are leading to new concepts in treatment of disease.

11:25 Enjoy Lunch on Your Own

12:55 pm Plenary Keynote Program (see page 2 for details)

2:40 Refreshment Break in the Exhibit Hall with Poster Viewing

3:25 Close of Conference
This meeting convenes discovery biologists and chemists to discuss the newest strategies for kinase inhibitor design. Participants will also stay abreast of the discovery and clinical-stage kinase inhibitor programs in oncology, inflammation, and CNS-related diseases. Kinases whose medical relevance have been validated and represent new druggable targets emerging from basic research are a part of the agenda as well.

**Suggested Event Package:**
- September 21 Short Course: Cancer Metabolism: Pathways, Targets and Clinical Updates
- September 21 Short Course: Phenotypic Screening and Chemical Probe Development
- September 21 Short Course: Targeting Protein-Protein Interactions: Biophysical Approaches
- September 23 Short Course: Introduction to Targeted Covalent Inhibitors
- September 22-23 Conference: Targeting the Microbiome
- September 23-24 Conference: Kinase Inhibitor Discovery

**WEDNESDAY, SEPTEMBER 23**

**11:30 am Registration**

**12:55 pm Plenary Keynote Program (see page 2 for details)**

**2:40 Refreshment Break in the Exhibit Hall with Poster Viewing**

**EMERGING STRATEGIES FOR KINASE INHIBITOR DISCOVERY**

**3:25 Chairperson’s Opening Remarks**
Suvit Thaisrivongs, Ph.D., Head, Immunoscience Chemistry, Pfizer Worldwide Medicinal Chemistry

**3:35 ’Back to Front’ Design of Potent and Selective DDR1/2 Inhibitors**
Valerio Berdini, Ph.D., Associate Director, Computational Chemistry, Astex Pharmaceuticals

**3:45 Chairperson’s Opening Remarks**
Sarah D. Lamore, Ph.D., Discovery Safety Scientist, Drug Safety and Metabolism, AstraZeneca

**6:10 De-Convoluting Kinase Inhibitor Cardiotoxicity Using Impedance-Based Assays**
John Robinson, Ph.D., Senior Research Investigator, Medicinal Chemistry, Array Biopharma, Inc.

**6:40 Close of Day**

**THURSDAY, SEPTEMBER 24**

**7:30 am Registration**

**8:00 Interactive Breakfast Breakout Discussion Groups (see website for details)**

**CANCER KINASE INHIBITORS AND IMMUNOTHERAPY**

**8:45 Chairperson’s Remarks**
John Robinson, Ph.D., Senior Research Investigator, Medicinal Chemistry, Array Biopharma, Inc.

**8:50 KEYNOTE PRESENTATION: Clinical Experience and Preclinical Insights into Kinase Inhibitor and Immunotherapy Treatments for Cancer**
Jason J. Luke, M.D., FACP, Assistant Professor of Medicine, Melanoma and Developmental Therapeutics Clinics, University of Chicago

Immunotherapy is emerging as a treatment in many cancers however kinase directed therapies also have a role. An imperative then is to understand the optimal combination of these approaches. Some combinations will be developed solely on clinical availability however a rational paradigm would be based on synergy between treatments or identifying new “targeted” therapies that could augment the immune response. I will also go over results from a recent study in a melanoma mouse model that shows the combination of BRAF inhibitor dabrafenib and MEK inhibitor trametinib can synergize with adoptive cell therapy or anti-PD-1 therapy. The combination increases melanoma tumor antigen expression and antigen recognition by T cells, increases T cell
homing to the tumors, and preserves effector functions. Three clinical trials are ongoing to test this triple combination.

9:55 Effect of Targeted Therapies on Anti-tumor Immunity
Taha Merghoub, Ph.D., Associate Biologist, Immunology, Memorial Sloan Kettering Cancer Center

10:25 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Winner Announced

CELL-CYCLE CHECKPOINT KINASE INHIBITORS

11:10 Identification of Novel, in vivo Active Chk1 Inhibitors Using Structure-Guided Drug Design
Stephen Stokes, Principal Scientist, Chemistry, Vernalis Research

This will be the first report of the structure of V158411, a novel inhibitor of the DNA-damage cell-cycle checkpoint protein Chk1. Inhibiting Chk1 enhances the anti-tumor activity of DNA-damaging chemotherapy drugs. Fragment elaboration by structure guided design was used to identify and develop a novel series of Chk1 inhibitors culminating in the identification of V158411, a potent ATP-competitive inhibitor of the Chk1 and Chk2 kinases.

11:40 Identification and Optimization of a Novel Class of Checkpoint Kinase 1 Inhibitors
Huiyen Chen, Ph.D., Senior Scientist, Discovery Chemistry, Genentech, Inc.

Checkpoint kinase 1 (Chk1) is a Ser/Thr protein kinase and a key mediator in the DNA damage-induced checkpoint network. It is hypothesized that inhibition of Chk1 might enhance the effectiveness of existing DNA-damaging chemotherapeutic agents in the treatment of cancer. The discovery and lead optimization of a novel class of Chk1 inhibitors will be presented.

12:10 pm Selective TTK Inhibitors with Long Target Residence Time and Potent Anti-Tumor Activity
Guido Zaman, Managing Director, Head, Biology, NTRC

Triple negative breast cancers are characterized by a high degree of chromosome instability and overexpress TTK. To explore the potential of TTK as a targeted therapy, we developed a highly potent and selective TTK inhibitor. Combination with docetaxel resulted in tumor remission and increased survival in a genetic mouse model.

12:40 Kinase Profiling Strips for Targeted and Flexible Kinase Inhibitor Profiling
Hicham Zegzouti, Ph.D., Senior Research Scientist, Research and Development, Cellular and Biochemical Technologies, Promega Corporation

Kinase profiling that can be simply implemented in-house would obviate logistical inconveniences, delays and confidentiality concerns associated with outsourcing. We developed a pre-configured profiling system for 112 kinases with standardized activities. Using this system, we could quickly and easily generate selectivity profiles with any size kinase panels, and identify compound promiscuity within the kinase.

12:55 Session Break

1:00 Luncheon Presentation: HP Inkjet Technology for Improved Kinase Assay Results
Ken Ward, Ph.D., New Product Development, HP Inc.

HP inkjet technology is now being used around the world to easily and precisely dispense both small molecule and biological compounds directly into assay ready plates. Join us for presentation of and active dialog about research case studies. Learn how fellow drug discovery researchers are accelerating learning through an improved understanding of drug dose response, MOA and drug-drug synergies.

1:40 Refreshment Break in the Exhibit Hall with Poster Viewing

VALIDATED KINASE TARGETS FOR CNS AND IMMUNE DISEASES

2:15 Chairperson’s Remarks
Roland Grenningloh, Ph.D., Director Preclinical Pharmacology, TIP Immunology, EMD Serono Research & Development Institute, Inc

2:20 Targeting JAK3 with Covalent Inhibitors
Chris Burns, Ph.D., Laboratory Head, Chemical Biology Division, Walter and Eliza Hall Institute, Australia

Selective inhibition of JAK3 has promise as treatment for auto-immune and inflammatory diseases because JAK3 expression is limited to cells of the immune system. Other members of the JAK family are widely expressed. Discussion on the optimization of JAK3-targeted agents has been embargoed until this year due to a multi-year collaboration with Novartis. The optimized compounds represent the most selective and potent JAK3 inhibitors reported.

2:50 JAK-1 Selective Clinical Candidate for the Treatment of Autoimmune Diseases
Suzi Thaisrivongs, Ph.D., Head, Immunoscience Chemistry, Pfizer Worldwide Medicinal Chemistry

The presentation will describe the discovery program of our JAK1 selective inhibitors and the identification of our clinical candidate, currently in Phase 2 clinical development. The discussion will cover our structure-based medicinal chemistry design and our JAK platform expertise from Tofacitinib clinical data to advance our discovery research program.

3:20 Session Break

3:30 Characterization of Novel PI3Kdelta Inhibitors as Potential Therapeutics for Systemic Lupus Erythematosus
Roland Grenningloh, Ph.D., Director Preclinical Pharmacology, TIP Immunology, EMD Serono Research & Development Institute, Inc

We identified selective PI3Kδ inhibitors that blocked B-, T-, and plasmacytoid dendritic cell activities and were efficacious in an IFNα-accelerated mouse SLE model. Efficacy correlated with reduced immune complex deposition, inflammation, fibrosis and tissue damage in the kidney. Using a pharmacodynamics/pharmacokinetic/efficacy model we established that a sustained PI3Kδ inhibition of 50% is sufficient to achieve full efficacy in this disease model.

4:00 Discovery and Preclinical Profiling of LRRK2 Kinase Inhibitors for the Treatment of Parkinson’s Disease
Paul Galatsis, Ph.D., Senior Principal Scientist, Worldwide Medicinal Chemistry, Pfizer

We will communicate our strategy for designing brain penetrant kinase inhibitors and share medicinal chemistry insights into targeting the key cause of familial Parkinson’s disease, LRRK2. We will provide examples of compounds that have in vivo activity at less than 1 mg/kg oral dosing.

4:30 ARRY382: Exploring the Role of CSF1R in Immuno-Oncology
John Robinson, Ph.D., Senior Research Investigator, Medicinal Chemistry, Array Biopharma, Inc.

Colony Stimulating Factor (CSF) 1 drives macrophage-mediated immune suppression in the tumor microenvironment. Therefore CSF1 inhibitors have the potential to augment immune responses when combined with established tumor immuno-therapeutics such as anti-PD-1 and anti-CTLA4. We present the design, discovery and phase 1 results of ARRY382, a potent, selective CSF1R kinase inhibitor.

5:00 Close of Conference
Discovering or designing new therapeutic agents that modulate G Protein-Coupled Receptors (GPCRs) in precise ways remains a challenge. However, new knowledge about receptor structure and ways to more precisely control their signaling via determining which G protein or other receptor-associated protein they couple to (biased signaling) is enabling progress. Part 1 of CHI's back-to-back GPCR meetings will focus on structural aspects of GPCR signalling and new technologies or approaches for discovering and designing GPCR-targeted compounds.

### TUESDAY, SEPTEMBER 22

**7:00 am Registration and Morning Coffee**

**8:00 Chairperson's Opening Remarks**

*Thomas P. Sakmar, M.D.*, Professor, Chemical Biology and Signal Transduction, The Rockefeller University

**8:10 Structural Biology of the Lipid Receptors**

*Mike Hanson, Ph.D.*, Director, GPCR Consortium

The lipid binding receptors have been widely studied using biochemical methods. The structure of the S1P1 receptor has been used to understand the binding mode of compounds for the treatment of relapsing multiple sclerosis. Recently, structural analysis of the LPA1 receptor has revealed alternate binding modes for lipid ligands that may be more permissive for binding a wide array of endogenous lipid ligands.

**8:40 Computational Methods to Identify Allosteric Binding Sites for Design of Biased Ligands for GPCRs**

*Nagarajan Vadehi, Ph.D.*, Professor, Immunology, City of Hope Beckman Research Institute

We have developed a computational method to identify residues that modulate the the allosteric communication from the extra-cellular to the intra-cellular domain of the receptor. This is useful for predicting residues that govern the biased signaling in GPCRs. I will demonstrate how this method can be used to predict allosteric binding sites that can be used to design biased ligands.

**9:10 Chemokines and their Receptors: Insights from Modeling and Crystallography**

*Inna Kufareva, Ph.D.*, Project Scientist, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego

Chemokines control cell migration in the context of immunity, inflammation, and development, by virtue of binding and activating 7TM chemokine receptors on the cell surface. The structural basis of this interaction remained elusive for many years, until we first accurately modeled and then solved experimentally a structure of the CXCR4:chemokine complex. Structural insights into recognition specificity, affinity and pharmacology of natural and engineered chemokine ligands of CXCR4 and other chemokine receptors will be presented.

### Suggested Event Package:

- September 21 Short Course: GPCR Structure-Based Drug Discovery
- September 21 Short Course: Targeting of GPCRs with Monoclonal Antibodies
- September 22-23 Conference GPCR-Based Drug Discovery, Part 1
- September 23-24 Conference GPCR-Based Drug Discovery, Part 2
- September 23 Short Course: Introduction to Allosteric Modulators and Biased Ligands of GPCRs
1:50 Chairperson’s Remarks
Brian J. Arey, Ph.D., Senior Principle Scientist, Cardiovascular Drug Discovery, Bristol-Myers Squibb Co.

1:55 KEYNOTE: New Structural and Biological Insights to Functional Selectivity
Bryan Roth, Ph.D., Professor, Department of Pharmacology, University of North Carolina Medical School

2:30 GPCR Kinetic and Conformational Dynamics
Thomas P. Sakmar, M.D., Professor, Chemical Biology and Signal Transduction, The Rockefeller University

3:00 All Functional Assays in One Cell Line for Studying GPCR Signaling Bias
Lisa Minor, Ph.D., Business Development Consultant, Multipan, Inc.

3:30 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Winner Announced

4:10 Biased Signaling as a Common Theme in Receptor Signaling
Brian J. Arey, Ph.D., Senior Principle Scientist, Cardiovascular Drug Discovery, Bristol-Myers Squibb Co.

4:40 Human Cannabinoid Receptor CB2: Expression, Functional and Structural Studies
Alexei Yeliseev, Ph.D., Staff Scientist, LMBB, NIH/NIAAA

5:10 Interactive Breakout Discussion Groups (see website for details)
10:55 Targeting Multiple GPCRs Simultaneously for CNS Disorders
Hugo Geerts, Ph.D., CSO, Computational Neuropharmacology, In Silico Biosciences
We have developed a Quantitative Systems Pharmacology platform that captures biophysically accurate representations of human firing networks and is calibrated with human imaging and clinical data. Reverse-engineering such platform offers the opportunity to identify a lean pharmacological profile of GPCRs that would support a rationally designed multi-target medicinal chemistry program. We will show an example in the field of schizophrenia.

11:25 Enjoy Lunch on Your Own
12:55 pm Plenary Keynote Program (see page 2 for details)
2:40 Refreshment Break in the Exhibit Hall with Poster Viewing
3:00 Presentation to be Announced

3:25 Close of Conference
Not only do GPCRs control multiple signaling pathways, but GPCRs have their own complicated kinetic, cellular location and signaling life cycle, which varies from one receptor type to another and its cellular environment. Part 2 of our back-to-back GPCR meetings focuses on recently tractable pharmacologic complexities in the field, receptor-associated proteins that are emerging as drug targets and case-studies of lead compounds, especially allosteric modulators and biased ligands, that are progressing in development.

Suggested Event Package:
- September 21 Short Course: GPCR Structure-Based Drug Discovery
- September 21 Short Course: Targeting GPCRs with Monoclonal Antibodies
- September 22-23 Conference GPCR-Based Drug Discovery, Part 1
- September 23-24 Conference GPCR-Based Drug Discovery, Part 2
- September 23 Short Course: Introduction to Allosteric Modulators and Biased Ligands of GPCRs

WEDNESDAY, SEPTEMBER 23

11:30 am Registration
12:55 pm Plenary Keynote Program (see page 2 for details)
2:40 Refreshment Break in the Exhibit Hall with Poster Viewing

GPCR MODIFICATIONS AND ASSOCIATED PROTEINS: NEW DISCOVERY TARGETS

3:25 Chairperson’s Opening Remarks
Paul Insel, Ph.D., Professor, Pharmacology & Medicine, University of California, San Diego

3:35 Exploring Protease-Activated Receptor Biased Signaling Inside and Outside of the Cell
JoAnn Trejo, Ph.D., Professor, Pharmacology, University of California, San Diego
PARs are a family of GPCRs that are uniquely activated by proteolysis. We have discovered that PAR1 exhibits biased signaling regulated through post-translational modifications and compartmentalization in caveolae. We are currently examining the molecular mechanisms by which PAR1 N-linked glycosylation controls G protein coupling specificity and how caveola distribution affects endothelial PAR1 signaling induced by thrombin versus activated protein C.

4:05 Crystal Structures of Peptide-Bound RAMP-GPCR Complexes
Augen A. Pioszak, Ph.D., Assistant Professor, Department of Biochemistry and Molecular Biology, University of Oklahoma Health Sciences Center
Receptor activity-modifying proteins (RAMPs) are membrane proteins that associate with several GPCRs to modulate their pharmacology. RAMPs of class B GPCR calcitonin receptor-like receptor (CLR) are thought to determine the peptide ligand binding preferences of the receptor. I present two high-resolution crystal structures of peptide-bound CLR-RAMP extracellular domain complexes that reveal how peptides selectively bind and may inform drug development targeting these complexes.

4:35 Selected Poster Presentations:
- Allosteric Modulators of the CB1 Receptor: Defining Structure-Activity Relationships
  Leepakshi Khurana, Ph.D. candidate, Laboratory of Debra Kendall, University of Connecticut
- Small Molecule Modulators of the Adrenomedullin 1 Receptor
  Lydia F. Liew, Ph.D., Research Fellow, University of Auckland
- Biased Ligand Quantification: From Theory to High Throughput Screening
  David Wimpenny, Ph.D., Principal Scientist, Pfizer World Wide R&D

5:05 Refreshment Break in the Exhibit Hall with Poster Viewing
5:40 Structure and Function of the Hypertension Variant A486V of G Protein-Coupled Receptor Kinase 4
Kevin Lumb, Ph.D., Director, Discovery Technologies, Janssen R&D LLC
G protein-coupled receptor (GPCR) kinases (GRK) bind to and phosphorylate GPCRs, initiating the process of GPCR desensitization and internalization. GRK4 is implicated in the regulation of blood pressure, and GRK4 polymorphisms are associated with hypertension. Here we present work performed at Merck on the X-ray structure and autophosphorylation of the human GRK4 hypertension variant A486V.

6:10 Heterologous Desensitization of GPCR-RTK Transactivation
Michael Beazely, Ph.D., Assistant Professor, School of Pharmacy, University of Waterloo, Canada
A typical GPCR-initiated receptor tyrosine kinase (RTK) transactivation pathway results in a transient activation and phosphorylation of the RTK and downstream effector. We have recently demonstrated that after this transient transactivation, there is ~ 3 hour blackout period where the RTK can not be “re-transactivated” either by repeated exposure to the same GPCR agonist, or to different GPCR agonists.

6:40 Close of Day

THURSDAY, SEPTEMBER 24

7:30 am Registration
8:00 Interactive Breakfast Breakout Discussion Groups (see website for details)

PHARMACOLOGICAL COMPLEXITIES

8:45 Chairperson’s Remarks
Andrew Alt, Ph.D., Director, Cell-Based Screening Technologies, Bristol-Myers Squibb

8:50 KEYNOTE: The Activated Conformation of GPCRs and the Mechanism of Activation of G Proteins
Roger K. Sunahara, Ph.D., Professor, Department of Pharmacology, University of California San Diego
G protein-coupled receptors (GPCRs) represent an important conduit through which cells detect environmental stimuli and communicate with one another. Extracellular signals pass through these 7 TM receptors through a dynamic process involving conformational changes in the receptor structure. These changes in
turn activate an intracellular transduction cascade through engaging a compliment of intracellular proteins. Here we characterize the activation mechanism of a prototypic GPCR, the b2-adrenergic receptor, and its interaction and activation of its cognate signaling partner, the heterotrimeric G protein, Gs. We utilized biochemical, biophysical and computational approaches to address this very important mechanism, one that is likely shared among the superfamily of GPCRs.

9:25 GPCR Trafficking and Endosomal Signaling
Adriano Marchese, Ph.D., Associate Professor, Pharmacology, Stritch School of Medicine, Loyola University Chicago
Membrane trafficking plays an important role in governing the magnitude and duration of GPCR signaling. It is now emerging that targeting novel aspects of GPCR trafficking could impact GPCR signaling and cellular responsiveness. This talk will focus on recent advances and highlight how targeting novel aspects of GPCR trafficking could be a useful strategy to treat diseases involving GPCRs.

9:55 Opioid Receptor Trafficking, Signaling and Physiology
Manoj Puthenveedu, Ph.D., Assistant Professor, Biological Sciences and The Center for the Neuroal Basis of Cognition, Carnegie Mellon University
The use of opioids in pain management has been limited by adverse effects. Efforts to identify better opioids with fewer limitations have had little success. I will discuss our work on the mechanisms of opioid receptor trafficking, which could potentially be used as a convergent strategy to regulate opioid responses by actively manipulating the localization of opioid receptors.

10:25 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Winner Announced

11:10 Receptor Binding Kinetics in GPCR Drug Discovery: The Good, the Bad, and the Confusing
Brian J. Murphy, Ph.D., Senior Principal Scientist, Fibrosis Drug Discovery, Bristol-Myers Squibb
Drug residence time is being increasingly appreciated as an important factor in GPCR compound optimization. Lack of efficacy of high affinity compounds can sometimes be explained by less than optimal receptor off-rates. Several low throughput methods used to determine kinetic parameters exist, but one can obtain different kinetic parameter values depending on which methodology is employed. Which is the correct off-rate to use for optimization?

11:40 Targeting Glutamate Receptors for Stress-Related Disorders
Sylvain Celenaire, Ph.D., Co-Founder and CEO, Pragma Therapeutics

12:00 pm Sponsored Presentation (Opportunity Available)

12:40 Session Break

12:50 Luncheon Presentation (Sponsorship Opportunity Available) or Lunch on Your Own

1:30 Refreshment Break in the Exhibit Hall with Poster Viewing

2:00 Allenic Modulators and Biased Ligands

2:20 Identification of Orthosteric and Allosteric Residues Important for FFAR1 Binding and Function
Gayathri Swaminath, Ph.D., Principal Scientist, Metabolic Disorders, Amgen
Fatty acids are considered orthosteric ligands for free fatty acid receptor (FFA1) receptor. Several FFA1 receptor mutants were generated to identify the potential sites that may allosterically regulate the orthosteric ligand’s function. Mutational analysis revealed previously unidentified sites that may allosterically regulate orthosteric ligand function including residues that are important for the interactions between orthosteric and allosteric binding sites.

2:50 Allosteric Ligands of Metabotropic Glutamate Receptor 5 Have Biased Agonism and Cooperativity
Karen Gregory, Ph.D., Laboratory Head, Family C GPCR Division, Department of Drug Discovery Biology, (former post-doctoral fellow, Arthur Christopolous Lab), Monash University, Australia
Drugs targeting metabotropic glutamate receptor 5 (mGlU5): a class C GPCR have promising preclinical profiles but potential adverse effects. On-target adverse effects of certain allosteric modulators may be due to specific ligand scaffolds which result in modulation of distinct mGlU5 signaling pathways and receptor regulation processes. Establishing a “biased modulation fingerprint” can provide a framework for future novel biased allosteric modulator discovery for mGlU5.

3:20 Session Break

3:30 Identifying Bias in CCR1 Antagonists
Annette Gilchrist, Ph.D., Assistant Professor, Pharmaceutical Sciences, Midwestern University
Six compounds targeting CCR1 have undergone clinical testing for several different diseases (multiple sclerosis, rheumatoid arthritis, and chronic obstructive pulmonary disease). There has been some speculation that CCR1 may also play a role in multiple myeloma and pain modulation. We compared several allosteric inhibitors for their ability to alter binding of 125I-CCL3, beta-arrestin translocation, surface expression of CCR1, and chemotaxis.

4:00 Discovery of a Biased Incretin Receptor Agonist
Peter DiStefano, Ph.D., CSO, Zebra Biologics
We combined autocrine expression of very large peptide libraries to receptors in a cellular context to identify unique agonists to the GLP-1 receptor. We discovered rare, potent agonist peptides with amino acid sequences distinct from those of mammalian or reptilian GLP-1 that signal via G-proteins but not b-arrestin. These peptides are superior to Ex4 in glucose and insulin homeostasis parameters

4:30 Development and Characterization of Dopamine D3 Receptor Selective Compounds
Robert Luedtke, Ph.D., Professor, Pharmacology and Neuroscience, University North Texas Health Science Center
We have explored the use of dopamine D2-like (D2 and D3) receptor subtype selective ligands as therapeutic agents for the treatment of neurological disorders and as in vivo PET imaging agents. We incorporate information provided by in vitro screens for D2-like
TUESDAY, SEPTEMBER 22

7:00 am Registration and Morning Coffee
8:00 Chairperson's Opening Remarks
Matt Holsti, Ph.D., Principal Scientist, Global BioTX Technologies, Pfizer

8:10 KEYNOTE PRESENTATION: Selection of Membrane Protein Targets: GPCRs as a Paradigm
Paul Insel, M.D., Ph.D., Vice-Chair and Distinguished Professor, Pharmacology; University of California, San Diego

GPCRs are the largest superfamily of membrane signaling receptors and the largest group of targets of approved drugs, but are the optimal GPCRs being targeted? Using a GPCRomic approach to define the GPCRs expressed by individual cell types from healthy and diseased subjects, we have discovered “novel” GPCRs, including potential therapeutic targets for diseases that are unmet medical needs.

IMMUNIZATION AND DISPLAY STRATEGIES FOR MEMBRANE PROTEINS

8:40 Computational Design of Epitope Scaffolds to Induce Antibodies against Membrane Proximal Epitopes
William R. Schief, Ph.D., Professor, Immunology & Microbial Science, Scripps Research Institute; Director, Vaccine Design, International AIDS Vaccine Initiative

Our HIV vaccine design work involves immunogen design projects aiming to induce antibodies against membrane proximal structural epitopes – with challenges including engineering membrane proteins, optimizing epitope conformation and designing antigens to select for specific H-CDR3 loops. This talk presents lessons that may assist induction of antibodies against other membrane targets.

9:10 Cell-Free Expression of G-Protein Coupled Receptors: New Pipelines for Challenging Targets
Frank Bernhard, Ph.D., Group Leader, Institute of Biophysical Chemistry, Goethe University, Germany

The unique variability of cell-free expression reactions allows systematic optimization screens to improve the quality of synthesized GPCRs. Preparative scale amounts of ligand binding active receptor can thus be obtained and structural approaches come into focus. Strategies for GPCR quality optimization will be exemplified and characteristic biochemical properties of the samples are presented.

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

10:25 Immunization Strategies for Antibody Generation against Multi-Spanning Proteins
Jane Seagal, Ph.D., Senior Scientist, AbbVie Bioresearch Center

Hybridoma generation against multi-spanning proteins is challenging. Expression levels of proteins on the cell surface may not be sufficiently high, and peptides corresponding to extracellular loops do not have natural conformation. We utilized cDNA immunizations to elicit immune response against multi-spanning proteins, leading to successful generation of hybridomas producing functional mAbs.

10:55 Identification of Biased Antagonists by Screening Single Domain Antibodies against GPCRs in Lipoparticles
Mick Foley, Ph.D., CSO, AdAlta, Australia

i-bodies are human single domains with a long CDR3 that enables access to proteins such as GPCRs. High affinity i-bodies specific for CXCR4 were obtained by screening on lipoparticles and each of the i-bodies have different functional profiles. These blocked SDF-1-induced leukocyte recruitment in a mouse model of inflammation and did not mobilize stem cells from bone marrow.

11:25 VelocImmune Mice for Generation of Antibodies against Complex Membrane Protein Targets
Nicole Alessandri-Haber, Ph.D., Staff Scientist, Pain Therapeutics, Regeneron Pharmaceuticals

The performance of the VelocImmune® platform is reflected in the pipeline of 14 fully-human antibodies (Abs) we have in clinical development and the 50 other Abs we have in preclinical development. VelocImmune® mice can generate antibodies with different binding characteristics and superior specificity against highly conserved and challenging targets. One example is the generation of specific functional mAbs against human ACCN2, an H+ gated ion channel implicated in pain transduction.

11:55 Discovery of MAbs against Difficult GPCRs, Ion Channels, and Transporters
Joseph Rucker, Ph.D., Vice President, Research and Development, Integral Molecular, Inc.

To enable the isolation, characterization, and engineering of MAbs against challenging membrane protein targets, Integral Molecular has developed the MPS Discovery Engine™ platform, encompassing lipoparticles for concentrating native membrane proteins and shotgun mutagenesis for membrane protein engineering and epitope mapping. Using MPS, we have generated functional MAbs against the ion channel P2X3 (neuropathic pain), GLUT transporter (diabetes), and CXCR4 (cancer), and have ongoing discovery programs against additional GPCR, ion channel, and transporter targets.

12:25 pm Towards Native and Stable GPCRs for Conformational Antibody Development. Case Study with Native and Functional Adenosine Receptor A2A
Anass Jawhari, Ph.D., CSO, CALIXAR

Adenosine receptor A2A plays an essential role in the central nervous system. Thanks to CALIXAR patented technology based on new chemistry approach to safely isolate membrane proteins, functional A2A2 was solubilized and purified without any single mutation, truncation or fusion for antibody development purposes and crystallization.

12:40 Session Break
12:45 Luncheon Presentation (Sponsorship Opportunity Available)

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

DISCOVERY STRATEGIES FOR FUNCTIONAL ANTIBODIES AGAINST MEMBRANE PROTEIN TARGETS

1:50 Chairperson’s Remarks
Barbara Swanson, Ph.D., Director, Research, Sorrento Therapeutics, Inc.
2:00 Selecting Antibodies Using a Combined in vitro and in vivo Approach
Andrew M. Bradbury, Ph.D., MB, BS, Staff Scientist, Biosciences, Los Alamos National Laboratory
The identification of antibodies suitable for in vivo use can be challenging. In this talk, we will present new data on the selection of antibodies against previously identified membrane protein targets using a combined in vitro/in vivo approach.

2:30 Protein Knockout Mice: A Novel in vivo Validation Approach for Membrane Targets
Stefan Dübel, Ph.D., Director, Institute of Biochemistry, Biotechnology and Bioinformatics, Technical University of Braunschweig, Germany
We present a novel drug discovery method which is applicable to all membrane and secretory proteins. We demonstrate that endoplasmic reticulum retained antibodies ("intrabodies") can induce a protein knockdown phenotype in transgenic mice. A single cloning step is needed from phage display selection of human antibodies to a target induction of the mouse knockdown phenotype for this target.

3:00 Identifying Antibodies against Cell-Surface Receptors Using Live Cells within an Emulsion
Michael Weiner, Ph.D., CSO, AxioMx, Inc.
Our goal is to produce a fully recombinant IgG antibody within 3-4 weeks of receiving a suitable antigen. We will demonstrate the use of emulsion screening to identify affinity binders from a > 10^10 library against protein receptors displayed in situ on a living cell surface. Emulsion panning generates a greater number of unique clones by effectively eliminating the clonal expansion seen with traditional panning methods that use multiple rounds of enrichment.

3:30 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Winner Announced

4:10 Engineering Conformation Selective Antibodies to Membrane Protein Complexes
Marcin Paduch, Ph.D., Technical Director, Synthetic Antibody & Crystallography Core Facility, Department of Biochemistry and Molecular Biology, Recombinant Antibody Network, The University of Chicago
To address the challenges of membrane protein complexes and their conformational states, we have developed a suite of high-throughput technologies exploiting multiple antigen presentation formats, novel phage display libraries and improved biopanning techniques networking them together on a modern automation system. This integrated pipeline generated antibodies to nuclear pore complex and several G3-tail anchored protein complexes.

4:40 Going Native: Direct High-Throughput Screening of Soluble, Secreted mAbs against Intact Target Cells
Karl Griswold, Ph.D., Associate Professor, Thayer School of Engineering, Dartmouth University
We describe an ultra-high throughput screening platform that enables identification and isolation of soluble, secreted, monoclonal antibodies that bind membrane proteins in their native environment: on the cell surface. Using gel microplate encapsulation combined with high-speed flow cytometry, we demonstrate recovery of rare clones producing IgG binders to targets such as EGFR.

5:10 Interactive Breakout Discussion Groups (see website for details)
6:10 Welcome Reception in the Exhibit Hall with Poster Viewing
7:15 Close of Day
Part 2, Structural Analysis, Characterization and Development, explores structural, biochemical and biophysical studies used to understand the behavior of membrane protein targets in native and inhibited or activated states – and then considers issues related to the preclinical and clinical development of antibodies and other biologics as drug products against these challenging targets.

**Suggested Event Package:**
- September 21 Short Course: Targeting of GPCRs with Monoclonal Antibodies
- September 21-22 Conference: GPCR Structure-Based Drug Discovery
- September 22-23 Conference: Antibodies Against Membrane Protein Targets Part 1
- September 23-24 Conference: Antibodies Against Membrane Protein Targets Part 2
- September 23 Short Course: Introduction to Allosteric Modulators and Biased Ligands of GPCRs

**WEDNESDAY, SEPTEMBER 23**

11:30 am Registration
12:55 pm Plenary Keynote Program (see page 2 for details)
2:40 Refreshment Break in the Exhibit Hall with Poster Viewing
3:25 Chairperson’s Opening Remarks

**3:35 KEYNOTE PRESENTATION: Expanding the Genetic Code to Probe Membrane Protein Drug Targets**
Thomas P. Sakmar, M.D., Richard M. & Isabelle P. Furhaim Professor, Laboratory of Chemical Biology & Signal Transduction, The Rockefeller University
Novel methods are now available to probe GPCRs, channels and other difficult-to-express membrane proteins. A variety of experimental approaches will be presented, including targeted photocrosslinking to map antibody epitopes, and bioorthogonal labeling reactions to introduce site-specific fluorophores and monoclonal antibody epitopes. These strategies can be used in combination with traditional approaches to enhance drug discovery strategies.

**STRUCTURAL BIOLOGY STUDIES TO SUPPORT DEVELOPMENT OF ANTIBODIES AGAINST MEMBRANE PROTEIN TARGETS**

4:05 Sodium Channel Structures in Complex with Drugs
Bonnie Ann Wallace, Ph.D., Professor, Institute of Structural and Molecular Biology, Birkbeck College, United Kingdom
Mutations in human sodium channels represent key targets for pharmaceutical drugs. We have shown that drugs that block human sodium channels also block the NavMs sodium channel from Magnetococcus marinus. Using crystallography and computational methods we have determined the locations of channel blockers within the NavMs channel cavity and validated these sites in designed mutants.

4:35 PComputational Approaches to Antibody Design: Improvements to the Predictions of Structure, Stability, and Affinity
David A. Pearlman, Ph.D., Senior Principal Scientist & Product Manager, Schrödinger
We discuss computational advances demonstrating significant promise both for improved prediction of antibody structure from sequence, and for the ability to predict the changes in stability and affinity resulting from residue mutations. The Prime approach to de novo loop prediction is an appreciable improvement over previous methods for CDR loop prediction, while substantive improvements to free energy calculations (FEP) allow us to calculate the effects of residue mutations on stability and affinity with high precision.

5:05 Refreshment Break in the Exhibit Hall with Poster Viewing
5:40 Structure of a Human Ion Channel
Christopher Koth, Ph.D., Senior Scientist, Structural Biology, Genentech
6:10 Use of Antibody Fragments to Solve GPCR Structures
Andrew Kruse, Ph.D., Assistant Professor, Biological Chemistry and Molecular Pharmacology, Harvard Medical School
Antibody fragments including Fabs and nanobodies have served as critical enabling tools in studies of GPCR structure, function, and dynamics. I will present an overview of key results using antibody fragments, as well as recent methodological advances and results using antibody fragments to study drug-like allosteric modulator function in the muscarinic acetylcholine receptor family.

6:40 Close of Day

**THURSDAY, SEPTEMBER 24**

7:30 am Registration

**CHARACTERIZATION OF MEMBRANE PROTEIN TARGETS**

8:00 Interactive Breakfast Breakout Discussion Groups (see website for details)
8:45 Chairperson’s Remarks
Benjamin Doranz, Ph.D., President & CSO, Integral Molecular Inc.

8:55 Back Scattering Interferometry for Characterization of Membrane Protein Targets
Denise M. O’Hara, Ph.D., Associate Research Fellow, Pharmacokinetics, Dynamics and Metabolism, Pfizer Inc.
Molecular interactions govern biology, human health, disease and pharmacological efficacy of therapeutics. Clinically relevant binding measurements are especially problematic since target proteins reside in complex physiological environments, such as biological fluids or tissue microenvironments as soluble and/or membrane-bound forms. This talk will describe how Back-scattering Interferometry (BSI), a label-free, low volume, mix-and-read technology has been used to solve measuring physiologically-relevant affinity used to predict clinical dose and efficacy.

9:25 Characterization Studies for ShK Toxin Peptide against Kv1.3
Christine Beeton, Ph.D., Associate Professor, Molecular Physiology and Biophysics, Baylor College of Medicine
CCRT- effector memory T lymphocytes are involved in chronic inflammatory diseases and upregulate Kv1.3 channels upon activation. We have used ShK, a peptide isolated from a sea anemone venom, to design dalazatide (formerly ShK-186) as a selective and potent Kv1.3 blocker.

9:55 Binding Analysis of Membrane Protein Targets with Label-Free Analytical Biosensor
Wei Wang, Ph.D., Senior Scientist, Therapeutic Discovery, Amgen
Using the emerging label-free analytical biosensor system MASS-1, we have been developing binding assays to characterize the binding activity of membrane protein targets. We aim to establish methods that can utilize membrane proteins prepared in various ways and maintain the protein activity. These assays will be applied to validate membrane protein targets and identify therapeutics for drug discovery.

10:25 Coffee Break in the Exhibit Hall with Poster Viewing and Poster Winner Announced

11:10 Strategies for Optimizing and Characterizing MAbs against Multi-Spanning Membrane Protein Targets
Benjamin Doranz, Ph.D., President & CSO, Integral Molecular Inc.
Integral Molecular has developed specialized strategies to systematically optimize and characterize MAbs against structurally complex membrane proteins, addressing the specific challenges posed by this class of targets. These strategies encompass antibody engineering, antibody characterization, and shotgun mutagenesis. MAAb optimization and characterization case studies will be discussed.

11:40 Potent and Efficacious Inhibition of CXCR2 Signaling by Biparatopic Nanobodies Combining Two Distinct Modes of Action
Michelle Bradley, Ph.D., former Investigator, Molecular Pharmacology, Respiratory Disease Area, Novartis Institutes for Biomedical Research (NIBIR), United Kingdom
Chemokine receptors are key modulators in inflammatory diseases. We describe the identification and pharmacological characterization of nanobodies selectively blocking CXCR2. Two classes of selective monovalent nanobodies were identified, and detailed epitope mapping showed that these bind to distinct, non-overlapping epitopes on the CXCR2 receptor. Biparatopic nanobodies were generated by combining nanobodies from these two classes.

12:10 pm Diverse Antibody Panels to GPCRs and Ion Channels Generated through Single B Cell Cloning from Avian Immune Repertoires
Bill Hariman, Ph.D., MBA, CSO, Crystal Bioscience
Chickens are known to generate antibodies to epitopes on therapeutic targets that are highly conserved amongst mammals. These antibodies often demonstrate reactivity across multiple species, and are preferred when rodent or primate models of disease are anticipated. Using alternative immunization strategies we can enhance the prevalence of such clones, and by evaluating antibody profiles through a multi-parameter GEM screen of primary B cells, we can efficiently recover antibodies with desired biological activity and/or multispecies cross-reactivity.

12:40 Session Break

12:50 Strategies for Discovery of Therapeutic Antibodies to Difficult Membrane Proteins
John Kenney, Ph.D., Founder and President, Antibody Solutions
Some membrane protein targets, including proteins with high homology, G-protein-coupled receptors (GPCRs), Ion Channels, and Multicomponent Receptor complexes present unique challenges in the generation of specific, high-affinity, and functional antibodies. Each target requires a tailored approach based upon the nature of the target and the desired characteristics of the antibody. Strategies for antigen design, antibody generation, and screening of antibodies to difficult membrane proteins, and results obtained will be presented.

1:30 Refreshment Break in the Exhibit Hall with Poster Viewing
EXPLORING NEW TARGETS & PATHWAYS

10:25 Identifying Regulatory Interactions Among Genes Linked to Alzheimer’s Disease
Michael Olimann, Ph.D., Principal Scientist, Genome Analysis Unit, Amgen, Inc.

10:55 High-Throughput RNAi Screening for Immune Modulatory Ligands on Tumor Cells
Philipp Beckhove. Ph.D., Head, Translational Immunology Division, German Cancer Research Center Heidelberg; Director, Regensburg Center for Interventional Immunology, University of Regensburg

Immune checkpoint inhibition has lately revolutionized cancer therapy. We have established the first high-throughput screening approach to characterize the entities of immune modulatory molecules on different tumors - the immune modulatome of cancer. We identified many novel candidates derived from gene families that were hitherto not reported to play a role in the immune system and will report functional validation data for some of them.

11:25 Functional Genomic Screening to Accelerate the Discovery of Combination Therapies
Roderick Beijersbergen, Ph.D., Group Leader, Netherlands Cancer Institute and Head, NKI Robotics and Screening Center

Single drug cancer therapies meet with limited success due to drug resistance from reactivation or activation of redundant pathways. Due to the complexity of the targeted signaling networks in addition to tissue-specific characteristics, the prediction of the best combination therapy remains a major challenge. We apply large scale functional genomic screening in clinically relevant models to identify such interactions with the goal to accelerate the discovery of clinically active combinations.

11:55 High Content RNAi Screening with Persomics: Discover More Faster With Turnkey Printed Libraries
Neil Emans, Ph.D., CEO, Persomics USA, Inc.

RNA interference is routinely used in High Content and Phenotypic screening. However, set-up and operational costs are beyond the reach of individual labs and limit core facilities. Persomics technology miniaturizes, accelerates and de-industrializes RNAi screening. Preprinted libraries integrate with conventional HCS platforms and image analysis to enable off-the-shelf screening in individual labs and now allow core facilities to do more.

12:10 pm An In vivo Pooled RNAi Screen Reveals New Drivers of Breast Cancer Metastasis
Simon Knott, Ph.D., Research Investigator, Cold Spring Harbor Laboratory

Recently, we developed a mouse model of breast cancer heterogeneity that identified cells with differential capacities for performing each step of the metastatic cascade. Here, we found that genes more highly expressed in cells capable extravasation and colonization were clinically relevant in terms of their elevated expression in patients with metastatic relapse. By performing an in vivo pooled shRNA screen, focused on these targets, we were able to extract a subset of 28 genes that were further enriched for clinical significance, with Asns and Icam1 having the most relevance based on patient data. By manipulating its expression levels using next generation RNAi reagents, we were able to show that Asns and its human orthologue ASNS influence invasion and metastases formation. Intracellular Adhesion Molecule 1 (Icam1), also a member of the 28 gene subset, was found to be over-expressed in lung metastases from Asns silenced cells. Silencing of Asns and Icam1 in combination, using a dual shRNA vector strategy, resulted in an even greater reduction in metastases than silencing either gene alone. Icam1 is a cell surface...
protein and ASNS is considered to be druggable. Thus, using our new shERWOOD UltramiR shRNA reagents, we have identified two targetable proteins that are likely to provide therapeutic benefit for patients with metastatic breast cancer.

12:25 Improving in vivo Delivery of RNAi and MessengerRNA to Enable and Accelerate Development of New Therapies
Nektaria Andronikou, Staff Scientist, Cell Biology, Thermo Fisher Scientific
There is now a great deal of interest in using siRNA and MessengerRNA in vivo to better understand diseases but also to be used as therapeutic molecules. In September 2010, we launched Invivofectamine® 2.0, the first in vivo delivery reagent commercially available, allowing researchers to utilize siRNA in vivo. Over the past few years, we have identified a new delivery reagent, Invivofectamine® 3.0, that is at least 10 times more potent than Invivofectamine 2.0, with an IC50 of 0.125 mg/kg compared to 1.2mg/kg. This fold improvement was the result of identifying new proprietary lipids, developing an improved formulation design by mixture DOE and incorporating an enhanced production method to control the size of the particle. This new formulation dramatically cuts down the cost of an in vivo experiment, but also allows for a simpler and easier to use protocol where a single dilution step replaces a 2-hour dialysis step. Recently, we’ve also demonstrated that Invivofectamine 3.0 can successfully deliver mRNA to the liver and to other areas of the body that are of therapeutic interest, such as spleen, muscle and xenograft tumors. In addition, we are also continuing to identify new formulations that are able to deliver mRNA to the lung. In this study, we will present the discovery and development of Invivofectamine 3.0 as well as highlight the new applications utilizing different payloads and organs.

12:40 Session Break

12:45 Luncheon Presentation: The Future of RNAi Screening: Complementary Technologies and Advancements
Ryan Raver, Ph.D., Product Manager, Short hairpin RNA (shRNA) / LentiORFs, Sigma Life Science
RNAi screening has made it possible to identify new genes, or gene networks, that are involved in a wide variety of biological processes, including assays relevant to signal transduction, cell viability, cell morphology, protein localization, and functions, and responses of host cells to pathogens. As such, RNAi continues to help us gain critical insights into the mechanisms underlying human disease and accelerate the development of treatments for cancer and a host of other disorders. The interaction between RNAi screening and complementary approaches such as CRISPR-Cas9-mediated genome editing has opened up new opportunities for assay development, screening, and validation. The successful implementation of genome-editing technologies in several species suggests this will serve as an important and relevant tool for validation studies in numerous cell lines and model systems. Additionally, RNAi rescue experiments using LentiORFs serve an important role in further validating and boosting confidence of screened hits. As we continue to develop new strategies to improve genome-wide RNAi screening and validation, the significance of RNAi as a research tool will remain for many years to come.

2:00 Development and Application of CARD, a Comprehensive Integrated Web-Based Platform for Analysis of RNAi Screening Data
Iain Fraser, Ph.D., Investigator, Laboratory of Systems Biology, National Institute of Allergy and Infectious Diseases, National Institutes of Health
CARD is a comprehensive web-application for integrated analysis and interactive visualization of RNAi screening data. CARD combines both existing and novel algorithms for data pre-processing, reducing false positive hits through gene expression and off-target filtering, implementing network/pathway enrichment of high-confidence hits and predicting active miRNAs. We will discuss the application of CARD to several datasets and demonstrate both increased hit validation rates and improved hit overlap between related screens.

2:30 RNAi for Rare Disease Drug Discovery: Signal or Noise?
Christopher Gibson, Ph.D., Co-Founder and CEO, Recursion Pharmaceuticals
RNAi has increasingly well-described off-target effects. High-content imaging essays, for which vast quantities of morphological data are collected, are particularly prone to confounding value to such effects. Findings will be presented from 1000+ feature high-content imaging data in various human cell types using up to 6 RNAi for each of more than 100 disease-related targets. A discussion of the usefulness and limitations of the data resulting from such RNAi-based results will also be discussed.

3:00 The Utility of CRISPR-Cas9 System Employing Synthetic RNAs to Validate Hits from an RNAi Functional Screen
Louise Baskin, Senior Product Manager, GE Healthcare Dharmacon, Inc.
We have previously performed an siRNA screen targeting 7500 genes in a reporter cell line that enables high-content readout to identify genes involved in the ubiquitin-proteasome proteolytic pathway. Here we describe the use of the CRISPR-Cas9 system in this proteasome reporter cell line to assess previously identified hits. We modified the cell line to stably express Cas9 and then transfected synthetic tracrRNA and crRNAs that resulted in DNA cleavage of proteasome subunits. This model demonstrates that CRISPR-Cas9 can be an effective, orthogonal tool for hit validation of an siRNA screen.

3:30 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Winner Announced

4:10 3D Phenotypic Screening for Target Identification and Drug Discovery
Arvind Rao, Ph.D., Assistant Professor, Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center
A high-throughput kinase siRNA screen (689 kinases) was carried out to study their effects on tumor architecture and hypoxic response induced in 3D tumor spheroids. We present a workflow to identify and interpret gene function in such large scale 3D RNAi experiments by analyzing such image-derived data in the context of associated molecular data. Apart from describing the components of this integrative workflow, we will also share some “lessons learnt” during this process.

4:40 The Path from Arrayed RNAi to Arrayed CRISPR Screens: Lessons Learned and Challenges
Eugen Buehler, Ph.D., Group Leader, Informatics, National Center for Advancing Translational Sciences, National Institutes of Health
The use of CRISPR for whole genome functional screens has now been demonstrated by several groups. However, these screens have been performed only in a pooled format, which severely limits the range of biological functions that can be interrogated. We will detail our experiments in arrayed CRISPR screening and discuss the challenges and opportunities for future work.
8:00 Chairperson’s Remarks  
Ralph Garippa, Ph.D., Director, RNAi Core Facility, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center

8:10 Pooled shRNA, Arrayed siRNA and CRISPR-Cas9: Three Essential Tools towards Understanding Gene Function in Cancer and Disease Biology  
Ralph Garippa, Ph.D., Director, RNAi Core Facility, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center

The addition of CRISPR-Cas9 systems to the incumbent technologies of arrayed siRNA and pooled shRNA have created an unparalleled gene perturbation toolbox for investigators to deploy. Specific examples, published and unpublished, of each of these types of experimental designs will attest to the power of these endeavors, particularly for cancer biology. Respective strengths and weaknesses of each technology will be presented.

8:40 Parallel shRNA and CRISPR/Cas9 Screens Reveal Biology of Stress Pathways and Identify Novel Drug Targets  
Michael Bassik, Ph.D., Assistant Professor, Department of Genetics, Stanford University

We have developed high-complexity shRNA libraries (25 shRNAs/gene) that greatly reduce false negatives/false positives, and have adapted these libraries to knock down gene pairs to perform systematic genetic interaction maps in mammalian cells. We have used these maps to study ER-trafficking toxins, and identified novel protein complexes as well as insights into retrograde trafficking. We are now using this strategy together with the CRISPR/Cas9 system to study stress signaling and identify novel drug targets.

9:00 TECHNOLOGY PANEL: Finding the Right Functional Genomics Tool to Address Your Biological Question  
Moderator: Ralph Garippa, Ph.D., Director, RNAi Core Facility, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center

This panel will bring together 4-5 technical experts from leading technology and service companies to discuss screening trends and improvements in assay platforms and reagents that users can expect to see in the near future.

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

10:25 Screening the Kinome: Lessons from Using Functional Screens in Glioblastoma Stem Cells  
Brent Cochran, Ph.D., Professor, Department of Developmental, Molecular and Chemical Biology, Tufts University School of Medicine

It is possible to isolate and maintain in culture glioblastoma cell lines with stem cell properties. We have conducted shRNA screens of three different GBM stem cell lines in both arrayed and pooled screening format for growth and survival of these cells, under normoxia and hypoxia. We have found that there are considerable differences in the kinase requirements between these cell lines. These results argue for a personalized therapeutic strategy for glioblastoma.

10:55 From Model Systems to Mammalian Applications: Learning from Functional Genomics Analyses in Drosophila  
Stephanie Mohr, Ph.D., Lecturer, Genetics & Director of the Drosophila RNAi Screening Center, Harvard Medical School

Drosophila cell and in vivo systems are exemplary platforms for functional genomics. We have developed algorithms for the design of RNAi and CRISPR reagents; platforms for efficient RNAi reagent production; and mature methods for large-scale screening and data analysis. Our workflows for CRISPR knockout and RNAi screens in human disease-relevant sensitized backgrounds will be discussed. Emphasis will be given to approaches, algorithms and analyses relevant to mammalian systems.

11:25 Enjoy Lunch on Your Own

12:55 pm Plenary Keynote Program (see page 2 for details)

2:40 Refreshment Break in the Exhibit Hall with Poster Viewing

3:25 Close of Conference
New Frontiers in Gene Editing will bring together experts to talk about how and where gene editing can be best applied. What are the different tools that can be used for gene editing, and what are their strengths and limitations? How does the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)/Cas system, compare to other systems and where are they being used? Scientists and clinicians will share their experiences leveraging the utility of gene editing for functional screening, disease modeling, and for creating cell and viral therapies.

Suggested Event Package:
- September 21 Short Course: Setting Up Effective RNAi Screens: From Design to Data to Validation
- September 21 Short Course: Setting Up Effective Functional Screens Using 3D Cell Cultures
- September 22 Symposium: Developing CRISPR-Based Therapies
- September 23 Short Course: A Primer to Gene Editing: Tools and Applications
- September 23-24 Conference: New Frontiers in Gene Editing

WEDNESDAY, SEPTEMBER 23

11:30 am Registration
12:55 pm Plenary Keynote Program (see page 2 for details)
2:40 Refreshment Break in the Exhibit Hall with Poster Viewing

FUNCTIONAL SCREENS USING GENE EDITING

3:25 Chairperson’s Opening Remarks
Bruce R. Conklin M.D., Investigator, Gladstone Institutes and Professor, University of California, San Francisco

3:35 KEYNOTE: Gene Editing and Gene Silencing with CRISPR-Based Systems
Bruce R. Conklin M.D., Investigator, Roddenberry Center for Stem Cell Biology and Medicine, Gladstone Institutes and Professor, Division of Genomic Medicine University of California, San Francisco

We have developed Rare Allele Induction and Detection (RAID), a method that allows for precise base-by-base genome editing in human iPSCs. We are also using CRISPR to rapidly inactivate genes in iPSCs, to induce disease phenotypes. CRISPR and RAID will advance genome engineering by allowing human iPSCs to model human genetics, revert disease mutations, and create engineered alleles with unparalleled precision and efficiency.

4:35 CRISPR and RNAi Platforms for Genome-Wide Loss-of-Function Genetic Screens
Paul Diehl, Director, Business Development, Cellecta, Inc.

We have developed similar pooled sgRNA libraries for functional CRISPR knockout screens and ran screens PDX-derived cell lines to compare the performance of each.

5:05 Refreshment Break in the Exhibit Hall with Poster Viewing
5:40 Assay Development for Phenotypic Screening: CRISPR-Mediated Knockout, Knockdown and Sensor Cell Lines
Melissa G. Mendez, Ph.D., Postdoctoral Fellow, Laboratory of assay Development & Screening Technology (ADST), National Center for Advancing Translational Sciences, NIH

In phenotypic screening, compound structure, titration data and multiple phenotypic readouts are multiplexed across hundreds of thousands of wells per, and across cell models. CRISPR-mediated editing allows these models to be created with deliberate complementarity while maintaining endogenous expression patterns, greatly easing historic restrictions on model selection. We have recreated the hallmark pathology of the rare disease Giant Axonal Neuropathy in a cell model system amenable to a variety of screening paradigms.

6:10 Latest Approaches to Genetic Screens with CRISPR Technology
John Doench, Ph.D., Research Scientist, Broad Institute of Harvard and MIT

The ease of programming Cas9 with a 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.

6:40 Close of Day

THURSDAY, SEPTEMBER 24

7:30 am Registration
8:00 Interactive Breakfast Breakout Discussion Groups (see website for details)

BUILDING IN VIVO MODELS FOR DRUG DISCOVERY

8:45 Chairperson’s Remarks
Myung Shin, Ph.D., Senior Principal Scientist, Biology-Discovery, Genetics and Pharmacogenomics, Merck Research Laboratories

8:55 Genome Editing Animal Models in Drug Discovery
Myung Shin, Ph.D., Principal Scientist, Biology-Discovery, Genetics and Pharmacogenomics, Merck Research Laboratories

Recent advances in genome editing have greatly accelerated and expanded the ability to generate animal models. These tools allow generating mouse models in condensed timeline compared to that of conventional gene-targeting knock-out/knock-in strategies. Moreover, the genome editing methods have expanded the ability to generate animal models beyond mice. In this talk, we will discuss the application of ZFN and CRISPR to generate various animal models for drug discovery programs.

9:25 In vivo Cancer Modeling and Genetic Screening Using CRISPR/Cas9
Sid Chen, Ph.D., Postdoctoral Fellow, Laboratories of Dr. Phillip A. Sharp and Dr. Feng Zhang, Koch Institute for Integrative Cancer Research at MIT and Broad Institute of Harvard and MIT

Here we describe a genome-wide CRISPR-Cas9-mediated loss-of-function screen in tumor growth and metastasis. We mutagenized a non-metastatic mouse cancer cell line using a genome-scale library. The mutant cell pool rapidly generates metastases when transplanted into immunocompromised mice. Enriched sgRNAs in lung metastases and late stage primary tumors were found to target a small set of genes, suggesting specific loss-of-function mutations drive tumor growth and metastasis.
NEW FRONTIERS IN GENE EDITING
Applications and Technologies For Use From the Lab to the Clinic

SEPTEMBER 22-23, 2015

TOWARDS A THERAPEUTIC ENDPOINT

2:15 Chairperson’s Remarks
Matthew Porteus, M.D., Ph.D., Associate Professor, Pediatrics, Stanford University School of Medicine

2:20 Going Native: Exploiting Endogenous CRISPR-Cas Systems for Genome Engineering
Chase Beisel, Ph.D., Assistant Professor, Department of Chemical & Biomolecular Engineering, North Carolina State University

An unexplored avenue is using native CRISPR-Cas systems as convenient tools for the diverse bacteria and archaea that harbor these systems. Here, we describe how the most prevalent type of CRISPR-Cas systems can be exploited for gene regulation, opening new opportunities for genome-wide functional screens and metabolic engineering. These findings also inspired a rapid screen to determine a system’s protospacer adjacent motif, facilitating the adoption of diverse CRISPR-Cas systems for biomolecular research and human therapy.

2:50 Therapeutic Genome Editing for Blood Diseases
Matthew Porteus, M.D., Ph.D., Associate Professor, Pediatrics, Stanford University School of Medicine

There are host of genetic diseases for which allogeneic hematopoietic stem cell transplantation (allo-HSCT) is curative. This curative approach has been called “allogeneic gene therapy” because it replaces the genome with a disease causing mutation with a genome that does not have the mutation. The toxicity and complexity of allo-HSCT precludes it being widely used but is the proof-of-concept that autologous HSCT using gene corrected cells could also cure such diseases without the associated complexity and toxicity.

3:20 Session Break

3:30 Using CRISPR as a Tool for Enabling Active Genetics
Ethan Bier, Ph.D., Professor, Division of Biological Sciences, University of California, San Diego

The high efficiency with which we have observed autocatalytic allelic conversion by a cas9/gRNA-based mutagenesis system in fruit flies has broad applications to controlling vector borne disease and invasive pest species. The implications of this new form of active genetics for human health, basic research, and gene drive systems will be discussed.

4:00 Inducible Genome Editing for Disease Modeling
Lukas Dow, Ph.D., Assistant Professor of Biochemistry in Medicine, Department of Medicine, Hematology and Medical Oncology, Sandra and Edward Meyer Cancer Center, Weill Cornell Medical College

CRISPR/Cas9-based genome editing enables the rapid genetic manipulation of any genomic locus without the need for gene targeting by homologous recombination. We will discuss our efforts to develop conditional transgenic approaches that allow temporal control of CRISPR/Cas9 activity for inducible genome editing in adult mice. The inducible CRISPR (CRISPR) system can be used effectively to create biallelic mutation in multiple target loci and thus, provides a flexible and fast platform for disease modeling in vivo.

4:30 Q&A with Session Speakers

5:00 Close of Conference
Gene therapy has seen its fair share of ups and downs, and yet has continued to progress relentlessly. While the challenges and risks associated with it still remain, there is a new and better understanding of how genes can be effectively manipulated and delivered. With the rise of gene editing tools and enhanced knowledge of targeted delivery, gene therapy may finally achieve its true potential. Gene Therapy Breakthroughs will bring together leading scientists, clinicians, executives and experts who can collectively disperse information on the impact of recent findings on gene therapy and how it can be applied.

Suggested Event Package:
- September 21 Symposium: Strategies for Rare Diseases
- September 23 Short Course: A Primer to Gene Editing: Tools and Applications
- September 22-23 Conference: Gene Therapy Breakthroughs
- September 23-24 Conference: New Frontiers in Gene Editing

TUESDAY, SEPTEMBER 22

7:00 am Registration and Morning Coffee

IMPROVING AAV-BASED GENE THERAPY

8:00 Chairperson's Opening Remarks
Charles P Venditti, M.D., Ph.D., Head, Organic Acid Research Section, Senior Investigator, National Human Genome Research Institute, National Institutes of Health

8:10 KEYNOTE: Next Generation AAV Vectors and Their Use in Rare Diseases
James Wilson, M.D., Ph.D., Professor, Department of Pathology and Laboratory Medicine, University of Pennsylvania

9:00 Genotoxicity of AAV in Murine Models: Implications for Human Gene Therapy
Charles P Venditti, M.D., Ph.D., Head, Organic Acid Research Section, Senior Investigator, National Human Genome Research Institute, National Institutes of Health

The safety of AAV as a vector has been questioned by several studies that have documented hepatocellular carcinoma (HCC) after AAV gene delivery in mice. In this talk, the experiments that have examined AAV genotoxicity will be reviewed and interpreted in the context of more recent genomic analyses that have widely surveyed the integration of AAV vectors. Comments on preclinical study design as it relates to AAV genotoxicity will be offered.

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

10:25 10:55 AAV-Mediated Therapy to Target Neuromuscular Dysfunction in Pompe Disease
Darin Falk, Ph.D., Assistant Professor, Department of Pediatrics, Powell Gene Therapy Center, University of Florida

Patients with Pompe disease experience profound muscle weakness resulting in respiratory and movement difficulties. Recent evidence suggests this weakness may result from the severe pathology observed within the peripheral nerve and neuromuscular junction. The current therapy for Pompe disease does not reach the central nervous system and limits therapeutic potential. Our recent work uses AAV vectors to simultaneously target the neuronal and skeletal muscle pathology in Pompe disease to restore neuromuscular function.

11:25 AAV Clinical Success and Vector Development, a Process That Goes Hand in Hand
R. Jude Samulski, Ph.D., Professor, Department of Pharmacology and Director, Gene Therapy Center, University of North Carolina-Chapel Hill

11:55 Sponsored Presentation (Opportunity Available)

12:10 Q&A With Session Speakers

12:25 pm Enjoy Lunch on Your Own

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

COMBINING GENE SILENCING/EDITING & GENE THERAPY

1:50 Chairperson’s Remarks
Peter French, Ph.D., CEO and Managing Director, Benitec Biopharma Ltd.

2:00 Combining Gene Therapy and Gene Silencing for Transformational Therapeutics
Peter French, Ph.D., CEO and Managing Director, Benitec Biopharma Ltd.

Benitec’s ddRNAi technology combines the specificity of gene therapy vectors with the power of RNA interference to produce novel therapies for serious life threatening diseases. ddRNAi works thorough DNA constructs that continuously silence the disease-associated genes for the lifetime of the cell, allowing for single administration treatments and cures. Benitec's pipeline includes hepatitis C, hepatitis B, non-small cell lung cancer, wet AMD and oculopharyngeal muscular dystrophy.

2:30 The Many Approaches of Gene Therapy for Liver Disorders
Clifford Steer, M.D., Professor of Medicine and Genetics, Cell Biology, and Development; Director, Molecular Gastroenterology Program, University of Minnesota Medical School

Liver plays a major role in many inherited and acquired genetic disorders. Research efforts have been intensified towards the development of targeted gene therapies using novel genetic tools, such as the ZFNs, TALENs and CRISPRs, as well as non-viral vectors, such as Sleeping Beauty, piggyBac transposons and PhiC31 integrase. While
each of these methods utilizes a distinct mechanism of gene modification, all of them are dependent upon the efficient delivery of DNA and RNA into liver cells.

3:00 Sponsored Presentation (Opportunity Available)

3:30 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Winner Announced

4:10 Nucleic Acid Delivery Systems for RNA Therapy and Gene Editing

Daniel Anderson, Ph.D., Professor, Department of Chemical Engineering, Institute for Medical Engineering & Science, Harvard-MIT Division of Health Sciences & Technology and David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology

Here we describe our work on high throughput methods for developing and characterizing RNA delivery and gene editing systems. Libraries of degradable polymers and lipid-like materials have been synthesized, formulated and screened for their ability to deliver RNA, both in vitro and in vivo. A number of delivery formulations have been developed with in vivo efficacy, and show potential therapeutic application for the treatment of genetic disease, viral infection, and cancer.

4:40 Next Generation Gene Therapy: Genome Editing

Matthew Porteus, M.D., Ph.D., Associate Professor, Pediatrics, Stanford University School of Medicine

There are now estimated to be 10,000 diseases caused by mutations in single genes (monogenic diseases). Curative therapy for these diseases would be based on treating these diseases at their foundation-by genetically modifying the genome. Genome editing now provides a powerful mechanism to precisely engineer the genome, with nucleotide precision, true precision therapy, and this talk will focus on both the various tools available for genome editing and ways that the genome can be edited for therapeutic purposes.

5:10 Interactive Breakout Discussion Groups (see website for details)

6:10 Welcome Reception in the Exhibit Hall with Poster Viewing

7:15 Close of Day

WEDNESDAY, SEPTEMBER 23

7:30 am Registration and Morning Coffee

NEW APPROACHES TO GENE THERAPY

8:00 Chairperson’s Remarks

Jaquelin Dudley, Ph.D., Professor, Department of Molecular Biosciences, The University of Texas at Austin

8:10 Using Retroviruses to Easily Increase Gene Expression

Jaquelin Dudley, Ph.D., Professor, Department of Molecular Biosciences, Center for Infectious Disease, and Institute for Cellular and Molecular Biology; The University of Texas at Austin

We recently described that transfection of lentiviral or gammaretroviral vectors into several different mammalian cell types increased expression of a co-transfected gene relative to standard plasmid vectors without changing levels of most endogenous cellular proteins (termed superinduction). Superinduction was not dependent on the cell type or species, the type of reporter gene, or the method of transfection. This has broad applications for the design of retroviral vectors for transfections, DNA vaccines, and gene therapy.

8:40 Ultrasound-Mediated Gene Delivery (UMGD): Applications in Cardiovascular Medicine

Howard Leong-Poi, M.D., Associate Scientist, Keenan Research Centre for Biomedical Science, and Associate Professor, Medicine/Cardiology, St. Michael’s Hospital, Toronto

UMGD is a non-invasive gene transfer technique, utilizing high power ultrasound and gene-bearing carrier microbubbles. Despite modest transfection efficiency, its high organ/tissue specificity and repeatability make it an attractive therapeutic option. UMGD has been used in a variety of in vivo applications, including cardiac and skeletal muscle. This talk will focus on cardiovascular applications, including UMGD for therapeutic angiogenesis in chronic ischemia, and for heart failure and acute myocardial infarction.

9:10 AAV-mediated Gene Therapy for Benign Tumors

Xandra Breakfield, Ph.D., Professor, Department of Neurology and Radiology, Massachusetts General Hospital and Program in Neuroscience, Harvard Medical School

Tuberous sclerosis and neurofibromatosis are caused by loss of tumor suppressor genes, with tumors forming throughout the body and nervous system. These tumors can compromise normal functions and cause pain due to compression of tissues through their expanding volume. Gene replacement and other constructs can be delivered systemically and across the blood-brain barrier to reduce tumor size.

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

10:25 Human Clinical Trials of AAV-Based Based Gene Therapies for Orphan Ocular Disorders

Stephen W. Potter, Chief Business Officer, AGTC

AGTC is a clinical-stage biotechnology company that uses its proprietary gene therapy platform to develop AAV-based gene therapy products for severe inherited orphan diseases in ophthalmology. AGTC expects initial data in human subjects for its lead programs, for the treatment of X-linked retinoschisis and achromatopsia, during the second half of 2015.

10:55 Targeting the Inflammasome Signaling in a Mouse Model of a Geographic Atrophy: A Gene Therapy Approach

Cristhian J. Ildefonso, Ph.D., Senior Postdoctoral Associate, Laboratory of Dr. Alfred S. Lewin, Molecular Genetics & Microbiology, University of Florida College of Medicine

Geographic Atrophy is associated with oxidative stress and inflammation driven by the inflammasome signaling pathway. We developed and characterized AAV vectors to deliver secretable and cell-penetrating proteins targeting this pathway. These vectors are being tested in a GA mouse model.

11:25 Enjoy Lunch on Your Own

12:55 pm Plenary Keynote Program (see page 2 for details)

2:45 The Many Approaches of Gene Therapy for Liver Disorders

Clifford Steer, M.D., Professor, Medicine and Genetics, Cell Biology, and Development; Director, Molecular Gastroenterology Program, University of Minnesota Medical School

3:25 Close of Conference
The pharmaceutical industry has been frustrated by the high failure rates of drug development programs, which suggest that the decision making process on various stages of the programs can benefit from some enhancement. One of the approaches rapidly gaining credibility, and showing good promise for informing better decision making is Quantitative Systems Pharmacology (QSP). Cambridge Healthtech Institute will be holding its Inaugural Quantitative Systems Pharmacology conference as part of Discovery on Target with the goal of bringing together experts in QSP and researchers who may be interested in using this methodology. The conference is designed as a knowledge and opinion exchange forum, and will be focusing on strategy and implementation of QSP from early discovery all the way to early clinical development.

### Suggested Event Package:

- September 23-24 Conference: Quantitative Systems Pharmacology
- September 23 Short Course: Using Mechanistic Physiological Models in Drug Development: A Proven Quantitative Systems Pharmacology (QSP) Approach

### APPLICATIONS OF QSP TO DRUG DISCOVERY AND DEVELOPMENT

3:25 Chairperson’s Opening Remarks
Anjit Chakravarty, Ph.D., Director, Modeling and Simulation (DMPK), Takeda Pharmaceuticals International Co.

3:35 Right Target, Right Dose, Right Trial with Limited Animal Use: QSP Doubles the 3R Benefits
Valenu Damian-Iordcahe, Ph.D., Head, Modelling and Translational Biology, GSK

Lack of efficacy is the most significant reason for late stage clinical failures. Drug discovery efforts are often based on qualitative link between the target and clinical outcomes and are supported by studies using animal models that may have limited clinical translation. Quantitative Systems Pharmacology provides the missing quantitative link between the target modulation and clinical outcomes allowing the selection of the best target, estimating the optimal target engagement, identifying the patients that would benefit the most from the therapy, and enabling the design of best trial. In this talk, I will demonstrate these QSP benefits by using several case studies in dermatology, rare cases and ophthalmology.

4:05 The QSP Extensibility Concept: A Physiology-Based Multi-Scale Model as a Platform to Address Wide-Ranging Clinical Questions
Mark C. Peterson, Ph.D., Director, Global Pharmacometrics, GIPB Clinical Pharmacology, Pfizer, Inc.

A key aspect of QSP models (QSPMs) is the multi-scale linking of target modulation to clinical outcomes (efficacy, safety). The physiologic linking renders a tool for asking/answering clinically relevant trial design and program development questions. Beyond the initial application, added value and accelerated understanding can be derived in alternate pathologies via QSPM extension. In this session, extensions of an existing QSPM will be presented, highlighting cross-disease area utility.

5:05 Refreshment Break in the Exhibit Hall with Poster Viewing

6:10 Building Translational Quantitative Pharmacology: The Merck Experience
Prajakti Kothare, Ph.D., Scientific Lead, Early Phase Quantitative Pharmacology & Pharmacometrics, Pharmacokinetics, Pharmacodynamics & Drug Metabolism, Merck

The emerging discipline of Quantitative and Systems Pharmacology has generated increasing interest recently across industry, academia and regulators. Built on the successful implementation of model-informed drug development, Merck has focused its efforts in the last few years on building similar capabilities in drug discovery. An overview of Merck’s experience in building translational and quantitative pharmacology in the discovery space will be presented and exemplified through case studies. A broad-based integration of these approaches through all facets of the discovery paradigm is critical to improving the probability of success to downstream pipeline milestones.

6:40 Close of Day
THURSDAY, SEPTEMBER 24

7:30 am Registration

8:00 Interactive Breakfast Breakout Discussion Groups (see website for details)

SYSTEMS DISEASE MODELS

8:45 Chairperson’s Remarks
Oliver Ghobrial, Ph.D., Senior Research Scientist III, Translational Modeling and Simulation, AbbVie

8:55 A Quantitative Systems Pharmacology (QSP) Framework for Oncology Translational and Early Clinical Development
Anjith Chakravarty, Ph.D., Director, Modeling and Simulation (DMFPK), Takeda Pharmaceuticals International Co.
We have developed a QSP framework for translational and early clinical development that is underpinned by an assumption of cancer as an evolutionary process. Our framework is based on rigorous empirical assessments in the preclinical and early clinical settings, and relies on the assessment and iterative refinement of model-based decision analytics as the guiding principle for early development. The proposed talk will outline the framework and provide examples of its application in a range of different contexts.

9:25 Applying Evolutionary Systems Biology To Design Dosing Regimens To Minimize Resistance
Franziska Michor, Ph.D., Professor, Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Department of Biostatistics, Harvard School of Public Health
Recent advances in high-throughput profiling of cancer genomes have enabled the generation of an unprecedented amount of data. The analysis of this data requires the development of novel computational and mathematical modeling approaches. This presentation will discuss state-of-the-art modeling methods addressing treatment response and the evolution of resistance.

9:55 Development and Application of the Coagulation Systems Model
Fei Hua, Ph.D., Clinical Pharmacology Lead, PharmaTx Clinical Research & Development, Pfizer Inc.
We have modified the coagulation systems model from literature and validated with internal data. The model has been used to help multiple programs on the pathways and the range of questions the model has addressed ranging from early discovery to clinical.

10:25 Coffee Break in the Exhibit Hall with Poster Viewing

11:00 Applications of Quantitative Systems Pharmacology (QSP) in Crohn’s Disease Drug Discovery and Development
Oliver Ghobrial, Ph.D., Senior Research Scientist III, Translational Modeling and Simulation, AbbVie
A CD QSP platform was developed to describe the homeostatic interactions between the gut microbiome, epithelial barrier, damage and repair mechanisms, and immune system in health and disease. A novel approach to virtual patient development will be presented and utility of this approach to explore competing hypotheses of CD pathophysiology will be demonstrated.

11:40 Adaptive Resistance and Fractional Response of Cancer Cells to Therapy
Mohammad Fallahi-Sichani, Ph.D., Merck Fellow of the Life Sciences Research Foundation, Department of Systems Biology, Harvard Medical School
Drug adaptation in melanomas and other cancers driven by different oncogenic pathways limits therapeutic effectiveness leading to temporary responses in patients, the primary challenge facing targeted therapy. I will describe a systems pharmacology approach combining multiplex biochemical measurements and computational modeling to characterize drug-induced adaptive responses and their consequences for cancer cell fate and to use that information to guide development of strategies to enhance drug maximal effect and to prevent drug resistance.

12:10 pm QSP Approaches Enabling Quantitative Decisions in Drug Discovery from Early Research to Clinical Trials
John Burke, Ph.D., Co-Founder, President and CEO, Applied BioMath, LLC
QSP approaches have been used successfully in Pharma and Biotechs to drive quantitative decisions to reduce late stage attrition, and accelerate best-in-class therapeutics to meet unmet medical need. Here we show several case studies in Immuno-Oncology where these approaches have driven quantitative decisions resulting in savings of millions of dollars and shortening timelines.

12:40 Session Break

12:50 Luncheon Presentation (Sponsorship Opportunity Available) or Lunch on Your Own

1:30 Refreshment Break in the Exhibit Hall with Poster Viewing

QSP FOR BIOMARKERS IDENTIFICATION AND DEVELOPMENT

2:15 Chairperson’s Remarks
Matthew Onsum, Ph.D., President and CEO, Silver Creek Pharmaceuticals

Lansing Taylor, Ph.D., Director, University of Pittsburgh Drug Discovery Institute & Allegheny Foundation, Professor of Computational and Systems Biology, University of Pittsburgh
A sufficient understanding of the biology underlying how disease phenotypes arise from predisposing genetic variations is often the limiting determinant for optimal target and companion biomarker selection for therapeutic development and patient stratification. Consequently, drug candidates exhibiting well defined pharmacokinetic and pharmacodynamics profiles entering Phase II and III trials often fail to demonstrate proof-of-concept. To address this challenge, we describe a broadly applicable, network-centric, quantitative systems pharmacology (QSP) drug discovery and development platform to complement and enhance current target-focused and phenotypic-based approaches. The integration of the clinical, computational and experimental elements of QSP will be addressed in examples from metastatic breast cancer, Huntington's Disease and Liver diseases.
2:50 Systems Pharmacology Insights for Patient Selection for Liposomal Anti-Cancer Therapy: From Idea to Clinical Evaluation
Jaeyeon Kim, Ph.D., Principal Scientist, Cancer Therapeutics, Memrinnck Pharmaceuticals
Quantitative systems pharmacology modeling of liposomal anti-cancer therapies has led to key insights surrounding the importance of tumor deposition on overall drug delivery. Model insight led to the concept of an imaging diagnostic that has been advanced to clinical evaluation. Model based analysis of patient tumor kinetic data further contributed to a detailed understanding of drug delivery in human tumors.

3:20 Session Break

TECHNOLOGIES FOR QUANTITATIVE PHARMACOLOGY

3:30 Engineering Targeted Growth Factors to Repair Heart Tissue Following Ischemic Injury
Matthew Onsum, Ph.D., President and CEO, Silver Creek Pharmaceuticals
Silver Creek is developing a new class of targeted, growth factor-based therapeutics (Smart Growth Factors, SGFs) for treating heart disease that are engineered to have optimized selectivity, pharmacokinetics, and safety profiles. Designed using principles of systems pharmacology, our SGFs selectively activate pro-survival and repair signaling pathways in heart tissue damaged by ischemia and lead to reduced infarct size in vivo without off-target effects.

4:00 Kriging is an Emerging Technology that Has the Potential of Improving the Precision of in silico Predictions and Eliminate the Need for Creating Local Models
Istvan Enyedy, Ph.D., Senior Scientist, Chemistry and Molecular Therapeutics, Biogen
We have built databases using in-house or literature compounds with measured hERG patch clamp IC50, volume of distribution, P450 inhibition IC50, MDCK permeability. This data was used to test the usefulness of kriging as a method for building in silico prediction tools. We tested the validity of the models using leave one class out approach which should be the most challenging for kriging. The advantages and disadvantages of this method will be presented.

4:30 A Massively Orthogonal Pharmacology Search Engine: Can All of Our Models and Data Be “Googled™”?
Douglas Selinger, Ph.D., Manager, Bioinformatics, Preclinical Safety, Novartis Institutes for BioMedical Research
We’ve developed a search engine which returns target data & predictions for a query small molecule. The search is automatically expanded to include compounds with structural similarity or a shared biological response, e.g. a similar transcriptional profile. Targets are then prioritized by consensus, as well as by algorithms such as PageRank, the algorithm made famous by Google™. Despite searching large numbers of heterogeneous data sets and in silico model results (currently >15 models and/or data sets; ~200 million data)

5:00 Close of Conference
Ophthalmological pharmacology has historically lacked systematic understanding of disease mechanisms, especially of those for the back of the eye. This is now changing with the discovery of novel targets and pathways, paired with a greater understanding of the role of genetics in ocular pathologies. The third annual Targeting Ocular Disorders will cover some of the most promising emerging therapies in the treatment of ocular diseases. Special focus will be given to Glaucoma, Age-Related Macular Degeneration and Retinopathy. Designated sessions will emphasize the role of precise imaging techniques in accelerating preclinical development. Recent solutions in drug delivery to the back of the eye will also be discussed.

**Suggested Event Package:**
- September 23 Short Course: Preclinical Animal Models for Ocular Indications
- September 22-23 Conference: Targeting Ocular Disorders

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**TUESDAY, SEPTEMBER 22**

**7:00 am Registration and Morning Coffee**

**NOVEL TARGETS, PATHWAYS AND MECHANISMS OF ACTION**

**8:00 Chairperson’s Opening Remarks**
Eric Furfine, Ph.D., CSO, Eleven Biotherapeutics, Inc.

**8:10 KEYNOTE PRESENTATION: New Horizons for Glaucoma Therapy**
Naj Shanf, Ph.D., FARVD, Executive Director and Head, Global Biomedical Sciences, Santen, Inc.

Glaucoma and the associated ocular hypertension seriously threaten vision in >60 million patients. Reduction of elevated intraocular pressure (IOP) in glaucoma remains the major treatment option. New classes of IOP-lowering agents worthy of clinical pursuit include NO-donor-PGA conjugates, Rho kinase inhibitors, ACE-2 activators, non-peptide bradykinin agonists, serotonin-2 and EP2 receptor agonists. An overview of such new therapeutics will be presented.

**8:40 Use of High Content Screening to Identify Targets for the Treatment of Glaucoma and the Retinal Degenerative Disease**
Donald Zack, M.D., Ph.D., Guernier Professor of Genetic Engineering and Molecular Ophthalmology, Johns Hopkins University

Phenotypic screening, as opposed to traditional target-based screens, has proven successful in the development of molecular probes and lead molecules for a number of complex diseases. We have taken such a phenotypic approach to identify small molecules that promote the differentiation, function, and survival of murine primary and human stem cell-derived retinal neurons.

**9:10 Nitric Oxide-cGMP Signaling as a Therapeutic Target for Glaucoma**
Emmanuel Buys, Ph.D., Assistant Professor, Anesthesiology, Harvard Medical School; Associate Scientist, Broad Institute of MIT and Harvard

The nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) pathway regulates intraocular pressure (IOP). Preclinical and clinical studies have demonstrated the ability of NO to lower IOP (e.g. VESNIO®). The therapeutic potential of targeting NO-cGMP signaling in glaucoma will be reviewed.

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

**10:25 Local modulation of cytokine signaling to treat anterior and posterior ocular disorders**
Eric Furfine, Ph.D., CSO, Eleven Biotherapeutics, Inc.
DMER in diabetic rats. No deleterious effects were detected after repeated topical administration to eyes of legally blind, diabetic humans.

3:00 Sponsored Presentation (Opportunity Available)
3:30 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Winner Announced

SUPPORTING IMAGING TECHNOLOGIES AND PRECLINICAL MODELS

4:10 Utility of in vivo Confocal Microscopy-Based Imaging Endpoints for the Assessment of Ocular Surface Inflammation
Pedram Hamrah, M.D., Assistant Professor, Ophthalmology, Harvard Medical School; Director, Ocular Surface Imaging Center, Massachusetts Eye and Ear Infirmary
Recent studies have shown the role of immune changes in the pathogenesis of dry eye disease (DED) and a sensitive test is needed to quantify the immune response. The purpose of this study is to evaluate the utility of in vivo confocal microscopy changes in corneal and conjunctival inflammation to therapeutic intervention.

4:40 Using Posterior Segment OCT as a Biomarker in Disease
Jay S. Duker, M.D., Professor and Chair, Ophthalmology, Tufts University School of Medicine; Director, New England Eye Center
Optical Coherence Tomography (OCT) is a non-invasive, highly reproducible imaging modality that provides quantitative measurements of retinal anatomy with micron resolution. OCT provides important biomarkers for disease states that permits researchers, clinicians and drug developers to monitor the status of a variety of ocular disease.

5:10 Interactive Breakout Discussion Groups (see website for details)
6:10 Welcome Reception in the Exhibit Hall with Poster Viewing
7:15 Close of Day

WEDNESDAY, SEPTEMBER 23

7:30 am Registration and Morning Coffee

DRUG DELIVERY TO THE POSTERIOR SEGMENT OF THE EYE

8:00 Chairperson’s Remarks
Abraham Scaria, Ph.D., Senior Scientific Director, Ophthalmology, Genzyme, a Sanofi Company

8:10 Gene Therapy for Wet-AMD
Abraham Scaria, Ph.D., Senior Scientific Director, Ophthalmology, Genzyme, a Sanofi Company
VEGF antagonists are useful for treating neovascular AMD, however current treatments require chronic intravitreal injections. We have demonstrated long-term efficacy with minimal side effects following a single intravitreal delivery of a gene therapy AAV-sFLT01 (soluble VEGFR) in rodents and non-human primate models. A Phase I clinical trial is almost completed at four clinical sites in the USA.

8:40 Long Acting Delivery of Antibody Therapeutics to the Back of the Eye
Debby Cheng, Ph.D., Associate Scientist, Genentech, Inc., a Member of the Roche Group
Successful macromolecular therapies for treating posterior eye diseases have spurred the development of long acting delivery technologies. The objective is to reduce treatment burden by decreasing frequency of intravitreal injection. Here, we present an overview of ocular delivery systems for long-term delivery of antibody therapeutics. Promising sustained release formulations and implanted devices will be discussed.

9:10 Intraocular Implant Technology Providing Sustained Delivery of Therapeutic Proteins to the Back of the Eye
Konrad Kauper, MSc, Vice President, Core Technology Development, Neurotech Pharmaceuticals, Inc.
While intravitreal therapies targeting VEGF have led to a paradigm shift in the treatment of neovascular AMD, dosing frequency and compliance issues remain. To address the need for sustained, long-term drug delivery, Encapsulated Cell Therapy, an intraocular implant of a proprietary human cell line genetically engineered to constitutively produce therapeutic proteins for two years, may provide a novel treatment solution.

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

NEW APPROACHES TO GENE THERAPY

10:25 Human Clinical Trials of AAV-Based Gene Therapies for Orphan Ocular Disorders
Stephen W. Potter, MBA, Chief Business Officer, AGTC
AGTC is a clinical-stage biotechnology company that uses its proprietary gene therapy platform to develop AAV-based gene therapy products for severe inherited orphan diseases in ophthalmology. AGTC expects initial data in human subjects for its lead programs, for the treatment of X-linked retinoschisis and achromatopsia, during the second half of 2015.

10:55 Targeting the Inflammasome Signaling in a Mouse Model of a Geographic Atrophy: A Gene Therapy Approach
Cristhian J. Ildefonso, Ph.D., Senior Postdoctoral Associate, Laboratory of Dr. Alfred S. Lewin, Molecular Genetics & Microbiology, University of Florida College of Medicine
Geographic Atrophy (GA) is associated with oxidative stress and inflammation driven by the inflammasome signaling pathway. We developed and characterized AAV vectors deliver secretable and cell-penetrating proteins targeting this pathway. These vectors are being tested in a GA mouse model.

11:25 Enjoy Lunch on Your Own

12:55 pm Plenary Keynote Program (see page 2 for details)
2:40 Refreshment Break in the Exhibit Hall with Poster Viewing
3:25 Close of Conference
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| ALL ACCESS (Includes access to 2 Short Courses or 1 Symposium and 2 conferences) | Commercial | Academic, Government Hospital-affiliated |
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CONFERENCE DISCOUNTS

Poster Submission · Discount ($50 Off): Poster abstracts are due by August 7, 2015. Once your registration has been fully processed, we will send an email containing a unique link allowing you to submit your poster abstract. If you do not receive your link within 5 business days, please contact jring@healthtech.com. *CHI reserves the right to publish your poster title and abstract in various marketing materials and products.

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**Monday, September 21, 8-11:00 am**

| SC1: Cancer Metabolism: Pathways, Targets and Clinical Updates |
| SC2: Leveraging Data and Analytics for Drug Discovery |

**SC3: Setting Up Effective RNAi Screens: From Design to Data to Validation**

**SC4: Phenotypic Screening and Chemical Probe Development**

**SC5: GPCR Structure-Based Drug Discovery**

**Monday, September 21, 3:30-6:30 pm**

| SC6: Targeting of GPCRs with Monoclonal Antibodies |
| SC7: Setting Up Effective Functional Screens Using 3D Cell Cultures |
| SC8: Targeting Protein-Protein Interactions: Biophysical Approaches |
| SC9: Preclinical Animal Models for Ocular Indications |

**Wednesday, September 23, 7-9:30 pm (Dinner provided)**

| SC8: Preclinical Animal Models for Ocular Indications |
| SC10: Introduction to Allosteric Modulators and Biased Ligands of GPCRs |
| SC11: Introduction to Targeted Covalent Inhibitors |
| SC12: Assays and High-Throughput Screening for Novel Epigenetic Inhibitors |
| SC13: Gamification and Drug Target Challenges |
| SC14: A Primer to Gene Editing: Tools and Applications |

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