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#BostonDOT16

The Industry's Preeminent Event on Novel Drug Targets

Cambridge Healthtech Institute's

14th Annual Discovery on TARGET

September 19-22, 2016 | Westin Boston Waterfront | Boston, MA

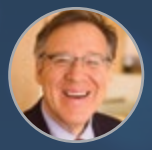
2016 Plenary Keynote Program

Sponsored by REACTION BIOLOGY CORP.

Meeting the New Challenges of Novel Drug Development

Jeffrey Barrett, D.Phil.,
Founding Director, Open Targets; Group Leader, Wellcome Trust Sanger Institute

Aaron Day-Williams, Ph.D.,
Biogen Scientific Lead, Open Targets; Associate Director and Head, Statistical Genetics, Biogen



Gregory L. Verdine, Ph.D.,
Erving Professor, Chemistry, Departments of Stem Cell and Regenerative Biology, Chemistry and Chemical Biology, and Molecular and Cellular Biology, Harvard University and Harvard Medical School

Event Features

- **50+** Exhibits — SPONSORSHIP & EXHIBIT OPPORTUNITIES
- **1,100+** Attendees
- **17** Conference Programs
- **12** Short Courses
- **5** Symposia
- **1** Training Seminar
- **135+** Posters

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DiscoveryOnTarget.com

Cambridge Healthtech Institute,
250 First Avenue, Suite 300,
Needham, MA 02494
www.healthtech.com

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14th Annual Discovery on TARGET

September 19-22, 2016 | Westin Boston Waterfront | Boston, MA

DiscoveryOnTarget.com

Cambridge Healthtech Institute will host the **14th Annual Discovery on Target** event this September 19-22, 2016 in Boston, MA. Spanning four days, the event showcases current and emerging "hot" targets for the pharmaceutical industry. Over 1,100+ attendees (from 26 countries) composed of scientists/technologists, executives, directors, and managers from biopharma, academic, and healthcare organizations participate annually. The 2016 event is comprised of 17 conference tracks, 1 training seminar, 5 symposia, 12 short courses, an exhibit hall of 50+ companies, 135+ posters, and dedicated networking sessions. Discovery on Target assembles an impressive group of 300+ distinguished speakers who look forward to sharing their knowledge, best practices, and expertise with all attendees.

Monday Sept. 19	PRE-CONFERENCE SHORT COURSES* AND SYMPOSIA*								
Tuesday Sept. 20 AM/PM	T1A: TARGETING HISTONE METHYLTRANS-FERASES AND DEMETHYLASES	T2A: TARGETING THE UBIQUITIN PROTEASOME SYSTEM	T3A: TARGETING THE MICROBIOME – PART 1	T4A: GPCR-BASED DRUG DISCOVERY – PART 1	T5A: ADVANCES IN GENE EDITING AND GENE SILENCING – PART 1	T6A: GENE THERAPY BREAK-THROUGHS	T7A: ANTIBODIES AGAINST MEMBRANE PROTEIN TARGETS – PART 1	T8A: TARGETING CARDIO-METABOLIC DISEASES	T9A: TARGETING OCULAR DISORDERS
Wednesday AM Sept. 21									
12:50-2:40 PM	PLENARY KEYNOTE PROGRAM								
Wednesday PM Sept. 21	T1B: TARGETING EPIGENETIC READERS AND CHROMATIN REMODELERS	T2B: KINASE INHIBITOR DISCOVERY	T3B: TARGETING THE MICROBIOME – PART 2	T4B: GPCR-BASED DRUG DISCOVERY – PART 2	T5B: ADVANCES IN GENE EDITING AND GENE SILENCING – PART 2	T6B: TRANSLATING CANCER GENOMICS	T7B: ANTIBODIES AGAINST MEMBRANE PROTEIN TARGETS – PART 2	T8B: METABOLOMICS IN DRUG DISCOVERY	TRAINING SEMINAR*: DATA VISUALIZATION
7:00 - 9:30 PM	DINNER SHORT COURSES* Wednesday, Sept. 21								
Thursday Sept. 22 AM/PM	T1B: TARGETING EPIGENETIC READERS AND CHROMATIN REMODELERS	T2B: KINASE INHIBITOR DISCOVERY	T3B: TARGETING THE MICROBIOME – PART 2	T4B: GPCR-BASED DRUG DISCOVERY – PART 2	T5B: ADVANCES IN GENE EDITING AND GENE SILENCING – PART 2	T6B: TRANSLATING CANCER GENOMICS	T7B: ANTIBODIES AGAINST MEMBRANE PROTEIN TARGETS – PART 2	T8B: METABOLOMICS IN DRUG DISCOVERY	TRAINING SEMINAR*: DATA VISUALIZATION

** Separate registration required for Short Courses, Symposia, Training Seminar*

14th Annual Discovery on TARGET

September 19-22, 2016 | Westin Boston Waterfront | Boston, MA

DiscoveryOnTarget.com

2016 Plenary Keynote Program | WEDNESDAY, SEPTEMBER 21 | 12:50 – 2:40 PM

Jeffrey Barrett, D.Phil., Founding Director, Open Targets; Group Leader, Wellcome Trust Sanger Institute

Aaron Day-Williams, Ph.D., Biogen Scientific Lead, Open Targets; Associate Director and Head, Statistical Genetics, Biogen

Gregory L. Verdine, Ph.D., Erving Professor, Chemistry, Departments of Stem Cell and Regenerative Biology, Chemistry and Chemical Biology, and Molecular and Cellular Biology, Harvard University and Harvard Medical School

Meeting the New Challenges of Novel Drug Development

The analysis of massive amounts of 'omics data is uncovering remarkable insights into disease biology, creating a wealth of new drug targets, and the potential for the development of novel pharmaceutical agents. Key to efficiently utilizing these new targets are the needs for preclinical validation and prioritization, as well as utilizing new therapeutic modalities to unlock the significant portion of targets currently unmet. Discovery on Target's 2016 Plenary Keynote Program will address these challenges during keynote lectures from Open Targets, a new bioinformatics-based target validation platform facilitating public-private open innovation, and Dr. Gregory Verdine, a pioneer in the field of Chemical Biology specializing in the development of new therapeutic modalities, a serial biotech entrepreneur, and a life science Venture Capitalist. Reaction Biology, an industry leader specializing in assay services for early-stage drug discovery, will provide our plenary keynote introduction.

PLENARY KEYNOTE INTRODUCTION:
Ekaterina Kuznetsova, Ph.D., Research Scientist, Reaction Biology Corporation

Sponsored by REACTION BIOLOGY CORP.

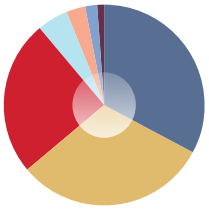
CHI's INTRO-NET
Networking at its Best

Maximize your experience on-site at Discovery on Target 2016!

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.

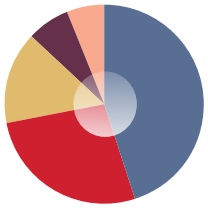
Here's Who You Can Expect to Meet at the Discovery on Target Event in 2016

COMPANY TYPE



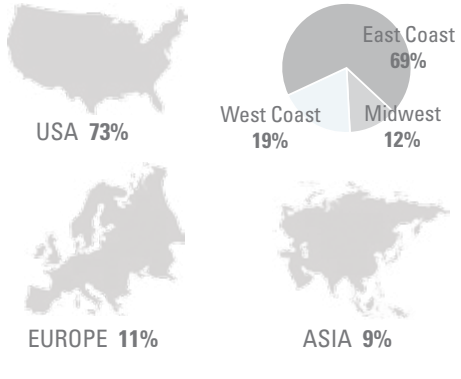
Biotech/Commercial	33%
Pharma	31%
Academic	25%
Healthcare/Hospital	5%
Government	3%
Services/Societies	2%
Financial	1%

COMPANY TITLE



Executive/Director	39%
Scientist/Technologist	31%
Professor	15%
Other	8%
Manager	7%

ATTENDEES BY GEOGRAPHIC LOCATION



FINAL WEEKS TO REGISTER

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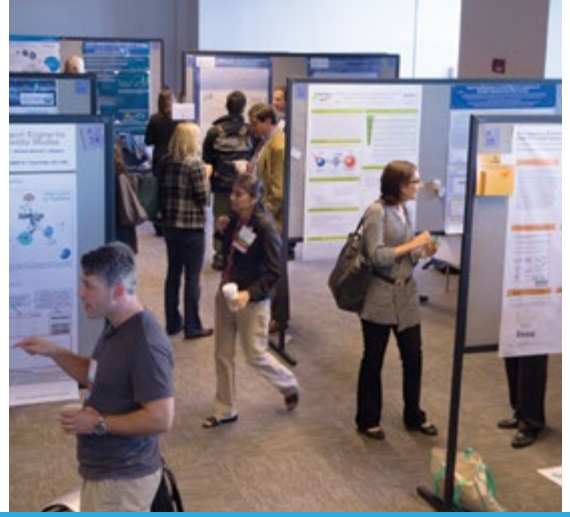

Present a Poster and Save $50!

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 5, 2016.

- Your poster will be available to 1,100+ Drug Discovery 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

Dedicated poster sessions for Symposia and Conference Programs.

Discovery on Target Student Fellowship

Full time graduate students and Ph.D. Candidates are encouraged to apply for the Discovery on Target Student Fellowship. Interested students must complete an online application for the 2016 Student Fellowship. Applications are due by July 8, 2016.

HOW STUDENTS BENEFIT FROM PRESENTING A POSTER:

1 Showcase Your Research to 1,100+ 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.

4 Attend Discovery on Target for the discounted price of $195: Accepted 2016 Student Fellows will receive a discounted conference rate of $195. Students not accepted for the 2016 Student Fellowship, can register at a discounted rate $295, and will not be required to present a poster.

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Sponsorship, Exhibit, and Lead Generation Opportunities

CHI offers comprehensive sponsorship packages which include presentation opportunities, exhibit space, branding and networking with specific prospects. Sponsorship allows you to achieve your objectives before, during, and long after the event. Any sponsorship can be customized to meet your company's needs and budget. Signing on early will allow you to maximize exposure to qualified decision-makers.

Podium Presentations – *Available Within the Main Agenda!*

Showcase your solutions to a guaranteed, targeted audience. Package includes a 15- or 30-minute podium presentation within the scientific agenda, exhibit space, on-site branding, access to cooperative marketing efforts by CHI, and more.

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 presentations are available for sponsorship and they will sell out quickly. Sign on early to secure your talk!

Invitation-Only VIP Dinner/Hospitality Suite

Sponsors will select their top prospects from the conference pre-registration list for an evening of networking at the hotel or at a choice local venue. CHI will extend invitations and deliver prospects, helping you to make the most out of this invaluable opportunity. Evening will be customized according to sponsor's objectives i.e.:

- Purely social
- Focus group
- Reception style
- Plated dinner with specific conversation focus

Exhibit

Exhibitors will enjoy facilitated networking opportunities with qualified delegates. Speak face-to-face with prospective clients and showcase your latest product, service, or solution.

One-on-One Meetings

Select your top prospects from the pre-conference registration list. CHI will reach out to your prospects and arrange the meeting for you. A minimum number of meetings will be guaranteed, depending on your marketing objectives and needs. A very limited number of these packages will be sold.

Additional branding and promotional opportunities are available, including:

- Conference Tote Bags
- Literature Distribution (Tote Bag Insert or Chair Drop)
- Badge Lanyards
- Padfolios
- Program Guide Advertisement

Looking for additional ways to drive leads to your sales team?

CHI's Lead Generation Programs will help you obtain more targeted, quality leads throughout the year. We will mine our database of 800,000+ life science professionals to your specific needs. We guarantee a minimum of 100 leads per program! Opportunities include:

- Whitepapers
- Web Symposia
- Custom Market Research Surveys
- Podcasts

For sponsorship and exhibit information, please contact:

Jon Stroup | Senior Manager, Business Development
781-972-5483 | jstroup@healthtech.com

FINAL WEEKS TO REGISTER

Short Courses:

CLICK TO REGISTER

MONDAY, SEPTEMBER 19 | 8:00 - 11:00 AM

SC1: Immunology Basics for Chemists

Immunology is a difficult subject to master, even for immunologists. Newly discovered cell types and their associated function in human health and disease have been continuously revealed over the last decade. In this course immunologists (non-physicians) with extensive experience in biopharmaceutical drug discovery and development will break it down for you by filling in the gaps that most chemists have. It's not a comprehensive course –but hopefully better – a useful course. The focus will range from basic background biology and terminology that immunologists take for granted and then jump to the biological underpinnings of the areas and targets a lot of medicinal chemists are developing compounds against.

Instructor:

Songqing Na, Ph.D., Senior Research Advisor, Biotechnology & Autoimmunity Res-AME, Eli Lilly and Company

Thomas Sundberg, Ph.D., Senior Research Scientists 1, Center for the Development of Therapeutics, Broad Institute of MIT and Harvard

SC4: Medical Dermatology Therapeutic R&D and Technical Innovation: Understanding Mechanisms, Novel Targets and Pathways & Industry Case Studies - Part 1

CLICK for full agenda

Skin is the largest organ and dermatology is a very unique Therapeutic Area (TA) with a breadth of indications. Now is a dynamic time for the prescription dermatological drug industry due to consolidation, rising demand for therapies, and a deeper understanding of novel targets and disease pathways. This two-part short course provides a platform to discuss and learn about key challenges and special considerations of dermatology drug development.

Instructors:

Jack Leonard, Ph.D., Professor, Microbiology and Physiological Systems, UMASS Medical School

Krishna Menon, Ph.D., President and Chief Scientific Officer, Cellceutix Corporation

Anne Parneix, M.D., Vice President, Therapeutic Area Head, Dermatology, Novartis

Yael Schwartz, Ph.D., CEO, Or-Genix Therapeutics, Inc.

Michael Sierra, Ph.D., Vice President, Head, LEO Science & Tech Hub USA, LEO Pharma

Thean Yeoh, Ph.D., Associate Research Fellow, Pfizer

Meng Zhou, Head, R&D, Contract Pharmaceutical Limited Canada

MONDAY, SEPTEMBER 19 | 12:00 - 3:00 PM

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 the most recently elucidated GPCR crystal structures and explore how 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 cover structural biology techniques, including the burgeoning field of applying nuclear magnetic resonance (NMR), to study GPCR structure and dynamics.

Instructors:

Matthew Eddy, Ph.D. Postdoctoral Fellow, Ray Stevens Laboratory, The Bridge Institute, University of Southern California

Huixian Wu, Ph.D., Senior Scientist, Groton Center of Chemistry, Pfizer Inc.

SC6: RNA as a Small Molecule Drug Target

Long considered a molecule that existed simply to transmit information for coding proteins, it has become clear that RNA regulates diverse biological phenomena on a number of levels. Additionally, RNA contributes to the pathogenesis of a variety of diseases, ranging from human cancers to bacterial and viral infections. However, targeting RNA with small molecules has historically proven challenging. Nonetheless, recent efforts have demonstrated that at least some types of RNA are in fact targetable with drug-like small molecules. This workshop will focus on approaches for targeting RNA with small molecules, including researchers from both academia and industry. Discussions will include the types of RNA that are druggable, strategies for identifying biologically active, RNA-binding small molecules, and the future of RNA as a drug target.

Instructors:

John "Jay" Schneekloth Jr., Ph.D., Investigator, Chemical Biology Laboratory; Head, Chemical Genetics Section, Center for Cancer Research, National Cancer Institute, NIH

Thomas Hermann, Ph.D., Associate Professor, Chemistry and Biochemistry; Co-Director, UCSD Center for Drug Discovery Innovation

Graham Smith, Ph.D., Director, Medicinal Chemistry, and Project Team Leader, Merck

Atwood Cheung, Ph.D., Investigator III, Global Discovery Chemistry, Novartis Institutes for BioMedical Research, Inc.

** Separate registration required for Short Courses, Symposia, Training Seminar*

Short Courses:

CLICK TO REGISTER

SC7: Using IP Landscape Studies to Improve Your Confidence While Navigating a Crowded IP and Technology Space

IP management sometimes feels a little like walking around in the dark surrounded by any number of known & unknown dangers. This course will explore how you can leverage an IP landscape study (generated by scientists and not software) to assess IP dangers and business opportunities. Analyzing the landscape from an IP and a technology perspective can highlight your company's strategic positioning at a product, technology, product attribute, and manufacturing level. Case studies will be presented.

Instructors:

David Berry, M.D., Ph.D., General Partner, Flagship Ventures

Ananda Chakrabarty, Ph.D., Department of Microbiology & Immunology, University of Illinois College of Medicine

Anu Daniel, Ph.D., Licensing Manager, Innovation, Partners Healthcare

Drew Lowery, Ph.D., Director of Life Sciences and Group Leader, Biotechnology Pharmaceuticals Group, Global Prior Art, Inc.

Amy Mendel, J.D., SVP, Intellectual Property, Evelo Biosciences

Daniel Neuman, Ph.D., Group Leader, Chemistry & Materials, Global Prior Art, Inc.

SC8: Medical Dermatology Therapeutic R&D and Technical Innovation: Early Formulation Considerations, Utilizing New Tech for Med Derm R&D, CMC, Formulation Development and Late Stage Clinical - Part 2

CLICK for full agenda

Skin is the largest organ and dermatology is a very unique Therapeutic Area (TA) with a breadth of indications. Now is a dynamic time for the prescription dermatological drug industry due to consolidation, rising demand for therapies, and a deeper understanding of novel targets and disease pathways. This two-part short course provides a platform to discuss and learn about key challenges and special considerations of dermatology drug development.

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Yael Schwartz, Ph.D., CEO, Or-Genix Therapeutics, Inc.

Michael Sierra, Ph.D., Vice President, Head, LEO Science & Tech Hub USA, LEO Pharma

Thean Yeoh, Ph.D., Associate Research Fellow, Pfizer

Meng Zhou, Head, R&D, Contract Pharmaceutical Limited Canada

MONDAY, SEPTEMBER 19 | 3:30 - 6:30 PM

SC9: Targeting of GPCRs with Monoclonal Antibodies

While GPCRs 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 antibody discovery, assays to measure antibody binding, *in vitro* assays to measure functional activity of the antibody and review of promising GPCR targets and antibodies in the clinic.

Instructor:

Barbara Swanson, Ph.D., Director, Research, Sorrento Therapeutics, Inc.

SC12: Introduction to Gene Editing

This course will cover the basics of gene editing, the terminologies and the techniques, the applications, their strengths and limitations. The course will discuss the differences between the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)/Cas, Transcription Activator-like Effector Nucleases (TALENs), Zinc Finger Nucleases (ZFNs) and other gene editing systems. It will introduce the concepts of CRISPRi, CRISPRa, when and where they can be used. Alternatives of Cas9, basics that guide RNA design and mechanism of action, will all be discussed in an informal, interactive setting. There will be plenty of time allocated to open discussion, sharing of ideas and exchange of best practices, as people are updated on the scientific and technical progress being made in the field, as well as a quick overview of the regulatory landscape.

Instructors:

Stephanie Mohr, Ph.D., Lecturer, Genetics & Director, Drosophila RNAi Screening Center at Harvard Medical School

Claire Yanhui Hu, Ph.D., Senior Bioinformatician, Drosophila RNAi Screening Center, Department of Genetics, Harvard Medical School

Paul Enríquez, J.D., LL.M., Ph.D. Candidate, Structural and Molecular Biochemistry, North Carolina State University

** Separate registration required for Short Courses, Symposia, Training Seminar*

Short Courses:

CLICK TO REGISTER

MONDAY, SEPTEMBER 19 | 7:00 - 9:30 PM

Dinner Provided

SC13: Convergence of Immunotherapy and Epigenetics for Cancer Treatment

In recent years the understanding of both the immunotherapy and epigenetics of cancer has increased. This course will provide some details of how immunotherapy and epigenetic pathways interact and how they can be exploited to enhance the efficacy of current cancer treatments. The instructors will review recent scientific evidence and pre-clinical data that support the development of combination therapies and offer their perspectives on challenges that may have to be tackled along the way.

- Epigenetic regulation of anti-tumor immune responses
- Combinatorial approaches of epigenetic modifiers (HDAC inhibitors, hypomethylating agents) with checkpoint blockade and other emerging immunotherapeutic strategies

Instructors:

Eduardo M. Sotomayor, M.D., Director, GW Cancer Center, Professor, Medicine, Division of Hematology/Oncology, George Washington University

Alejandro Villagra, Ph.D., Assistant Professor, Department of Biochemistry and Molecular Medicine, School of Medicine and Health Sciences, The George Washington University

Gian Luca Araldi, Ph.D., Co-founder and CEO, Vela Therapeutics LLC and Co-Founder and CSO, Avanti Biosciences Inc.

WEDNESDAY, SEPTEMBER 21 | 7:00 - 9:30 PM

Dinner Provided

SC14: 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., Scientist, Ribon Therapeutics; formerly Postdoctoral Research Fellow, Discovery Oncology, Genentech

Vipin Suri, Ph.D., Head, Biology, Raze Therapeutic

SC15: Introduction to Allosteric Modulators and Biased Ligands of GPCRs

Allosteric modulators and pathway-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 in part to 'context-dependent phenomena'. Aimed at scientists working on GPCRs this course will provide information on the identification and validation of allosteric, pathway-biased drugs including emerging screening approaches, practical tips and tools for identification and validation, and the structural basis underlying such drugs.

Instructor:

Corey Hopkins, Ph.D., Associate Professor, Department of Pharmaceutical Sciences, University of Nebraska Medical Center

Annette Gilchrist, Ph.D., Professor, Pharmacology, Midwestern University

SC16: Functional Screening Strategies Using CRISPR and RNAi

This course will offer details on how the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)/Cas technology works, how to set up CRISPR-based screens and how to complement it with existing RNAi-based screens using proper analysis and follow-up studies. The instructors will share their experiences on how to go about evaluating reagents/libraries, designing and setting up assays, and interpreting results when dealing with complex biology and informatics. The applications of such functional genomics screens for drug discovery and disease modeling will be discussed, along with design and workflows when working with different model systems. Ideas and best practices will be shared in an informal, interactive setting and attendees will walk away with practical advice and resources.

Instructors:

Jennifer Smith, Ph.D., Deputy Director, ICCB-Longwood Screening Facility, Harvard Medical School

Scott Martin, Ph.D., Group Lead, Functional Genomics, Genentech Inc.

John Doench, Ph.D., Research Scientist, Broad Institute of Harvard and MIT

Eugen Buehler, Ph.D., Group Leader, Informatics, National Center for Advancing Translational Sciences, National Institutes of Health

** Separate registration required for Short Courses, Symposia, Training Seminar*

Tenth Annual Symposium | *September 19, 2016*

Next-Generation Histone Deacetylase Inhibitors

New Chemistries. New Biology. New Combination Therapies.

Histone deacetylases (HDACs) have proven to be a promising target for drug intervention and there are a number of HDAC inhibitors (HDACi) currently being tested at various pre-clinical and clinical stages. HDACi were primarily developed as anti-tumor agents for cancer, but many are now being explored for treating neurodegenerative, immunologic, metabolic, inflammatory and cardiovascular disorders. More recently, they are being developed as combination treatments along with small molecule cancer immunotherapy agents. However, much remains to be elucidated about the functional implications of modulating HDACs and understanding the signaling pathways that are triggered downstream.

BEST VALUE:

- September 19 Symposium: Next-Generation Histone Deacetylase Inhibitors
- September 20-21 Conference: Targeting Histone Methyltransferases and Demethylases
- September 21-22 Conference: Targeting Epigenetic Readers and Chromatin Remodelers

MONDAY, SEPTEMBER 19

7:00 am Registration Open and Morning Coffee

HDACi IN CANCER IMMUNOTHERAPY

8:30 Chairperson's Opening Remarks
Edward Holson, Ph.D., CSO, KDAc Therapeutics

» 8:40 KEYNOTE PRESENTATION: TARGETING HDACs AND HATs FOR CANCER THERAPY
Edward Seto, Ph.D., Professor, Biochemistry and Molecular Medicine, School of Medicine and Health Sciences, George Washington University
Histone deacetylases (HDACs) are potentially good targets for anti-cancer therapy because early studies indicate that HDAC inhibitors cause cell cycle arrest, revert cell transformation, and restrain tumor growth in animals. Recent data uncovered novel mechanistic insights of HDACs, which confirm and extend the tremendous value of further developing HDAC inhibitors for cancer treatment. These new findings also help to begin addressing challenges in exploiting HDAC inhibitors to ultimately benefit cancer patients.

9:10 Genetic and Pharmacologic Evidence of the Importance of HDAC8 Targeting in Tumor Immunotherapy
Wayne W. Hancock, M.D., Ph.D., Professor of Pathology and Chief of Transplant Immunology, Children's Hospital of Philadelphia and University of Pennsylvania
Our conditional targeting of HDAC8 in T-cells, as well as our use of isoform-selective HDAC8 inhibitors in WT mice, show that HDAC8 targeting can impair Foxp3+ Treg cell function while preserving conventional T-cell responses, and promote anti-tumor immunity in immunocompetent hosts. These data indicate new options in immuno-oncology beyond the PD-1 and CTLA4 pathways, and provide insights into the biology of HDAC8 in adaptive immunity.

9:40 Entinostat Development: Targeting Immune Suppressor Cells to Expand Utility of Immune Checkpoint Inhibitors
Peter Ordentlich, Ph.D., CTO and Founder, Syndax Pharmaceuticals
Entinostat is a class 1 HDAC selective inhibitor with direct effects on cancer cells and immune regulatory cells. Entinostat is being evaluated in a Phase 3 clinical trial for advanced hormone receptor positive breast cancer, and in Ph 1b/2 trials in combination with immune checkpoint inhibitors in melanoma, lung, ovarian, and triple-negative breast cancers. A review of the data and rationale for the combination of entinostat with immune checkpoint inhibitors will be provided.

10:10 Coffee Break

ROLE OF HDACi IN MODULATING CANCER PATHWAYS

10:40 HDACi Activate Innate Immune Cells and Regulatory Molecules
Pamela Munster., M.D., Professor, Department of Medicine; Director, Early Phase Clinical Trials Unit, and Leader, Developmental Therapeutics Program, University of California San Francisco
The effects of HDACi on tumor cell growth and survival have been well documented. However, HDACi also have immunomodulatory properties that could be important for anti-tumor responses and could be harnessed to enhance the activities of other anti-cancer agents. I will present data showing that HDACi can activate different components of the innate immune response and these properties are important for the anti-tumor effects of HDACi.

11:10 Design and Development of Novel, Orally-Active, Selective HDAC6 Inhibitors for the Treatment of Cancer
Stephen Shuttleworth, Ph.D., CSO, Karus Therapeutics Ltd.

11:40 Enhancing the Anti-Cancer Activity of Oncolytic Viruses by Using Histone Deacetylase Inhibitors
Antonio Marchini, Ph.D., Principal Investigator, Tumor Virology Division, German Cancer Research Center (DKFZ)
Oncolytic viruses (OVs) are promising anti-cancer agents due to their capacity to selectively kill cancer cells and to elicit robust anti-cancer immune responses. However, OVs alone are only rarely able to fully eradicate tumors in humans, calling for the rational design of combinatorial approaches. The possibility to enhance the anti-cancer potential of OVs by using histone deacetylase inhibitors will be discussed with a look into the future.

12:10 pm Enjoy Lunch on Your Own

** Separate registration required for Short Courses, Symposia, Training Seminar*

EMERGING HDAC CHEMISTRY & BIOLOGY

1:40 Chairperson's Opening Remarks

Timothy A. McKinsey, Ph.D., Associate Professor and Associate Division Head for Translational Research, and Director, Consortium for Fibrosis Research and Translation, Department of Medicine, Division of Cardiology, University of Colorado Denver

1:50 Light-Controlled Modulation of Gene Expression by Chemical Optoepigenetic Probes

Ralph Mazitschek, Ph.D., Assistant Professor, Harvard Medical School and Co-Director of the Chemical Biology Platform, Center for Systems Biology, Massachusetts General Hospital

We present a novel and generalizable approach, referred to as 'Chemo-Optical Modulation of Epigenetically-regulated Transcription' (COMET), that enables high-resolution, optical control of histone deacetylases based on photochromic inhibitors using visible light. The presented compounds have high isoform selectivity and exhibit a differential activity of three orders of magnitude in the presence of light.

2:20 Dual Inhibitor of HDAC and PDE5 Rescues Hippocampal Synaptic Impairment in Alzheimer's Disease Mice

Julen Oyarzabal, Ph.D., Director, Translational Sciences, Center for Applied Medical Research (CIMA), University of Navarra

First-in-class molecule (CM-414), inhibitor of PDE5 and HDACs, rescued the impaired long-term potentiation evident in hippocampal slices from APP/PS1 mice. Chronic treatment of Tg2576 mice with CM-414 diminished brain Aβ and pTau levels, increased the inactive form of GSK3β, reverted the decrease in dendritic spine density and reversed their cognitive deficits, at least in part by inducing the expression of genes related to synaptic transmission.

2:50 HDAC Inhibitors in Neurodegeneration: Challenges and Progress

Berkley A. Lynch, Ph.D., Senior Director, CNS Research, Rodin Therapeutics

Numerous studies in recent years have supported the role of histone deacetylase 2 (HDAC2) in synaptic plasticity, learning and memory, and in neurodegenerative diseases, including Alzheimer's disease. HDAC inhibitors have been shown to reverse decreased synaptic gene expression and improve cognitive function in animal models of neurodegenerative diseases. Critical challenges include managing peripheral toxicity by synthesizing HDAC2 isoform selective compounds, and related strategies.

3:20 Refreshment Break

4:00 Epigenetics in the Brain: Happier and Smarter Mice through Inhibition of HDACs

Matthew Jarpe, Ph.D., Associate Vice President of Biology, Acetylon Pharmaceuticals

Histone deacetylases play a number of important roles in the nervous system. The extranuclear deacetylase HDAC6 regulates microtubule function and activity of the glucocorticoid receptor. The primarily nuclear Class I deacetylases regulate expression of synapse formation through control of positive and negative regulators of synapse formation. Newly discovered brain penetrant HDAC inhibitors affect cognition and mood in rodent models of neurodegenerative and psychiatric disorders.

4:30 HDAC Inhibitors for Cardiometabolic Disease

Timothy A. McKinsey, Ph.D., Associate Professor and Associate Division Head for Translational Research, and Director, Consortium for Fibrosis Research and Translation, Department of Medicine, Division of Cardiology, University of Colorado Denver

Heart failure (HF) afflicts ~6 million people in the U.S. alone, and is associated with a 5-year mortality rate that approaches 50%. Obesity is a major risk factor for the development of HF. I will discuss our recent findings that suggest novel roles for specific HDAC isoforms at the interface between obesity and HF, and the potential for isoform-selective HDAC inhibitors for the treatment of cardiometabolic disease.

5:00 Therapeutically Targeting HDAC9 in Inflammatory Bowel Diseases

Dimitrios Iliopoulos, Ph.D., MBA, Professor, David Geffen School of Medicine and Founding Director, Center for Systems Biomedicine, University of California at Los Angeles

A novel epigenomic profiling assay revealed the importance of HDAC9 in IBD pathogenesis. HDAC9 was found to be activated in colonic biopsies from 3 different cohorts of IBD patients. It was found to regulate a network of 21 IBD susceptibility loci. A novel HDACi, having specificity for HDAC9 was developed and it blocked the inflammatory response in IBD cellular and animal models. Furthermore, we have developed an HDAC9 companion diagnostic test for IBD patient stratification.

5:30 Exploring the Role of HDAC6 in Myeloproliferative Neoplasms

Lanzhu Yue, Ph.D., Post-doctoral Fellow, Department of Immunology, H. Lee Moffitt Cancer Center

The JAK-STAT pathway is constitutively activated in myeloproliferative neoplasms (MPNs) and JAK2 is a clinically validated drug target. HDAC6 may modulate JAK activity at least in part through HSP90 deacetylation in certain transformed cell lines. We thus utilized highly selective HDAC6 inhibitors and HDAC6-deficient mice to investigate the role of HDAC6 in JAK-STAT activation and its therapeutic potential in MPN.

6:00 Close of Symposium

Second Annual Symposium | *September 19, 2016*

Strategies for Tackling Rare Genetic Diseases

Update on Scientific Breakthroughs and Novel Approaches

According to the National Institutes of Health, there are nearly 7000 rare diseases and more than 25 million Americans are suffering from one of them. Approximately 80% of these rare diseases are genetic in origin. Cambridge Healthtech Institute's symposium on Strategies for Tackling Rare Genetic Diseases will bring together leading scientists, clinicians, executives and experts who are deeply involved in bringing to market the treatments for such rare genetic disorders. This symposium will highlight scientific breakthroughs, use of innovative technologies and approaches to tackle translational challenges and bring together the right mix of people to discuss potential opportunities in this field.

RECOMMENDED ALL ACCESS PACKAGE:

- September 19 Symposium: Strategies for Tackling Rare Genetic Diseases
- September 20-21 Conference: Gene Therapy Breakthroughs
- September 21-22 Conference: Translating Cancer Genomics

MONDAY, SEPTEMBER 19

7:00 am Registration Open and Morning Coffee

EXPLORING NEW THERAPIES FOR TREATING RARE DISEASES

8:30 Chairperson's Opening Remarks

Colin Nichols, Ph.D., Carl Cori Professor in Cell Biology and Physiology, and Director of the Center for the Investigation of Membrane Excitability Diseases, Washington University School of Medicine

8:40 Gene Therapy for Lysosomal Storage Diseases

Christian Hinderer, Ph.D., Post-Doctoral Fellow, Laboratory of Dr. James Wilson, Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania

Enzyme replacement therapies have revolutionized the treatment of many lysosomal storage diseases (LSDs). However, the central nervous system manifestations of these disorders remain difficult to address due to the challenges of protein delivery beyond the blood-brain barrier. Using adeno-associated virus vectors to deliver genes encoding lysosomal enzymes to the CNS, we have developed a platform for efficient, long-term correction of CNS pathology associated with LSDs.

9:10 Messenger RNA (mRNA) Therapeutics for the Treatment of Rare Diseases

Ron Lahav, Ph.D., CEO, ART Bioscience Ltd.

The supplementation of proteins that are not expressed or are not functional is the most obvious application for mRNA-based drugs. The development of mRNA-based therapeutics is being accelerated by companies such as BioNTech and Moderna, which are supported by considerable venture capital inflows. The production of mRNA-based drugs is highly flexible, and represents a truly disruptive technology that may revolutionize the therapeutic intervention of diseases in general, and Duchenne Muscular Dystrophy (DMD) in particular.

9:40 Superior Effects of GSK-3 Inhibitors in the Treatment of Brain Cancers

Alan P. Kozikowski, Ph.D., Professor, College of Pharmacy, Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago and Actuate Therapeutics Inc.

Glioblastoma multiforme (GBM), also known as glioblastoma and grade IV astrocytoma, is the most common and aggressive of all brain cancers. Given the difficulty in treating GBM tumors, better agents are clearly needed. Here I disclose our results with a GSK-3 inhibitor to potentiate the inhibitory effects of irinotecan in PDX orthotopic xenografts. The results are fascinating and have led to orphan drug status approval with the FDA.

10:10 Coffee Break

USE OF VALIDATED PROGNOSTIC, PREDICTIVE FACTORS AND BIOMARKERS

10:40 A Drug Algorithm Decision Matrix Designed to Identify and Assemble a De-Risked Therapeutic Pipeline

Rachel Salzman, DVM, CSO, The Stop ALD Foundation

The ALD Connect consortium of researchers, clinicians, industry, and patient advocacy have established a robust algorithm for identifying promising preclinical and clinical agents in order to determine where and how limited resources and attention should be focused within the adrenoleukodystrophy and adrenomyeloneuropathy therapeutic pipelines. This process also identifies pre-competitive opportunities and laboratory workflow plans that will benefit multiple sponsors. This process can be applied to almost all rare genetic diseases.

11:10 Precision Medicine: Personalized Proteomics for the Diagnosis and Treatment of Idiopathic Inflammatory Disease

Vinit Mahajan, M.D., Ph.D., Assistant Professor of Ophthalmology and Visual Sciences, University of Iowa College of Medicine

A patient's genetic profile often does little to improve treatment in the near-term. To address an inherited inflammatory disease, we took a personalized proteomics approach using liquid biopsies of the diseased organ. Our proteomic analysis identified specific pathological cytokines and guided a targeted treatment with approved therapeutic drugs. Personalized therapy reversed the vision loss, illustrating how proteomics replaced a trial-and-error approach.

11:40 Sponsored Presentation *(Opportunity Available)*

12:10 pm Enjoy Lunch on Your Own

** Separate registration required for Short Courses, Symposia, Training Seminar*

INNOVATIVE SCREENS FOR UNCOVERING NEW TARGETS & MECHANISMS

1:40 Chairperson's Opening Remarks

Ronald Alfa, M.D., Ph.D., Director, Translational Biology, Recursion Pharmaceuticals LLC

1:50 Chemogenomic Screening to Identify New Targets for Rare Diseases

Lyn Jones, Ph.D., Head of Rare Diseases Chemistry and Chemical Biology Group Leader, Pfizer Worldwide Medicinal Chemistry

Bioinformatics analyses and computational chemistry techniques, combined with crowdsourcing efforts and human curation, were used to create a chemogenomic library (CGL) of well-defined, selective small molecule pharmacological agents that cover a significant number of biological targets. The CGL was screened in a phenotypic assay relevant to the treatment of myotonic dystrophy to identify potential therapeutic opportunities.

2:20 Repurposing as a Source of Chemical Probes for Target Identification

Paul C. Trippier, Ph.D., Assistant Professor in Pharmaceutical Sciences at the Texas Tech University Health Sciences Center School of Pharmacy

The neuronal ceroid lipofuscinoses (NCLs), although rare, are the most common neurodegenerative disorders of childhood. These diseases have poorly understood pathophysiology and no validated targets making for a highly challenging landscape for drug discovery. A unique library of designed chemical probes demonstrate protective effects in NCL phenotypic cell lines. We are employing these probes to identify targets of action for continued therapeutic development.

2:50 Whole Organism Repurposing Drug Screening Brings Forward Novel Targets for Spinocerebellar Ataxia Type 3

Patricia Maciel, Ph.D., Associate Professor and Senior Researcher at the School of Health Sciences of the University of Minho, Braga, Portugal

We have performed a motor phenotype-based screening of a library of mostly FDA-approved compounds in a *C. elegans* model of Spinocerebellar ataxia type 3 and identified several promising compounds, with effect on behavior but also mutant protein aggregation. The SSRI citalopram was validated as a very promising therapeutic compound in worm and mouse models, and serotonin signaling was proven to be a major modifier of SCA3 pathogenesis.

3:20 Refreshment Break

PURSUING DRUG REPURPOSING & COLLABORATIVE WORK

4:00 Rare Disease Drug Discovery at Scale

Ronald Alfa, M.D., Ph.D., Director, Translational Biology Recursion Pharmaceuticals LLC

4:30 Cantu Syndrome: Cardiovascular Complexity and Complications Revealed in a Sentinel Monogenic Disease

Colin Nichols, Ph.D., Carl Cori Professor in Cell Biology and Physiology, and Director of the Center for the Investigation of Membrane Excitability Diseases, Washington University School of Medicine

Cantu Syndrome is caused by mutations in two genes that underlie cardiovascular KATP channels. Disease features are manifold, ranging from hypertrichosis, to cardiomegaly, to low blood pressure, persistent PDA, migraine and lymphedema. To understand how the features arise, and to develop therapy for this and other diseases with such features, we have assembled a team of basic scientists, clinicians and drug discovery experts. These channels are targets of sulfonylurea drugs, bringing the chance for both new and already approved drugs to be used.

5:00 Drug Repurposing as a Strategy to Improve Patient Outcomes

Clare Thibodeaux, Ph.D., Director of Scientific Affairs, Cures Within Reach

Drug repurposing is a critical aspect of treating rare diseases, where basic research has lagged behind therapeutic impact. Cures Within Reach has been catalyzing repurposing research to improve patient outcomes since 2010. This presentation will highlight the repurposing research process, including questions to ask when evaluating a potential research project, strategies for bringing the different stakeholders together and success stories in rare diseases.

5:30 Close of Symposium

Second Annual Symposium | *September 19, 2016*

Understanding CRISPR: Mechanisms and Applications

New Biology. Alternative Apporaches. Emerging Uses.

Gene editing is rapidly progressing from being a research/screening tool to one that promises important applications downstream in drug development, cell and gene therapy. Cambridge Healthtech Institute's symposium on Understanding CRISPR: Mechanisms to Applications will bring together experts to talk about how gene editing works and where it can be best applied. How does the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)/Cas system, compare to other gene editing tools? What do we now know about the biology of CRISPR and what lessons have we learnt from working with RNA interference (RNAi)? Scientists will discuss new findings in CRISPR mechanisms and share their experiences leveraging the utility of CRISPR-based gene editing.

RECOMMENDED ALL ACCESS PACKAGE:

- September 19 Symposium: Understanding CRISPR: Mechanisms and Applications
- September 19 Short Course: Introduction to Gene Editing
- September 20-21 Conference: Advances in Gene Editing and Gene Silencing - Part 1
- September 21-22 Conference: Advances in Gene Editing and Gene Silencing - Part 2

MONDAY, SEPTEMBER 19

7:00 am Registration Open and Morning Coffee

USING CRISPR/Cas9 FOR FUNCTIONAL SCREENING

8:00 Chairperson's Opening Remarks

Scott Martin, Ph.D., Group Lead, Functional Genomics, Genentech Inc.

8:10 Comparing Arrayed siRNA and CRISPR Approaches Towards Functional Genomics Screening

Scott Martin, Ph.D., Group Lead, Functional Genomics, Genentech Inc.

RNAi has been a workhorse for loss-of-function screening. Although powerful, RNAi is hampered by false positives. New screening technologies based on CRISPR/Cas9 appear less prone to off-target effects. CRISPR/Cas9 screens are conducted in pooled formats. However, this format is not amenable to many assays. In an effort to expand its utility, we explored the use of arrayed CRISPR/Cas9 screening with synthetic CRISPR RNAs.

8:40 Getting from Alpha to Omega: Successfully Conceptualizing, Starting and Finishing CRISPR/Cas Screens

Ralph Garippa, Ph.D., Director, RNAi & Gene Editing Core Facility, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center

For certain molecular targets, to unravel the underlying biology of loss-of-function studies, it is simply not enough to potently knockdown the protein. In some cases, a complete functional knockout is called for. Here we summarize our early experiences, highlighting the strengths of this new powerful system but also calling attention to technical areas which need to be addressed and further improved as the technology moves deeper into the mainstream.

9:10 Genome Editing-Enabled HTS Assays for Genetically Inherited Disease Drug Discovery

James Inglese, Ph.D., Head Assay Development & Screening Technologies, National Center for Advancing Translational Sciences, National Institutes of Health

The targeted precision of genome editing was used in combination with advances in reporter gene design to modify the genetic loci of neurologic target genes to create HTS assays for compound library interrogation. Our goal was to identify transcriptionally active pharmacological agents acting by a variety of mechanisms, including through chromatin co-regulators accessible by our assay design. Specific case studies will serve to illustrate progress and findings to date.

9:40 Use of CRISPR and Other Genomic Technologies to Advance Drug Discovery

Namjin Chung, Ph.D., Head, Functional Genomics Platform, Discovery Research, AbbVie, Inc.

Advances in CRISPR gene editing and genomics technologies are rapidly changing biopharmaceutical R&D landscape, from target ID and validation, to drug mechanism of action, and to translational science. We will use vignettes of various genomics research applications within AbbVie R&D environment as a witness to this paradigm shift currently ongoing in the drug industry.

10:10 Coffee Break

10:40 Vignettes From the Bench: CRISPR Engineering Lymphoma Lines

Arthur L. Shaffer, III, Ph.D., Staff Scientist, Laboratory of Dr. Louis Staudt, Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health

CRISPR/CAS9 technology is a powerful tool that permits the easy exploration of human genetics using cell line models. Our lab focuses on understanding the wiring of lymphoma cells in an effort to discover new therapeutic options. I will relate some lessons we've learned as we adapt CRISPR/Cas9 to the study of lymphoma.

** Separate registration required for Short Courses, Symposia, Training Seminar*

11:10 PANEL DISCUSSION: Will Interference from CRISPR Silence RNAi?

Moderator: Scott Martin, Ph.D., Group Lead, Functional Genomics, Genentech Inc.

Participants: Session Speakers

Each speaker will spend a few minutes sharing their viewpoints and experiences using CRISPR/Cas system for functional screening and complementing it with RNAi screening. Attendees will have an opportunity to ask questions and share their opinions.

11:40 Sponsored Presentation *(Opportunity Available)*

12:10 pm Enjoy Lunch on Your Own

EMERGING APPLICATIONS OF CRISPR/Cas9

1:40 Chairperson's Opening Remarks

James Inglese, Ph.D., Head Assay Development & Screening Technologies, National Center for Advancing Translational Sciences, National Institutes of Health

1:50 MicroRNA Target Site Editing of Chondrocyte Master-Regulators in Primary Human Cells Using CRISPR-Cas9

Christine Seidl, Ph.D., Post-Doctoral Research Associate, Cell Signaling, Kennedy Institute of Rheumatology, Oxford University

MicroRNAs (miR) are important regulators of gene expression. Frequently, several potential target sites are located on a transcript but only one constitutes the dominant regulatory element. In this talk, a method will be discussed that allows for endogenous miR target site identification in primary human chondrocytes using CRISPR-Cas9 without the need of clonal selection of edited cells.

2:20 Massively Parallel Combinatorial Genetic Perturbation Screening with CRISPR-Cas9 in Human Cells

Cheryl H. Cui, Ph.D. Candidate, Harvard-MIT Division of Health Science and Technology, MIT

The systematic analysis of combinatorial gene functions is labor-intensive and challenging to scale. Our platform enables massively parallel screening of barcoded combinatorial gene perturbations in human cells. This technology leverages the simplicity of the CRISPR-Cas9 system for multiplexed targeting of specific genomic loci and the scalability of CombiGEM (Combinatorial Genetics En Masse)-based DNA assembly to construct barcoded combinatorial genetic libraries that can be quantified with high-throughput sequencing.

2:50 The Scientist's Guide to CRISPR Law

Paul Enríquez, J.D., LL.M., Ph.D. Candidate, Structural and Molecular Biochemistry, North Carolina State University

CRISPR systems are revolutionizing science and biotechnology. However, great uncertainty exists surrounding how the law will treat this nascent biotechnology. This talk provides an overview of the key regulatory issues every CRISPR scientist should know. Drawing parallels from stem cells and gene therapy, the talk highlights the importance of law and policy in fostering CRIPSR-based research, and makes recommendations for scientists studying CRISPR mechanisms and applications.

3:20 Close of Symposium

Inaugural Symposium | *September 19, 2016*

Autoimmunity - Small Molecule Approaches

Promising Drug Targets and New Chemical Entities for Lupus, RA, IBD and other Autoimmune Indications

This one-day symposium will cover the progress of new small-molecule drug candidates and the promise of emerging intracellular drug targets in the autoimmune disease arena.

RECOMMENDED ALL ACCESS PACKAGE:

- September 19 Symposium: Autoimmunity – Small Molecule Approaches
- September 20-21 Conference: Targeting Cardio-Metabolic Diseases
- September 21-22 Conference: Kinase Inhibitor Discovery

MONDAY, SEPTEMBER 19

7:00 am Registration Open and Morning Coffee

TARGETING THE INNATE IMMUNE SYSTEM AND RORG PATHWAYS

8:30 Chairperson's Opening Remarks
Kamal Puri, Ph.D., Director, Immunology & Inflammation, Celgene Corp.

8:40 FEATURED PRESENTATION: Modulators of RORγ for the Treatment of Autoimmune Diseases
Robert Hughes, Ph.D., Senior Associate Director, Small Molecule Discovery Research, Boehringer-Ingelheim
RORγ is a nuclear hormone receptor expressed in Th17 cells and distinct subsets of lymphoid cells, including innate lymphoid cells (ILC), and γδ T-cells. RORγ is required for Th17 cell and innate lymphocyte differentiation and regulates the transcription of the effector cytokines genes such as IL17A. We describe our approach, including screening, structure-based design and optimization, which led to the discovery of potent, selective ROR g modulators with favorable ADME properties.

9:40 Quinoline Tertiary Alcohols as RORgt Modulators for the Treatment of Psoriasis
Kristi Leonard, Ph.D., Associate Scientific Director, Immunology Research, Janssen Research & Development
The IL-23/IL-17 pathway plays an important role in the pathogenesis of psoriasis and biologics targeting IL-23 and IL-17 are clinically validated for the treatment of psoriasis. The inhibition of Th17 cell differentiation and IL-17 production through modulation of the RORgt receptor has generated much interest. Optimization of a high-throughput screening hit produced potent quinoline tertiary alcohol modulators of RORgt that are full inverse agonists.

10:10 Coffee Break

KINASE INHIBITORS FOR AUTOIMMUNE DISEASES

10:40 Discovery of the Highly Specific BTK inhibitor M2951 and Pharmacodynamic Modeling of BTK Occupancy versus Efficacy in RA and SLE models
Roland Grenningloh, Ph.D., Director, Preclinical Pharmacology, EMD Serono
Bruton's tyrosine kinase (BTK) is a promising target for the treatment of autoimmune disease such as RA and SLE. We have developed M2951, a novel, highly selective BTK inhibitor that is suitable for the treatment of chronic diseases. M2951 potently inhibits BCR- and FcR-mediated signaling and displays robust efficacy in RA and SLE models. Pharmacodynamic modeling showed that mean BTK occupancy of 80 % led to near complete disease inhibition.

11:10 Design of a JAK3 Inhibitor to Interrogate JAK Signaling
Suvit Thaisrivongs, Ph.D., Head of Immunoscience Chemistry, Pfizer Worldwide R&D
JAK3 signals in pair with JAK1 to transduce signal elicited from six known cytokines (IL-2, IL-4, IL-7, IL-9, IL-15 & IL-21) binding to the gamma-common chain cytokine receptors. We have identified a JAK inhibitor which showed JAK3 selective inhibition in biochemical and cellular assays. JAK inhibitors, targeting multiple JAK isoforms, are currently utilized in clinical practice or being developed for the treatment of various inflammatory and oncological diseases.

11:40 Sponsored Presentation *(Opportunity Available)*

12:10 pm Enjoy Lunch on Your Own

NEW TARGETS IN AUTOIMMUNITY

1:40 Chairperson's Opening Remarks
Irina Kufareva, Ph.D., Project Scientist, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego

1:50 Development of Immunoproteasome Subunit Selective Inhibitors
Dustin McMinn, Ph.D., Director, Head of Medicinal Chemistry, Kezar Life Sciences, Inc.
Selective immunoproteasome inhibition blocks inflammatory cytokine production and alters pro-inflammatory T-cell plasticity without affecting cell viability. Animal models of rheumatoid arthritis, type-I diabetes, multiple sclerosis, IBD, and lupus maintain normal immune function while responding well to small-molecule immunoproteasome inhibitors. Kezar's first candidate from this compound class, KZR-616, enters Phase I clinical trials this year. Our design toward selective immunoproteasome inhibitors will be discussed.

** Separate registration required for Short Courses, Symposia, Training Seminar*

2:20 KPT-350, a Selective Inhibitor of Nuclear Export (SINE) Compound, Targets Multiple Autoimmune Processes in Lupus

Margaret S. Lee, Ph.D., Vice President, Research & Translational Development, Karyopharm Therapeutics, Inc.

Exportin-1 (XPO1) is the sole nuclear exporter of multiple anti-inflammatory regulatory proteins and transcription factors relevant to systemic lupus erythematosus (SLE) disease pathology. KPT-350 is an orally bioavailable, reversible, small-molecule inhibitor of XPO1 with potent effects on murine lupus *in vivo*. KPT-350 treatment reduces germinal center reactions, auto reactive plasma cells, pro-inflammatory cytokines and autoantibodies leading to improvements in nephritis and proteinuria in lupus prone mice. Thus inhibition of XPO1 represents a novel therapeutic approach for SLE.

2:50 Mechanism of Action and Clinical Efficacy of mTOR Blockade in Lupus

Andras Perl, M.D., Ph.D., Professor of Microbiology and Immunology, Chief, Division of Rheumatology, State University of New York, UMU, College of Medicine

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting 1.5 million Americans with ~10% mortality over 5 years. Our recent studies unveiled a significant involvement of the mechanistic target of rapamycin (mTOR) in abnormal T-cell activation and lineage specification and autoantibody production in SLE. In accordance with a critical role for mTOR in pathogenesis, rapamycin reduced disease activity in a recently completed clinical trial.

3:20 Refreshment Break

4:00 Targeting Chemokine Receptors for Autoimmunity

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

Chemokines are a family of 7-12 kDa secreted proteins that control cell migration in the context of development, immunity, inflammation, and cancer, all by virtue of their interaction with 7TM cell surface receptors. Inhibitors of receptor-chemokine interactions attract immense attention in several therapeutic areas. By a combination of molecular modeling, biophysical and functional experiments, and X-ray crystallography we elucidate the structural determinants of these interactions, with the goal of rationalizing the discovery of therapeutics targeting the chemokine receptor axis.

4:30 Inhibition of an E2/E3 Ubiquitin Ligase Protein-Protein Interaction as a Novel Strategy to Counteract Autoimmune Diseases

Kamyar Hadian, Ph.D., Principal Investigator, Head of Assay Development and Screening Platform, HelmholtzZentrum München, Germany

This lecture will give insights into the discovery of a novel E2/E3 protein-protein interaction small molecule inhibitor that we were able to validate and characterize in a variety of biochemical as well as cell-based assays including primary mouse and human cells. More importantly, we can show that this first-in-class inhibitor is effective in pre-clinical autoimmune mouse models for Psoriasis as well as Rheumatoid Arthritis.

5:00 Targeting Inflammatory Bowel Diseases (IBD)

Kamal Puri, Ph.D., Director, Immunology & Inflammation, Celgene Corp.

5:30 Close of Symposium

Inaugural Symposium | *September 19, 2016*

NK Cell-Based Cancer Immunotherapy

Harnessing NK Cells for the Development of New Cancer Immunotherapies

To date, most immune-modulatory strategies have focused on agents and cell-based therapies developed to enhance T cell immunity. Recently, there has been a surge of interest in harnessing the relatively underexplored natural killer (NK) cell system for therapeutic intervention. A growing number of studies into elucidating NK cell biology, the development of pharmacological and genetic methods to enhance NK cell anti-tumor immunity, and the ability to expand NK cells *ex vivo* have set the stage for a new generation of cancer immunotherapies.

Cambridge Healthtech Institute's inaugural NK Cell-Based Cancer Immunotherapy Symposium will convene immuno-oncology researchers, cancer immunotherapy developers, and technology providers to discuss current challenges and opportunities from discovery NK immuno-oncology to clinical studies, share latest technologies and development approaches, as well as to provide updates on preclinical, clinical, and combination studies.

RECOMMENDED ALL ACCESS PACKAGE:

- September 19 Symposium: NK Cell-Based Cancer Immunotherapy
- September 20-21 Conference: Antibodies Against Membrane Protein Targets - Part 1
- September 21-22 Conference: Antibodies Against Membrane Protein Targets - Part 2

MONDAY, SEPTEMBER 19

7:00 am Registration Open and Morning Coffee

KEYNOTE SESSION: ADVANCES IN NK CELL-BASED CANCER IMMUNOTHERAPY

8:30 Chairperson's Opening Remarks

Jeffrey Miller, M.D., Professor, Medicine; Deputy Director, Masonic Cancer Center; Roger L. and Lynn C. Headrick Chair in Cancer Therapeutics, University of Minnesota

8:40 Novel Ways to Target and Activate NK Cells to Treat Cancer

Jeffrey Miller, M.D., Professor, Medicine; Deputy Director, Masonic Cancer Center; Roger L. and Lynn C. Headrick Chair in Cancer Therapeutics, University of Minnesota

We have performed a number of clinical trials using NK cell infusions. IL-15, a natural cytokine that is critical for NK cell development and homeostasis, will be discussed. We have recently developed a class of molecules that combine antigen specificity and IL-15's proliferative activity together into a novel class of multifunction molecules we call trispecific killer engagers (TriKEs). Lastly, we have discovered a new subset of NK cells termed adaptive with properties of immunologic memory induced by cytomegalovirus that mediate potent CD16 signaling.

9:10 Off the Shelf, Engineered Allogeneic Natural Killer Cell Therapeutics: aNK, haNK, taNK

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

NantKwest has developed the NK cell line NK-92 into an "off the shelf" activated NK (aNK) cell therapeutic. The safety of aNK as well as their activity against a broad range of cancers have been confirmed in several Phase I clinical trials in the U.S., Canada and Europe. The aNK cell platform has been bioengineered to incorporate a high-affinity antibody binding Fc-receptor (haNK). Both aNK and haNK cells can be equipped with chimeric antigen receptors (CARs) (called taNK) to further optimize targeting and potency in the therapeutic setting.

9:40 The Bispecific CD30/CD16A Antibody AFM13 Induces Strong NK Cell Cytotoxicity towards CD30+ Hodgkin Lymphoma and Is Enhanced by Checkpoint Modulation

Thorsten Gantke, Ph.D., Project Leader, Affimed

AFM13 is an NK cell-engaging CD30/CD16A bispecific tetravalent antibody currently in clinical development. While monotherapy with AFM13 was potent itself, significant synergy was observed in the AFM13 and anti-PD-1 combination *in vitro*, and in *in vivo* PDX models with human CD30+ HL tumors. Analysis of the tumors revealed a strong correlation between tumor growth inhibition and levels of tumor-infiltrating NK cells, T-cells, myeloid cells and intratumoral cytokines such as IFN-gamma.

10:10 Coffee Break

NK CELL IMMUNO-ONCOLOGY AND CLINICAL STUDIES

10:40 Harnessing Adaptive NK Cells in Cancer Therapy

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

We have recently completed a Phase I/II clinical trial with transfer of haploidentical NK cells to patients with high-risk myelodysplastic syndrome. Six of the 16 treated patients achieved morphological complete remission and five of these underwent allogeneic stem cell transplantation resulting in long-term survival in four patients. These results suggest that adoptive transfer of allogeneic NK cells may hold utility as a bridge to transplant in patients who are refractory to induction therapy.

** Separate registration required for Short Courses, Symposia, Training Seminar*

11:10 Update on Systemic and Locoregional Cancer Immunotherapy with IL-21-Expanded NK Cells

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

We translated our IL-21-based NK cell expansion platform to clinical grade and scale and initiated 7 clinical trials that administer NK cell immunotherapy with high cell doses or repeated dosing in transplant, adjuvant, or stand-alone settings. We will discuss the importance of STAT3 signaling in this setting, describe early outcome and correlative data from these studies, and present preclinical data supporting future clinical trials that build on this platform.

11:40 Sponsored Presentation *(Opportunity Available)*

12:10 pm Enjoy Lunch on Your Own

NK CELL-BASED DEVELOPMENT PLATFORMS FOR CANCER IMMUNOTHERAPY

1:40 Chairperson's Opening Remarks

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

1:50 oNKord® - The First Allogeneic, "Off-the-Shelf" NK Cell Product in Oncology

Jan Spanholtz, Ph.D., CSO, Glycostem Therapeutics

Glycostem's NK cell product (oNKord®) has successfully passed Phase I clinical trial (elderly AML patients) showing safety and biological activities including response on MRD leading to prolonged PFS and OS. These results show that oNKord® can be safely infused in elderly AML patients. After infusion, NK cells repopulate, mature and migrate to bone marrow. The reduction in MRD lead to a sustained CR in elderly AML patients resulting in an improved overall survival (90% after 1 year) for AML patients at this age.

2:20 Potent *ex vivo* Expanded, Human CD34+ Cord Blood-Derived Natural Killer Cells for Cancer Immunotherapy

Xiaokui Zhang, Ph.D., Director, Research & Development, Celgene Cellular Therapeutics

Celgene Cellular Therapeutics has established a cultivation process to generate human NK cells from umbilical cord blood (UCB) CD34+ cells with substantial cytolytic activity against several human tumor cell lines, primary AML and primary MM cells. A Phase I, multicenter, open-label, dose-escalating safety study of PNK-007 infusion with subcutaneous recombinant human IL-2 in adults with relapsed and/or refractory AML will be discussed.

2:50 Naïve Human-Induced Pluripotent Stem Cells: An Ideal Platform for Developing Off-the-Shelf and Genetically Enhanced Natural Killer Cell Adoptive Therapeutics

Bahram (Bob) Valamehr, Ph.D., MBA, Executive Director, Reprogramming Biology, Fate Therapeutics Inc.

Coupling the unique capacity of our naïve human-induced pluripotent stem cell (hiPSC) technology platform to efficiently facilitate multiple genomic modifications at the single hiPSC level with our ability to accurately recapitulate the stages of early embryonic hematopoiesis towards the definitive program, we demonstrate a viable method for the derivation of engineered hematopoietic cells, including NK cells, from hiPSCs in a highly scalable manner. The hematopoietic cells generated can be successfully cryopreserved and banked.

3:20 Refreshment Break

TECHNOLOGICAL INNOVATIONS ENABLING NK CELL-BASED CANCER IMMUNOTHERAPY

4:00 Autologous *ex vivo* Expanded NK Cells for Solid Tumor Immunotherapy

Ali Ashkar, D.V.M., Ph.D., Professor, Pathology and Molecular Medicine, McMaster Immunology Research Centre, McMaster University

Recent advances in NK cell expansion and activation have generated renewed interest in adoptive NK cell therapy for cancers. We have expanded NK cells from blood of breast, lung and ovarian cancer patients and have investigated their activities against autologous primary tumor cells. In addition, we have established xenograft models with the primary tumors to study the anti-tumor activities of autologous NK cells against primary tumor cells *in vivo*. *Ex vivo* expanded NK cells survive and proliferate *in vivo* in the presence of autologous PBMCs.

4:30 Novel CARs Introduced into NK Cells Facilitate Potent Tumor Cell Killing that Results in Tumor Regression

Rohit Duggal, Ph.D., Director, Experimental Cellular Therapy, Sorrento Therapeutics

This presentation features an introduction of chimeric antigen receptors (CARs), which provide homing and specificity to cytotoxic cells of the immune system. Novel CARs isolated from Sorrento's G-MAB library targeting various tumor antigens will be described. The characterization of the NK cells modified to express these CARs will also be described.

5:00 Understanding of NK Cell Effector Functions: A Single-Cell Lab-on-a-Chip Perspective

Tania Konry, Ph.D., Assistant Professor, Department of Pharmaceutical Sciences, Northeastern University

Here we present a novel single-cell method of analyzing the mechanisms underlying the cellular interactions of NK cells with multiple myeloma cells. The integrated droplet microfluidics device developed by our group permits compartmentalization of cell pairs and secreted products within sub-nanoliter volumes and thereby controls cell-to-cell communication by limiting it to interactions between the co-encapsulated cells. It allows monitoring of both contact-dependent and contact-independent cellular interactions simultaneously.

5:30 Close of Symposium

PART ONE | MONDAY, SEPTEMBER 19 | 8:00 - 11:00 AM

SC4: Understanding Mechanisms, Novel Targets and Pathways & Industry Case Studies

NOVEL DRUG DEVELOPMENT FOR DERMATOLOGY AND SOME PROMISING PATHWAYS

8:00 am Chairperson's Opening Remarks and Welcome

8:05 Lay of the Land: Novel Drug Development for Dermatology and Some Promising Pathways

Michael Sierra, Ph.D., Vice President, Head, LEO Science & Tech Hub USA, LEO Pharma

- The current and future treatments for skin diseases (e.g., psoriasis, eczema, AK/NMSC)
- The direction diagnostics are moving for predicting, monitoring and diagnosing skin disease
- Integrating data into the digital universe to empower patients

8:30 Biology of Skin Disease Mechanisms: Promising Pathways

M. Joyce Rico, M.D., MBA, Chief Medical Officer, Novan, Inc.

Understanding Mechanisms, Novel Targets and Pathways in: Inflammatory Skin Diseases and Skin Cancer

INDUSTRY CASE STUDIES

8:50 A New Therapeutic Approach to Control Aberrant Beta Catenin Signaling in Hyperproliferative Skin Disorders

Jack Leonard, Ph.D., Professor, Microbiology and Physiological Systems, UMASS Medical School

The biology behind Psoriasis and inflammatory skin disease

Identification of a novel and untapped therapeutic target for silencing the dys-regulated β-catenin signaling that drives hyperproliferation in skin disease

9:10 Topical Treatment of Hormonal Skin Aging: The 3rd Wave of Innovation

Yael Schwartz, Ph.D., CEO, Or-Genix Therapeutics, Inc.

After the onset of menopause, women lose more than 30% of skin collagen rendering skin to become wrinkled and thin

- There has been nothing new and scientifically-validated to improve aging skin since the retinoids and alpha-hydroxy acids
- Smart chemical engineering can replace the estrogen that declined during menopause without risk of systemic exposure

9:30 Prurisol, a New Small Molecule to Treat Psoriasis, Completed Phase 2 Trial and now Geared up for Phase 3

Krishna Menon, Ph.D., President and Chief Scientific Officer, Cellceutix Corporation

- Strategy and science behind breakthrough oral small molecule, which is an immune-modulator affecting IL-20 and PRINS
- Lessons from discovery and early development, opening up a new pathway to treat psoriasis
- Obtaining a 505B(2) pathway; Key challenges and lessons on how this innovative small molecule was developed

9:50 Coffee Break

INTERACTIVE PANEL DISCUSSION WITH PRESENTERS, PANELISTS AND ATTENDEES

10:05 Understanding Mechanisms, Novel Targets and Pathways to Further Novel Therapeutic Development in Dermatology

Moderator:

Michael Sierra, Ph.D., Vice President, Head, LEO Science & Tech Hub USA, LEO Pharma

Panelists:

Jack Leonard, Ph.D., Professor, Microbiology and Physiological Systems, UMASS Medical School

Krishna Menon, Ph.D., President and Chief Scientific Officer, Cellceutix Corporation

M. Joyce Rico, M.D., MBA, Chief Medical Officer, Novan, Inc.

Yael Schwartz, Ph.D., CEO, Or-Genix Therapeutics, Inc.

Thean Yeoh, Ph.D., Associate Research Fellow, Pfizer

Meng Zhou, Head, R&D, Contract Pharmaceutical Limited Canada

- The current and future treatments for skin diseases (e.g., psoriasis, eczema, AK/NMSC): Where will the opportunities be for innovation?
- Understanding Mechanisms, Novel Targets and Pathways in: Inflammatory Skin Diseases (acne, rosacea, psoriasis, atopic dermatitis, eczema); Cancer and Pre-Cancers of the Skin (SCC, BCC, AK, non-melanoma); and Scleroderma and Other Orphan Skin Diseases
- What are we learning about Autoimmune Diseases in Dermatology and what does this mean for new therapies?
- What are some business models for this Therapeutic Area (biotech approach, big pharma approach, repurposing, out/in-licensing, public-private partnerships, managing a dual portfolio of Rx+Cosmeceuticals) and how do you evaluate them?

10:55 Closing Comments

11:00 Part 1 of Course Ends, Part 2 Begins at 12:00 pm

PART TWO | MONDAY, SEPTEMBER 19 | 12:00 - 3:00 PM

SC8: Early Formulation Considerations, Utilizing New Tech for Med Derm R&D, CMC, Formulation Development and Late Stage Clinical

KEY CHALLENGES AND SPECIAL CONSIDERATIONS OF DERMATOLOGY DRUG DEVELOPMENT

12:00 Chairperson's Opening Remarks and Welcome

12:05 Biology of Skin Disease: Exploring New Mechanisms of Action & Understanding Internal/External Development Challenges
Hans Hofland, Ph.D., Vice President Research and Nonclinical Development, Dermira, Inc.

- Understanding the pathophysiology of inflammatory skin disease (acne, rosacea, psoriasis, atopic dermatitis)
- Exploring new pathways and mechanisms of action to treat these skin diseases
- Using new preclinical models to provide proof of mechanism in development of novel therapies
- Beyond the science, understanding internal (optimizing resources) and external challenges (payers and medical need, planning for regulatory hurdles) of dermatology drug development
- Choosing where to innovate: Some tips on making the decision in which programs and projects to invest

EARLY FORMULATION CONSIDERATIONS & UTILIZING NEW TECH FOR MED DERM R&D

12:30 Drug Delivery into Skin: Early Formulation Considerations
Thean Yeoh, Ph.D., Associate Research Fellow, Pfizer

- Molecular properties for topical delivery and integration of topical delivery into compound selection funneling
- Research formulation versus commercial formulation: design consideration
- When to trigger commercial formulation development?

12:55 Utilizing New Tech for Med Derm Research and Development
Krishna Menon, Ph.D., President and Chief Scientific Officer, Cellceutix Corporation

- Biomarkers, Diagnostics, Imaging
- Target Engagement
- Skin Pharmacokinetics (PK)

1:25 Coffee Break

CMC, FORMULATION DEVELOPMENT AND LATE STAGE CLINICAL

1:40 CMC, Formulation Development and Late Stage Clinical
Meng Zhou, Head, R&D, Contract Pharmaceutical Limited Canada

- You get your molecule, now what? API sourcing, Formulation Development, Tox batch/POC CTM supply, Non-clinical and POC study
- Phase I/II: CTM supply, Formulation Development to enhance penetration and delivery, building manufacturing process knowledge, tech transfer
- Phase III: Final formulation, CTM supply, tech transfer for future commercialization
- Special CMC consideration regarding 505(b)2
- Bioequivalence for topical generics

INTERACTIVE PANEL DISCUSSION WITH PRESENTERS, PANELISTS AND ATTENDEES

2:10 Understanding Key Challenges and Special Considerations of Dermatology Drug Development
Moderator:
Yael Schwartz, Ph.D., CEO, Or-Genix Therapeutics, Inc.
Panelists:
Hans Hofland, Ph.D., Vice President Research and Nonclinical Development, Dermira, Inc.
Krishna Menon, Ph.D., President and Chief Scientific Officer, Cellceutix Corporation
Michael Sierra, Ph.D., Vice President, Head, LEO Science & Tech Hub USA, LEO Pharma
Thean Yeoh, Ph.D., Associate Research Fellow, Pfizer
Meng Zhou, Head, R&D, Contract Pharmaceutical Limited Canada

- Understanding challenges specific to the disease and the application
- Early formulation considerations & utilizing new tech for med derm R&D
- CMC, formulation development and late stage clinical considerations
- Choosing where to innovate: Making the decision in which programs and projects to invest

2:55 Closing Comments

3:00 Part 2 of Course Ends

Visit the registration page for pricing discounts and registration options.

Inaugural Training Seminar

Data Visualization

for Effective Drug Discovery Decisions

Cambridge Healthtech Training SEMINARS
Comprehensive and Practical Training

Day 1: Wednesday, September 21 - 3:30 pm - 6:30 pm

Day 2: Thursday, September 22 - 8:30 pm - 5:00 pm

Instructor:

Georges Grinstein, Ph.D., Professor Emeritus, Computer Science Department and Director, Institute for Visualization and Perception Research, University of Massachusetts Lowell; CSO, Weave Visual Analytics

About this Training Seminar:

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

- Introduction to Visualization Techniques, Theory and Systems
- Analytics and Visualization Integrations
- Visual Analytics and Applications for Drug Discovery

About the Instructor:

Dr. Georges Grinstein is Professor of Computer Science at the University of Massachusetts Lowell, past head of its Bioinformatics and Cheminformatics Program, Co-director of its Institute for Visualization and Perception Research, and CSO of Weave Visual Analytics. He received his Ph.D. in Mathematics from the University of Rochester. His work is broad and interdisciplinary, ranging from perceptual foundations of visualization to techniques for high-dimensional visualization, with the emphasis on the modeling, visualization, and analysis of complex information systems, most often b3iomedical in nature. He has over 40 years in academia with extensive private consulting, over 100 research grants, products in use nationally and internationally, several patents, numerous publications in journals and conferences, a book on interactive data visualization, founded several companies, and has been the organizer or chair of national and international conferences and workshops in Computer Graphics, in Visualization, and in Data Mining. He has mentored over 30 doctoral students and hundreds of graduate students. He has been on the editorial boards of several journals in Computer Graphics and Data Mining, a member of ANSI and ISO, a NATO Expert, and a technology consultant for various public agencies. For the last ten years he has co-chaired the InfoVis and VAST contests and has been developing the open source interactive visual analytics platform called Weave.

Who Should Attend:

Directors, Managers, Researchers, and Scientists from Pharma, Biotechs, Academia, Government and Healthcare Organizations working in Analytics, Bioinformatics, Biostatistics and Statistical Programming, Business Development, Chemistry, Computational/Medicinal Chemistry, Drug Discovery, Discovery and Translational Science, R&D, and Translational Systems Biology

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

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

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

** Separate registration required for Short Courses, Symposia, Training Seminar*

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Fifth Annual | *September 20-21, 2016*

Targeting Histone Methyltransferases and Demethylases

Tools and Strategies for Modulating Histone Methylation

The Targeting Histone Methyltransferases and Demethylases meeting focuses on targeting the histone methylome as a therapeutic strategy. Adding to the more established series of histone methyltransferase inhibitors, histone demethylase inhibitors have also advanced into clinical studies, and are now showing favorable outcomes. Notably, recent interest and success in developing inhibitors against arginine methyltransferase enzymes, JmjC domain demethylases and lysine-methyl readers have substantially deepened the possibilities of regulating chromatin environments via histone methylation.

BEST VALUE:

- September 19 Short Course: RNA as a Small Molecule Drug Target
- September 20-21 Conference: Targeting Histone Methyltransferases and Demethylases
- September 21-22 Conference: Targeting Epigenetic Readers and Chromatin Remodelers

TUESDAY, SEPTEMBER 20

7:00 am Registration Open and Morning Coffee

DISCOVERY AND DESIGN OF NOVEL LYSINE DEMETHYLASE INHIBITORS

8:05 Chairperson's Opening Remarks

Xiaodong Cheng, Ph.D., Professor, Department of Biochemistry, Emory University

» 8:10 KEYNOTE PRESENTATION: PROBING THE FUNCTIONS OF HISTONE DEMETHYLASES

Richard Hopkinson, Ph.D., Research Fellow, Schofield Group, Chemistry Research Laboratory, Department of Chemistry, University of Oxford

Two families of oxidative enzymes catalyzing histone demethylation have been defined – the LSD and JmjC demethylases (KDMs). The lecture will discuss efforts to assign functions to the KDMs (and related enzymes), at biochemical, cellular, and whole organism levels, employing genetic, biochemical and chemical methods. Challenges in the field will be highlighted including with respect to medicinal targeting of KDMs.

8:50 Structure-Based Approaches to Identify Novel and Specific Inhibitors for Different Subfamilies of Jumonji Demethylases

Udo Oppermann, Ph.D., Professor, Molecular Biology; Director, Molecular Laboratory Sciences, Botnar Research Centre; Principal Investigator, Epigenetics and Metabolism, Structural Genomics Consortium, University of Oxford

Inhibitor development has been hampered by structural information and identification of novel chemotypes. We here present a fragment screening approach combining high-throughput structure determination (based on >200 novel ligand complexes) and functional profiling (for chemotype prioritisation) against four subfamilies of human histone demethylases (KDM3, 4, 5, 6) leading to identification of novel chemotypes that were used to generate novel, selective inhibitors.

9:20 Structure, Kinetics and Inhibition of KDM5A, a Key Drug Target in Histone H3 Lysine 4 Demethylation

Xiaodong Cheng, Ph.D., Professor, Department of Biochemistry, Emory University

KDM5 is unique among the Jumonji domain-containing histone demethylases in that there is an atypical insertion of a DNA-binding ARID domain and a histone-binding PHD domain into the Jumonji domain, which separates the catalytic domain into two fragments (JmjN and JmjC). We demonstrated that internal deletion of the ARID and PHD1 domains has a negligible effect on *in vitro* enzymatic kinetics of KDM5 enzymes. Making use of the minimal catalytic domain constructs, I will discuss the structure, kinetics, and inhibition of KDM5A.

9:50 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

10:35 Jumonji Inhibition Affects Multiple Disease Pathways

Elisabeth Martinez, Ph.D., Assistant Professor, Pharmacology, Hamon Center for Therapeutic Oncology Research, University of Texas Southwestern Medical Center

Jumonji histone demethylases are deregulated in multiple disorders including cancer and control transcriptional patterns. Here, I will discuss our findings on the impact of pharmacological inhibition of these enzymes on multiple cellular pathways across various cancer types. We find that Jumonji inhibition affects surprising biological cascades beyond transcription including hedgehog signaling and translation efficacy.

11:05 Targeting Histone Lysine Methylation for Cancer Therapy

Yongcheng Song, Ph.D., Associate Professor, Department of Pharmacology, Baylor College of Medicine

Despite still being in an early stage, discovery and development of histone methylation modulators have been growing rapidly in the past few years. We are particularly interested in histone H3 lysine 79 (H3K79) methyltransferase DOT1L, lysine specific demethylase 1 (LSD1), and mutations of isocitrate dehydrogenases (IDH), which are drug targets for several types of cancer. Efforts in the discovery and development of potent small molecule inhibitors and their preclinical activity testing are presented.

11:35 Characterization of a Novel LSD1 Inhibitor in Preclinical Models of Cancer

Sang Hyun Lee, Ph.D., Principal Scientist, Pharmacology, Incyte Corporation

LSD1 is an epigenetic eraser that has been implicated in the development and progression of various cancers. INCB059872 is a potent and selective LSD1 inhibitor. This presentation will focus on the characterization of INCB059872

in preclinical models of cancer, both as a single agent and in combination with standard of care and other novel agents.

12:05 pm Screening for Modulators of Methylation and Demethylation Using Bioluminescent Homogenous Detection Assays

Sponsored by Promega

Hicham Zegzouti, Ph.D., Senior Research Scientist, Research and Development, Cellular and Biochemical Technologies, Promega Corporation

Because of the implication of methylation in cancer and other diseases, methyltransferases and demethylases have become validated drug targets. To facilitate the identification of selective and potent inhibitors of these enzymes for drug discovery and as basic research tools, we developed bioluminescent assays for all methyltransferases and JmjC demethylases based on SAH and succinate detection, respectively.

12:35 Session Break

12:45 Luncheon Presentation *(Sponsorship Opportunity Available)*
or Lunch on Your Own

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

DISCOVERY AND DEVELOPMENT OF NOVEL LYSINE METHYLTRANSFERASE INHIBITORS

2:05 Chairperson's Remarks

Masoud Vedadi, Ph.D., Principal Investigator, Molecular Biophysics, Structural Genomics Consortium; Assistant Professor, Department of Pharmacology and Toxicology, University of Toronto

2:15 Substrate Specificity of Histone Methyltransferases

Masoud Vedadi, Ph.D., Principal Investigator, Molecular Biophysics, Structural Genomics Consortium; Assistant Professor, Department of Pharmacology and Toxicology, University of Toronto

Here we will discuss substrate specificity of histone methyltransferases with a focus on contribution of multiple methyltransferases to methylation of specific histone marks such as H3K4, H3K9 and H4K20. We will also present the latest progress in our quest for discovery of potent, selective and cell active inhibitors of HMTs.

2:45 Targeting Protein Methyltransferases via Novel Models of Interaction

Minkui Luo, Ph.D., Associate Member & Associate Professor, Chemical Biology Program, Memorial Sloan Kettering Cancer Center

In contrast to genetic perturbation small-molecule inhibitors can act via distinct modes of interaction (MOI) and thus lead to different outcomes even if being designed against the same target. My laboratory leveraged multiple approaches to identify PMT inhibitors with novel MOI. Our sinefungin analogues are SAM-competitive inhibitors with the potency and selectivity for multiple PMTs. Our SET8 inhibitors covalently modify the target. The selectivity of these PMT inhibitors largely stems from their abilities to target the distinct conformations.

3:15 AptaFluor Methyltransferase Assay: A Homogenous, Universal HMT Assay Based on a Microbial Riboswitch

Sponsored by BellBrook Labs

Meera Kumar, M.S., Senior Applications Scientist, Research & Development, BellBrook Labs

We used a microbial metabolite-sensing riboswitch that binds SAH with nanomolar affinity and exquisite selectivity to develop a universal methyltransferase activity assay with fluorescence polarization and time resolved Förster resonance energy transfer signals. The AptaFluorTM Methyltransferase Assay enables sensitive (100nM SAM), robust, universal detection of HMTs in an HTS-compatible format.

3:45 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

4:25 Fragment-Based Discovery of WDR5-MLL1 Disruptors

Shaun Stauffer, Ph.D., Research Assistant Professor, Pharmacology; Associate Director, Medicinal Chemistry, Vanderbilt University

Fragment-based screening methods coupled with X-ray crystallography offer the potential for rapid optimization of high-affinity ligands for target protein. We have utilized this approach to afford small molecule disruptors of the WDR5-MLL1 complex with subnanomolar affinity.

4:55 Discovery of Selective Inhibitors for Protein Methyltransferases

Jing Liu, Ph.D., Assistant Professor, Structural and Chemical Biology, Icahn School of Medicine at Mount Sinai

Selective small-molecule inhibitors of PMTs have been pursued by both academia and the pharmaceutical industry as chemical tools for testing biological and therapeutic hypotheses. To create high-quality selective inhibitors of HMTs, our lab has taken a systematic approach by targeting the HMT substrate binding groove, cofactor binding site, and potential allosteric binding site. This presentation will focus on our recent research progresses on the PMT projects related to type I PRMTs, G9a/GLP, and SETD8.

5:25 Welcome Reception in the Exhibit Hall with Poster Viewing

6:25 End of Day

WEDNESDAY, SEPTEMBER 21

7:30 am Registration Open and Morning Coffee

ASSESSING THE THERAPEUTIC POTENTIAL OF LYSINE METHYLTRANSFERASE INHIBITORS

8:00 Chairperson's Opening Remarks
Dominique Verhelle, Ph.D., MBA, Strategic Advisor, Third Rock Ventures

8:10 FEATURED PRESENTATION: The EZH2 Inhibitor Tazemetostat as a Potential Therapeutic for Non-Hodgkin Lymphoma and Genetically Defined Solid Tumors
Scott Ribich, Ph.D., Director, Biological Sciences, Epizyme
This presentation will include a discussion of the current model for tazemetostat's mechanism-of-action in NHL, based upon emerging preclinical, translational and clinical data. Additionally, the therapeutic potential of tazemetostat in genetically defined solid tumors will be presented. This discussion will include preclinical and clinical data for tazemetostat undifferentiated tumors with deficient expression of the mSWI/SNF subunits, such as INI1 and SMARCA4.

8:40 Targeting Histone Lysine Methylation in Cancer
Shilpi Arora, Ph.D., Senior Scientist, Biology, Constellation Pharmaceuticals
The development of small molecule KMT and KDM inhibitors constitutes an attractive approach to selectively alter histone methylation patterns and transcriptional programs, ultimately allowing for the suppression of aberrant gene expression in cancer cells. The discovery of KMT and KDM inhibitors, their application in various oncology contexts, as well as mechanistic consequences of target inhibition will be discussed.

9:10 Development of Lysine-Specific Demethylase Inhibitors for Oncological and Neurodegenerative Disease
Tamara Maes, Ph.D., Co-Founder, Vice President & CSO, Oryzon Genomics S.A.
Here we will discuss the advances in the development of ORY-1001, a potent selective inhibitor of LSD1, for the treatment of leukemia and other malignancies; and of ORY-2001, a dual inhibitor of LSD1 and MAO-B, for the treatment of neurodegenerative diseases. ORY-1001 is currently in a Phase I/IIa trial in recurrent or recalcitrant acute leukemia nearing completion. We have recently initiated a Phase I trial with ORY-2001 to assess the compounds' tolerability, pharmacokinetics and pharmacodynamics in healthy young and elderly volunteers.

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

ADVANCES IN TARGETING ARGININE METHYLTRANSFERASE PRMT5

10:25 PRMT5 Inhibition as a Therapeutic Strategy for Solid and Heme Malignancies
Olena Barbash, Ph.D., Investigator, Oncology R&D, GlaxoSmithKline
This presentation will highlight new data by GSK on targeting PRMT5 as a therapeutic strategy for solid and hematological malignancies.

10:55 PRMT5 is an Oncogenic Driver and an Ideal Therapeutic Target for Solid and Hematologic Cancers
Robert A. Baiocchi, M.D., Ph.D., Associate Professor, Division of Hematology, Department of Internal Medicine, The Ohio State University
Recent work has identified the PRMT5 enzyme to be dysregulated and acting as an oncogenic driver in both solid and hematologic malignancies. PRMT5 overexpression exhibits these driver properties by methylating both histone and non-histone proteins promoting transcriptional silencing of regulatory genes, supporting cell signaling networks (BCR, PI3K), cell cycle (CYCLIND1), and survival (P53, NFkB) and growth pathways (MYC). Here we will summarize the biologic relevance of PRMT5 in malignant disease and our efforts in developing highly selective inhibitors.

11:25 Enjoy Lunch on Your Own

12:50 pm Plenary Keynote Program *(See page 3 for details.)*

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

3:20 End of Conference

Fourth Annual | *September 21-22, 2016*

Targeting Epigenetic Readers and Chromatin Remodelers

Targeting Protein-Protein Interactions of Epigenetic Readers

The Targeting Epigenetic Readers and Chromatin Remodelers meeting focuses on one of the most exciting areas of discovery research, targeting chromatin modifying proteins, particularly those responsible for the recognition of the histone code written in acetyl and methyl marks. With several clinical trials underway, and many discovery programs initiated, particular interest has been given to targeting the BET family of proteins across a diverse range of therapeutic indications. Widespread efforts have also begun to develop novel chemical matter targeting non-BET bromodomain proteins to assess their therapeutic potential. Most recently, interest and success in developing chemical tools targeting methyl-lysine readers have substantially expanded the possibilities of modulating chromatin states by disrupting epigenetic reading.

BEST VALUE:

- September 19 Short Course: RNA as a Small Molecule Drug Target
- September 20-21 Conference: Targeting Histone Methyltransferases and Demethylases
- September 21-22 Conference: Targeting Epigenetic Readers and Chromatin Remodelers

WEDNESDAY, SEPTEMBER 21

11:20 am Conference Registration Open

11:25 Enjoy Lunch on Your Own

12:50 pm Plenary Keynote Program *(See page 3 for details.)*

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

DEVELOPING NOVEL BROMODOMAIN INHIBITORS

3:20 Chairperson's Opening Remarks

Claes Wahlestedt, M.D., Ph.D., Leonard M. Miller Professor & Associate Dean, Therapeutic Innovation, Miller School of Medicine, University of Miami

3:25 FEATURED PRESENTATION: Targeting BET Protein Degradation for New Cancer Therapeutics

Shaomeng Wang, Ph.D., Warner-Lambert/Parke-Davis Professor, Medicine; Professor, Medicine, Pharmacology and Medicinal Chemistry; Director, Center for Therapeutics Innovation, University of Michigan

BET proteins have emerged as exciting new therapeutic targets for cancer and other human conditions. Several classes of potent and selective small-molecule inhibitors of BET proteins have been discovered and a number of them are now in clinical development. Preclinical and clinical data have demonstrated both the promises and limitations of BET inhibitors as new therapeutics. Recently, a new small-molecule approach has been employed to target degradation of BET proteins through the design of bifunctional, Proteolysis-Targeting Chimera (PROTAC) molecules. Based upon our new classes of highly potent small-molecule BET inhibitors, we have designed and optimized highly potent and efficacious small-molecule degraders of BET proteins. We have performed critical and extensive evaluation of our BET degraders for their therapeutic potential and mechanism of action in models of acute leukemia and solid tumors.

4:05 Structure-Based Design of an *in vivo* BRD9 Probe

Laetitia Martin, Ph.D., Research Laboratory Head & Project Leader, Medicinal Chemistry, Boehringer Ingelheim

We set out to develop an inhibitor compound targeting the bromodomain of BRD9. The discovery and structure-based optimization of a potent and selective BRD9 bromodomain inhibitor series will be presented. These compounds modulate BRD9 bromodomain cellular function and display anti-tumor activity in an AML xenograft model. Two chemical probes, BI-7273 and BI-9564, were identified that should prove useful in further exploring BRD9 bromodomain biology in both *in vitro* and *in vivo* settings.

4:35 Development of Cell-Active Low Nanomolar, Selective CREBBP Bromodomain Inhibitors

Dimitrios Spiliotopoulos, Ph.D., SNF SystemsX.ch Postdoctoral Fellow, Department of Biochemistry, University of Zurich

A fragment-based docking campaign led to identification of novel ligands of the CREBBP bromodomain, which were efficiently derivatized into potent inhibitors. These compounds displayed remarkable selectivity for the CREBBP inhibitors over other human bromodomain subfamilies (Xu et al., J Med Chem, 2016, Unzue et al., J Med Chem, 2016). Recently, the combination of computational methods (viz. docking and molecular dynamics) and protein X-ray crystallography has guided the development of inhibitors with double-digit nanomolar affinity coupled with more than 1,000-fold selectivity for the CREBBP bromodomain over the most promiscuous bromodomain, BRD4(1). Importantly, activity in a cellular context was confirmed by FRAP and further evaluations of the inhibitors are currently ongoing in suitable biological models.

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

5:40 Inducible Binding Conformations that Enabled the Identification of Selective *in vitro* Bromodomain Inhibitors from a Common Scaffold

Terry Crawford, Senior Scientific Researcher, Medicinal Chemistry, Genentech, Inc.

Through a fragment screening approach we identified 6-methyl pyrrolopyridone as a highly ligand efficient scaffold. We discovered that lipophilic substitutions on this scaffold directed towards the conserved water network found in the bromodomain binding pocket were able to induce two distinct binding conformations, either through rearrangement of the conserved water network or the formation of a hydrophobic channel directed below the waters. These inducible conformations led to the identification of selectivity handles for BRD7/9, CECR2, and TAF1-BD2.

6:10 FEATURED PRESENTATION: Bromodomain Chemical Probes to Explore Epigenetic Pathways

Oleg Fedorov, Ph.D., Group Leader, Biophysics and Biochemical Screening, Structural Genomics Consortium and Target Discovery Institute, University of Oxford

The Structural Genomics Consortium (SGC) together with major pharmaceutical companies initiated the program of developing chemical tool compounds for these proteins. We developed more than 30 chemical probes which are released to the academic community without restriction of use. I will highlight the recent progress in the field of bromodomain inhibitors, especially outside the BET subfamily. We achieved a good coverage of the family and identified the potential application in multiple disease areas such as inflammation and osteoporosis.

6:40 End of Day

THURSDAY, SEPTEMBER 22

7:30 am Registration Open and Morning Coffee

EVALUATING THERAPEUTIC POTENTIAL

8:30 Chairperson's Remarks

Norman C.W. Wong, M.D., FRCPC, Professor of Medicine and Biochemistry & Molecular Biology, Cumming School of Medicine, University of Calgary; CSO & Co-Founder, Resverlogix

8:35 Mechanism-Based Combination Strategies for BET Inhibitors in Solid and Hematologic Cancers

Anastasia Wyce, Ph.D., Investigator, R&D Oncology, GlaxoSmithKline

BET (bromodomain and extra-terminal) family proteins are transcriptional regulators known to control expression of genes involved in cell growth and oncogenesis. Selective small molecule BET inhibitors prevent binding of BET proteins to acetylated histones and inhibit transcriptional activation of BET target genes. BET inhibitors attenuate cell growth and survival in a number of hematologic and solid tumor cancer models. Data will be presented characterizing the single agent activity, mechanisms of action, and potential combination strategies for GSK525762, a potent and selective pan-BET inhibitor in early clinical development.

9:05 Tumor-Intrinsic and Immune Modulatory Activities of the BET Inhibitor INCB054329

Phillip Liu, Ph.D., Associate Director, Applied Technology, Incyte Corporation

BET proteins may play a role in shaping the tumor environment in addition to direct inhibition of malignant cells. We have investigated the efficacy of INCB054329, a novel BET inhibitor currently in Phase I clinical studies, as monotherapy and in combination with targeted agents and immune checkpoint blockade. Data will be presented from syngeneic tumor models using immunocompetent mice that characterize the effect of INCB054329 on markers of immune cell function. The results support a model in which BET inhibition can block tumor growth by complementary tumor-intrinsic and immune modulatory mechanisms.

9:35 Novel Bromodomain Inhibitors with Broad Activities

Claes Wahlestedt, M.D., Ph.D., Leonard M. Miller Professor & Associate Dean, Therapeutic Innovation, Miller School of Medicine, University of Miami

A collaborative effort between the University of Miami, Epigenetix Inc. and the NeoMed Institute has resulted in the generation of a range of novel bromodomain inhibitors. Some of these molecules showed unexpected efficacy and potency in *in vitro* and *in vivo* in cancer models. Notably, unlike reference compounds, these compounds bind to not only the BET bromodomains but also to several other bromodomain-containing proteins. Some of the resulting synergies will be discussed.

9:50 Speaker has Cancelled ~~Novel BET Bromodomain Inhibitors to Treat Disease~~

~~*Christopher Burns, Ph.D., Laboratory Head, ACRF Chemical Biology Division, The Walter and Eliza Hall Institute of Medical Research*~~

~~We have identified chemically novel series of BET bromodomain proteins based on a novel benzodiazpine scaffold, that are readily prepared and possess potent activity in cells. Studies to improve their molecular and ADME properties will be presented. We have also explored apoptosis mechanisms involved in BET bromodomain inhibitor activity as well as their potential in osteosarcoma.~~

10:05 Selected Presentation (Late-Breaking Research): Development of Dual-Activity Small Molecules that Target BRD4 and Dopamine Receptor D2

Jeffrey W. Strovel, Ph.D., President and CEO, ConverGene

ConverGene has developed a series of small molecule inhibitors of BET family of bromodomain-containing proteins. BET family includes BRD4, an epigenetic reader protein that mediates expression of MYC oncogene. Thus, BRD4 is considered a cancer therapeutic target to indirectly suppress MYC expression. Our compounds showed high activity in a binding test against BRD4; exhibited long half-lives and 100% bioavailability upon oral administration; profoundly suppressed MYC expression both *in vitro* and *in vivo*; and strongly inhibited growth of AML cells in a mouse xenograft model. Importantly, a lead candidate has been developed from a subclass of our BET inhibitors that showed additional activity against dopamine receptor D2 (DRD2). In addition to being a therapeutic target for psychiatric diseases, DRD2 is emerging as a therapeutic target for cancer/leukemia stem cells. Therefore, our dual activity BET inhibitors may hold promise as a therapeutic that inhibits MYC pathway and maintenance of cancer stem cells.

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

11:10 BET Bromodomain Inhibitors in Prostate Cancer

Irfan A. Asangani, Ph.D., Assistant Professor, Cancer Biology, Perelman School of Medicine, University of Pennsylvania

BET bromodomain inhibitors were shown previously to attenuate AR signaling in mCRPC; here, we demonstrate the efficacy of bromodomain and extraterminal (BET) inhibitors in enzalutamide-resistant prostate cancer models. Interestingly, AR-variant 7 (AR-v7), which has been reported to be associated with resistance to antiandrogen treatments, was markedly repressed by BET inhibitors. AR antagonists, enzalutamide, and ARN509 exhibit enhanced prostate tumor growth inhibition when combined with BET inhibitors, JQ1 and OTX015, respectively.

11:40 FEATURED PRESENTATION: Bromodomain Inhibition of the Transcriptional Coactivators CBP/EP300 as a Therapeutic Strategy to Target the IRF4 Network in Multiple Myeloma

Andrew Conery, Ph.D., Senior Scientist II, Constellation Pharmaceuticals

Selective targeting of multiple myeloma cell lines through CBP/EP300 bromodomain inhibition is the result of direct transcriptional suppression of the lymphocyte-specific transcription factor IRF4, which is essential for the viability of myeloma cells, and the concomitant repression of the IRF4 target gene c-MYC. Ectopic expression of either IRF4 or MYC antagonizes the phenotypic and transcriptional effects of CBP/EP300 bromodomain inhibition, highlighting the IRF4/MYC axis as a key component of its mechanism of action.

12:10 pm Selected Presentation (Late-Breaking Research): NUE7770 - A BET-BD1 Selective Chemical Probe with Potent Cellular and *in vivo* Anti-Inflammatory Activity

Jimmi Seitzberg, Ph.D., Research Scientist & Project Manager, Nuevolution AS

Several inhibitors of BET proteins are in clinical development primarily for oncology indications but inhibition of the BET BDs has also proven efficacious in numerous animal models of inflammatory diseases. As most BET inhibitors reported in the literature are pan-BET inhibitors, the contribution of individual BDs to the biological activity of BET proteins is currently unclear, and domain-specific inhibition (intra- and/or inter-BET) remains largely unexplored. We have developed NUE7770, a chemical probe with high potency and pronounced selectivity towards the first BD (BD1) of the BET family. We have characterized this compound in various cellular assays of inflammation. In the BioMap Diversity Plus system, NUE7770 shows potent and very selective quenching of markers in the BT system with very little activity outside of immune-related systems. In pharmacokinetic experiments, NUE7770 shows good rodent exposure with dose-proportionality up to super-therapeutic doses and high oral bioavailability. We will present the results of *in vivo* efficacy studies conducted with NUE7770 in several mouse models of inflammatory disease.

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

BET BROMODOMAIN INHIBITORS IN THE CLINIC

2:15 Chairperson's Remarks

Andrew Conery, Ph.D., Senior Scientist II, Constellation Pharmaceuticals

2:20 Apabetalone (RVX-208); Actions of a Selective BET Inhibitor that Lowers Cardiovascular Risk in Humans

Norman C.W. Wong, M.D., FRCPC, Professor of Medicine and Biochemistry & Molecular Biology, Cumming School of Medicine, University of Calgary; CSO & Co-Founder, Resverlogix

Apabetalone (RVX-208) is a selective inhibitor with affinity for the second ligand binding domain in BET proteins. This feature of RVX-208 gives it unique activity compared to a pan BET inhibitor like JQ-1. For example, in liver cells, JQ-1 affects gene expression of more than 700 genes while RVX-208 modulates activity of less than 50. The actions of RVX-208 have been tested in clinical trials that have enrolled nearly 1000 patients, many of whom have cardiovascular disease (CVD). The results arising from these trials point to a variety of beneficial effects of RVX-208 in affecting the complement, coagulation, inflammatory, metabolic and lipid pathways. These actions of RVX-208 may underlie the observed improvement in CVD outcomes. Findings from our studies support the ongoing Phase III clinical trial called BETonMACE to examine the use of apabetalone (RVX-208) in CVD patients with diabetes mellitus receiving standard-of-care therapy.

2:50 New BET Inhibitor Combination Strategies and Lessons Learned from Clinical Trials Conducted 25 Years Ago

Jonas Nilsson, Ph.D., Professor, Experimental Cancer Surgery, Surgery, Sahlgrenska Cancer Center, University of Gothenburg

We have found new combination therapies of cancer. We also have strong evidence showing that BET inhibitors were already in Phase II trials in the 1980s. The BETi we disclose is a BD2-selective. During this presentation attendees will learn about the trial results from the first BETi in Phase II. They will also learn about the chemical starting point of BD2-selective BETi.

3:20 Session Break

TARGETING METHYL-LYSINE AND ACETYL-LYSINE READERS

3:25 Chairperson's Remarks

Tatiana Kutateladze, Ph.D., Professor, Department of Pharmacology, Anschutz Medical Campus, University of Colorado

3:30 PHD and YEATS Domains and Their Roles in Epigenetic Mechanisms

Tatiana Kutateladze, Ph.D., Professor, Department of Pharmacology, Anschutz Medical Campus, University of Colorado

Plant homeodomain (PHD) fingers and YEATS domains are found in proteins involved in a wide array of fundamental biological processes including transcription, replication, DNA damage repair, cell differentiation and survival. These domains comprise the largest families of epigenetic readers, capable of recognizing PTMs (posttranslational modifications) of histones. Here, we detail the binding mechanisms and biological functions of the readers that select for methylated, acetylated, and unmodified histone H3 tails. We compare the specificities and discuss the significance of crosstalk between PTMs and the consequence of combinatorial readout for the recruitment of these readers to chromatin.

4:00 Targeting Chromatin Regulation via Methyl-Lysine Reader Chemical Probes

Lindsey Ingerman James, Ph.D., Research Assistant Professor, Center for Integrative Chemical Biology and Drug Discovery, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill

Plant homeodomain (PHD) fingers and YEATS comprise the largest families of epigenetic readers, capable of recognizing PTMs histones. Here, we detail the binding mechanisms and biological functions of the readers that select for methylated, acetylated, and unmodified histone H3 tails. We compare the specificities and discuss the significance of crosstalk between PTMs and the consequence of combinatorial readout for the recruitment of these readers to chromatin.

4:30 Speaker has Cancelled ~~Identification and Validation of CBX2 as a Therapeutic Target~~

~~*Cheryl D. Helgason, Ph.D., Senior Scientist, Experimental Therapeutics, British Columbia Cancer Agency Research Centre*~~

~~Our studies have identified the chromodomain protein CBX2, an epigenetic reader, as a potential oncogene and therapeutic target in numerous tumor types. In this presentation we will present data demonstrating the identification of CBX2 as an oncogene worthy of targeting. We will also demonstrate that targeting CBX2 in prostate cancer cells results in significant cell death. Future perspectives will focus on attempts to target CBX2, as well as to identify co-interactors that may serve as complimentary therapeutic targets.~~

4:30 Selected Presentation (Late-Breaking Research): Ultra-Sensitive Regulation of the Nucleosome Binding of FACT, a Chromatin Remodeler, through Multiple Phosphorylation to Its Intrinsically Disordered Regions (IDRs)

Shin-ichi Tate, Ph.D., Professor, Graduate School of Science, Hiroshima University

A chromatin remodeler, Facilitates Chromatin Transcription (FACT), engages in the transcription in the context of chromatin by destroying nucleosome structures. FACT comprises two subunits, SPT16 and SSRP1; SPT16 binds to H2A/H2B histone components, while SSRP1 binds to nucleosomal DNA. We reported the long IDR in SSRP1 is responsible for the DNA binding and IDR is subjected to multiple phosphorylation. The IDR in SSRP1 is divided into two parts. The N-terminal IDR is rich in acidic residues, thus called as AID, while the C-terminal part preferentially contains basic residues, names as BID. AID part has 10 potential phosphorylation sites, and actually 8 sites are phosphorylated by CKII. We found the extent of the phosphorylation to AID changes the binding ability of FACT to nucleosome and the binding ability changes according to the number of phosphate in a sigmoidal manner, 'ultra-sensitive' response. We reported the sensitivity is achieved by the scissoring motion to make the AID and BID folded; the increased level of the phosphorylation stabilizes intra-molecular AID-BID contact form to mask the basic resides in BID to diminish the binding ability of the IDR. In the scissoring motion, the Gly-rich region located at the junction between AID and BID should roles as a hinge. To explore if the scissoring motion is functionally relevant, we studied the regulatory roles of Gly-rich region in the scissoring motion by using the mutations to the part. The NMR structure and dynamics analyses in combination with biochemical assays revealed how the Gly-rich part participates in the ultra-sensitivity of FACT.

5:00 Close of Conference

Fourth Annual | *September 20-21, 2016*

Targeting the Ubiquitin Proteasome System

Chemically Modulating Protein Homeostasis by Targeting DUBs and E3 Ligases

The ubiquitin proteasome system (UPS) is an essential and highly regulated mechanism operating to tightly control intracellular protein degradation and turnover. While the concept of targeting specific components of the UPS to modulate protein degradation has been around for some time now, recent advances in our understanding of the role and molecular mechanisms of UPS components in disease – mainly DUBs and E3 ligases, the development of high-quality chemical tools and novel inhibitors, as well as preclinical studies demonstrating chemical tractability and therapeutic potential – have dramatically taken the ubiquitin proteasome system from an improbable target class, to one of the most robust and exciting arenas for the discovery of novel drugs. Indeed, over the past year, we have seen the generation of several DUB inhibitors poised for clinical development, novel approaches and inhibitors disrupting the protein-protein interactions of E3 ligases and UPS-mediated degradation of target proteins.

Cambridge Healthtech Institute's fourth 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.

BEST VALUE:

- September 19 Short Course: RNA as a Small Molecule Drug Target
- September 20-21 Conference: Targeting the Ubiquitin Proteasome System
- September 21-22 Conference: Targeting Epigenetic Readers and Chromatin Remodelers

TUESDAY, SEPTEMBER 20

7:00 am Registration Open and Morning Coffee

STRUCTURAL AND MECHANISTIC INSIGHTS INTO DEUBIQUITINASE ENZYMES AND INHIBITORS

8:05 Chairperson's Opening Remarks

Tauseef R. Butt, Ph.D., President and CEO, Progenra, Inc.

8:10 FEATURED PRESENTATION: Mechanism and Specificity of Deubiquitinating Enzyme USP14

Daniel Finley, Ph.D., Professor, Cell Biology, Harvard Medical School

USP14 can suppress degradation of a subset of proteasome substrates, raising the question of USP14 specificity. We studied this using the N-terminus of cyclin B as an *in vitro* model. Surprisingly, what seems to be the dominant aspect of USP14 specificity is that it will not remove ubiquitin groups from substrates, or will do so only quite slowly, when only a single ubiquitin chain is present on the substrate. Multichain specificity could possibly bias degradation towards single-chain substrates produced by highly processive ubiquitin ligases.

8:50 Developing a Quantitative Profiling Platform to Evaluate Endogenous Deubiquitinase Activity

Ingrid E. Wertz, M.D., Ph.D., Senior Scientist, Discovery Oncology and Early Discovery Biochemistry, Genentech, Inc.

Here we describe the development of an analysis platform that combines DUB ABPs with chemical multiplexing, targeted mass spectrometry, novel internal reaction standards, and a customized statistical analysis program. We illustrate the efficacy of this technology by evaluating the activity of disease-relevant DUBs, in analyzing DUB inhibitor selectivity, and in evaluating how compounds that target other components of the ubiquitin/proteasome system impact DUB activity.

9:20 Chemical Proteomics in the Ubiquitin System – DUBs Take Center Stage

Benedikt Kessler, Ph.D., Professor, Biochemistry and Life Science Mass Spectrometry, Target Discovery Institute, Nuffield Department of Medicine, University of Oxford

The ubiquitin-specific protease USP7 has been suggested as a potential drug target for a variety of cancers, in particular for Multiple Myeloma, where the treatment with small molecule USP7 inhibitors overcomes resistance to clinical proteasome inhibitors. We have utilized ubiquitin-based active site probes in combination with chemical proteomics workflows to determine the potency and selectivity of deubiquitylating enzyme (DUB) inhibitors in cancer cell culture models.

9:50 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

DESIGN AND DEVELOPMENT OF NOVEL DUB INHIBITORS

10:35 Ubiquitin Pathway: A New Frontier in Cancer Immunotherapy

Tauseef R. Butt, Ph.D., President and CEO, Progenra, Inc.

Progenra has identified ubiquitin pathway enzymes that control pivot points of immune regulation. Small molecules discovered at Progenra suppress Treg function and unleash anti-tumor Teffector cell responses to melt the tumors in immune competent mice. Detailed mechanisms of the de-ubiquitylase USP7 that are critical for the activity of Tregs will be described. These inhibitors synergistically augment the activity of anti-PD1 antibody, CAR T cell therapy, and cancer vaccines.

11:05 Development and Exploitation of Ubi-*Plex*™, an Innovative Purpose-Built Drug Discovery Platform for Deubiquitinating Enzymes (DUBs)

Gerald Gavory, Ph.D., Director, Head of Biology, Almac Discovery

Herein, we describe the design and implementation of Ubi-*Plex*™, a purpose-built drug discovery platform for the identification and optimization of DUB inhibitors. We will highlight the versatility and robustness of Ubi-*Plex*™ by describing a new case study spanning *de novo* target identification, focused library screening and hit finding to the development of novel, potent and selective inhibitors ready for lead optimization.

11:35 Discovery of Highly Selective Macrocyclic Inhibitors of DUBs: USP9x as a Case Study

Deborah Dodge, Senior Scientist, Ensemble Therapeutics

We have developed a productive discovery engine based on DNA-encoded libraries of macrocycles that has successfully identi ed novel lead compounds against a number of ubiquitin-speci c proteases. Compounds targeting USP9x exemplify the potency, selectivity, and "drug likeness" potential of this class of inhibitors. Specifcally, these highly selective compounds targeting USP9x exhibit mixed non-competitive and competitive modes of inhibition and possess cytotoxic cellular activity.

12:05 Comprehensive Profiling of DUB Inhibitors

Mark Albertella, D.Phil., Director, Biology, Medivir

As part of our internal drug discovery efforts, we have comprehensively characterized a number of publically disclosed DUB inhibitors in our in-house biochemical and biophysical assays. We outline some of our observations, highlighting the low specificity or high chemical reactivity of a number of these compounds, and the caution that should be exercised when interpreting data obtained using these molecules as pharmacological tools.

12:35 Session Break

12:45 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Lunch on Your Own**

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

HARNESSING THE UPS FOR TARGETED PROTEIN DEGRADATION

2:05 Chairperson's Remarks

Gerald Gavory, Ph.D., Director, Head of Biology, Almac Discovery

» 2:15 KEYNOTE PRESENTATION: PROTACS: INDUCED PROTEIN DEGRADATION AS A THERAPEUTIC STRATEGY

Craig M. Crews, Ph.D., Lewis B. Cullman Professor of Molecular, Cellular, and Developmental Biology; Professor, Chemistry & Pharmacology, Yale University

The current "inhibitor-/binder-based" paradigm of pharmaceutical control has inherent limitations. Based on an "event-driven" paradigm, this approach offers a novel, catalytic mechanism to irreversibly inhibit protein function, namely, the intracellular destruction of target proteins. This is achieved via recruitment of target proteins to the cellular quality control machinery using PROTACs (Proteolysis Targeting Chimeras) that can achieve "degradation concentrations" (DC_{50} values) in the picomolar range.

2:45 Targeted Protein Degradation by Small Molecules

Alessio Ciulli, Ph.D., Associate Professor, Chemical & Structural Biology, School of Life Sciences, University of Dundee

The application of small molecules to induce selected protein degradation is emerging as a transformative new modality of chemical intervention in drug discovery. We have previously shown that linking a VHL ligand that we had discovered with a pan-BET inhibitor creates highly selective PROTAC molecule MZ1. MZ1 triggers preferential intracellular degradation of Brd4, leaving the homologous BET members untouched, and exhibits greater anti-proliferative activity in leukemia cell lines than pan-BET inhibition.

3:15 Sponsored Presentation *(Opportunity Available)*

3:45 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

4:25 A New Paradigm in Drug Action: Differentiated Gain of Function among IMiD Structural Analogues Binding the E3 Ubiquitin Ligase, CRL4CRBN

Brian Cathers, Ph.D., Executive Director, Co-Leader & Head, Drug Discovery, Protein Homeostasis Thematic Center of Excellence, Celgene

Solution of the ligand bound CRBN target complex provides a rationale for distinguishing "gain of function" targeting of key substrates, including the transcription factors aiolos (IKZ3) and ikaros (IKZ1) or the protein kinase CK1alpha. Is it possible to harness the action of a single E3 ligase and direct its actions toward new and different substrates? The presentation will explain distinctions among existing drugs, address guiding concepts applicable to determining new therapeutic applications, and point its therapeutic power.

4:55 PANEL DISCUSSION: Hijacking the UPS for Targeted Protein Degradation

The design of small molecules to hijack the UPS has received significant attention over the past year, with several groups working on various strategies, and biotech spinouts formed. Collectively, this has formed a new paradigm in drug action, and is poised to have broad application and utilization in drug discovery. This panel, comprised of experts at the forefront of this field, will discuss these approaches, applications, and challenges for further development.

Moderator:

John "Jay" Schneekloth Jr., Ph.D., Investigator, Chemical Biology Laboratory; Head, Chemical Genetics Section, Center for Cancer Research, National Cancer Institute, NIH

Panelists:

Craig M. Crews, Ph.D., Lewis B. Cullman Professor of Molecular, Cellular, and Developmental Biology; Professor, Chemistry & Pharmacology, Yale University

Andrew Phillips, Ph.D., CSO, C4 Therapeutics

Alessio Ciulli, Ph.D., Associate Professor, Chemical & Structural Biology, School of Life Sciences, University of Dundee

Brian Cathers, Ph.D., Executive Director, Co-Leader & Head, Drug Discovery, Protein Homeostasis Thematic Center of Excellence, Celgene

5:25 Welcome Reception in the Exhibit Hall with Poster Viewing

6:25 End of Day

WEDNESDAY, SEPTEMBER 21

7:30 am Registration Open and Morning Coffee

DIVERSE STRATEGIES MODULATING THE UPS

8:00 Chairperson's Opening Remarks

Benedikt Kessler, Ph.D., Professor, Biochemistry and Life Science Mass Spectrometry, Target Discovery Institute, Nuffield Department of Medicine, University of Oxford

8:10 Discovery of Novel Protein Homeostasis Inhibitors Utilizing FORMA's Drug Discovery Engine

Stephanos Ioannidis, Ph.D., Director, Medicinal Chemistry, FORMA Therapeutics

Protein homeostasis is important in oncology, neurodegenerative and other medical disorders involving a network of pathways controlling the biogenesis, folding, transport and degradation of proteins. Using FORMA's innovative chemical libraries approach has led to the discovery of novel protein homeostasis inhibitors which allowed the understanding of pathways and targets associated with excessive protein degradation. The discovery of novel protein homeostasis inhibitors provides the potential for widespread clinical applications.

8:40 Inhibition of an E2/E3 Protein-Protein Interaction as a Novel Strategy to Interfere with E3 Ligase Activity

Kamyar Hadian, Ph.D., Principal Investigator & Head, Assay Development and Screening Platform, HelmholtzZentrum München

This lecture will give insights into the discovery of a novel E2/E3 protein-protein interaction small molecule inhibitor that we were able to validate and characterize in a variety of biochemical as well as cell-based assays including primary mouse and human cells. More importantly, we can show that this first-in-class inhibitor is effective in preclinical autoimmune mouse models for psoriasis as well as rheumatoid arthritis.

9:10 Targeting the Proteasome for Cancer Chemotherapy

Sai Pulukuri, Ph.D., Senior Scientist & Project Team Leader, Millennium: The Takeda Oncology Company

Experienced leader and creative scientist with >9 years of oncology discovery experience. Leader and manager of team of researchers and biology project leader supporting oncology programs from early target validation to Phase I studies. Led a first in class ubiquitin pathway oncology target from inception to successful IND filing and Phase I. Experience in the drug discovery process from early target validation to translational research.

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

TARGETING THE PPIs OF E3 LIGASES

10:25 UbFluor: A Novel Tool for HTS Screening to Discover Chemical Probes for HECT and RBR E3 Ubiquitin Ligases

Alexander Statsyuk, Ph.D., Assistant Professor, Department of Pharmacological and Pharmaceutical Sciences, University of Houston

We present our work toward the rational and systematic approaches to develop small molecule inhibitors of HECT E3 and RBR E3s ubiquitin ligases. These are single subunit ligases that harbor the catalytic cysteine and form the obligatory HECT E3/RBR E3~Ub thioesters prior to ligation of the ubiquitin onto the lysines of protein substrates. Memebers of HECT and RBR E3s include Nedd4-1, Nedd4-2, ITCH, Parkin, and E6-AP. We used UbFluor to screen 50,000 compounds against two HECT E3s, and identified promiscuous and selective inhibitors.

10:55 Stealing Secrets from the Germline: Alterations of Tumor Metabolism by a Testis-Specific Ubiquitin Ligase Hijacked in Cancer

Ryan Potts, Ph.D., Associate Member, Faculty, Cell & Molecular Biology, St. Jude Children's Research Hospital

AMP-activated protein kinase (AMPK) is a master sensor and regulator of cellular energy status. Upon metabolic stress, AMPK suppresses anabolic and promotes catabolic processes to regain energy homeostasis. Cancer cells can occasionally suppress the growth restrictive AMPK pathway by mutation of an upstream regulatory kinase. Here, we describe a widespread mechanism to suppress AMPK through its ubiquitination and degradation by the cancer-specific MAGE-A3/6-TRIM28 ubiquitin ligase.

11:25 Enjoy Lunch on Your Own

12:50 pm Plenary Keynote Program *(See page 3 for details.)*

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

3:20 End of Conference

Ninth Annual | September 21-22, 2016

Kinase Inhibitor Discovery

Emerging Targets, Tools and Development Strategies

The human kinome is a large and highly druggable class of targets spanning numerous disease indications, and driving a significant portion of drug discovery and development efforts to date. Despite the hundreds of kinase inhibitors currently in discovery, preclinical, and clinical phases, a relatively small subset of the kinome has been thoroughly explored with selective small molecule inhibitors. Stirred by the clinical success of many approved anti-cancer kinase inhibitors, developers are now finding new ways to expand into a broader portion of the human kinome, move beyond cancer and into chronic diseases, develop immune-modulatory agents as single or combination therapies, shift toward allosteric modulation, and harness irreversible compounds.

Cambridge Healthtech Institute's ninth annual Kinase Inhibitor Discovery meeting will once again unite leading kinase inhibitor discovery and development scientists to discuss emerging targets, tools, and development strategies.

BEST VALUE:

- September 19 Short Course: RNA as a Small Molecule Drug Target
- September 20-21 Conference: Targeting Histone Methyltransferases and Demethylases
- September 21-22 Conference: Kinase Inhibitor Discovery

WEDNESDAY, SEPTEMBER 21

11:20 am Conference Registration Open

11:25 Enjoy Lunch on Your Own

12:50 pm Plenary Keynote Program *(See page 3 for details.)*

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

KINASE INHIBITORS FOR CANCER IMMUNOTHERAPY COMBINATIONS

3:20 Chairperson's Opening Remarks

Guido J.R. Zaman, Ph.D., Managing Director & Head of Biology, Netherlands Translational Research Center B.V. (NTRC)

3:25 FEATURED PRESENTATION: Inhibition of PI3K and Tubulin

Doriano Fabbro, Ph.D., CSO, PIQUR Therapeutics

The PI3K signaling pathway is frequently activated in tumors. PQR309 is a selective dual inhibitor of PI3K and mTOR (currently in Phase I) in cancer patients. The preclinical pharmacology and toxicology of PQR309 is presented, including its activity in lymphoma preclinical models. In addition, we elucidate structural factors defining the PI3K inhibitory activity and tubulin-binding of PQR309 derivatives.

4:05 Design and Development of a Novel PI3K-p110β/δ Inhibitor, KA2237 with Combined Tumor Immunotherapeutic, Growth Inhibition and Anti-Metastatic Activity

Stephen Shuttleworth, Ph.D., FRSC, CChem, CSO, Karus Therapeutics Ltd.

The design and development of KA2237, a novel and selective inhibitor of PI3K-p110β/δ, will be described. This molecule has clinical potential in the treatment of solid and hematological malignancies, through its direct inhibition of tumor growth and metastatic spread, and through immunotherapeutic mechanisms. Phase I studies for KA2237 are scheduled to commence in Q2 2016 at the MD Anderson Cancer Center.

4:35 InCELL Pulse: A Novel Cellular Target Engagement Assay Platform for Drug Discovery

Sponsored by DiscoverX

Daniel Treiber, Ph.D., Vice President, KINOMEscan, DiscoverX Corporation

InCELL Pulse is a quantitative and rapid method for measuring cellular target engagement potencies for small molecule inhibitors. InCELL Pulse capitalizes on two novel DiscoverX technologies, Enzyme Fragment Complementation (EFC) and Pulse Denaturation, which overcome the limitations of related target engagement methods. Examples across multiple target classes will be described.

4:50 Potential Application of Fluorescence Lifetime Assays to Enable Robust, Rapid Protein Binding Assays

Sponsored by ttplabtech natural innovators

Paul Wylie, Ph.D., Head, Applications, TTP Labtech

Current methods to screen protein binding interactions often have limitations due to the reliance on antibodies, but also interference from fluorescent molecules. Fluorescence lifetime has the potential to overcome these problems through directly labelled proteins and lifetime measurements that are independent of total fluorescence intensity.

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

KINASE INHIBITORS FOR AUTOIMMUNE AND INFLAMMATORY DISEASES

5:40 Selected Presentation: Comparative Cancer Cell Line Profiling Differentiates the Mechanism of Action of Different Kinase Inhibitors

Guido J.R. Zaman, Ph.D., Managing Director & Head of Biology, Netherlands Translational Research Center B.V. (NTRC)

Profiling of drug candidates in cell line panels is an important tool to compare the selectivity and targeting of new anti-cancer agents. In addition, comparative profiling may be used to repurpose established therapeutics by identifying new mechanisms of action or cross-selectivities. A collection of more than 120 anti-cancer agents, targeting all important oncogenic signaling pathways, including classic cytotoxic agents as well as many epigenetic modulators and kinase inhibitors, was profiled on a panel of 44 or 66 parallel cell line proliferation assays (OncolinesT). The OncolinesT profiles of the compounds were compared by Pearson correlations of their inhibitor responses. Inhibitor sets were clustered using hierarchical trees. Response profiles were correlated to the genetic background of the cell lines by Analysis of Variance (Anova). Reproducibility of the NTRC OncolinesT cell panel was validated by monitoring cell growth rate and the variation in IC50s of replicate profiles over a period of three years. The Pearson correlation between replicates ranged between 0.60 and 0.99 for 16 different inhibitors, depending on dose-response curve shape. Correlation analyses of the greater than 120 profiled anti-cancer agents revealed separate clusters of, a.o., taxanes, platins, topo-isomerase inhibitors, and EGFR, ABL, MEK and BRAF inhibitors. This demonstrates that the OncolinesT profiles are an unbiased representation of the compound's mechanisms. The profile of the BTK inhibitor ibrutinib correlated with EGFR inhibitors. In biochemical experiments we showed that this due to its cross-reactivity with EGFR. Profiling of EZH2 inhibitors indicates that there are essentially two classes and that these have a cellular profile that is distinct from HDAC, DOT1L or BET inhibitors. The six Aurora kinase inhibitors profiled fall into two separate clusters, which are related to their biochemical selectivity. Thus, Aurora A-selective inhibitors are relatively more active in cell lines with mutations in cell cycle checkpoint-related genes such as TP53 and RB1; whereas pan-Aurora inhibitors are more active in cell lines with mutations in growth factor signaling pathways, such as NRAS. Profiling of eleven PI3 kinase and mTOR inhibitors revealed four distinct clusters. PI3Kalpha and PI3Kdelta isoform selective inhibitors each target genetically distinct subgroups of cell lines. Rapamycin-analogs, such as everolimus, specifically target PTEN-mutant cell lines. In conclusion, comparative cancer cell line profiling is a powerful tool to rapidly explore the pharmacogenomics of drug action in cancer cells and to identify new or previously un-noted activities of compounds.

6:10 Inhibition of Autoimmune Pathways with Dual Inhibition of JAK1 and TYK2

Suvit Thaisrivongs, Ph.D., Head of Immunoscience Chemistry, Pfizer Worldwide R&D

This work describes the discovery of selective JAK1 / TYK2 inhibitors for a range of inflammatory disorders such as inflammatory bowel disease, systemic lupus erythematosus and psoriasis. Balancing the in-family kinase selectivity is important to optimize the inhibition of pathogenic cytokines while limiting immune suppression, as well as to limit effects driven by JAK2 signaling through EPO. The lead is a well-behaved molecule with excellent *in vitro* potency and a superior off-target profile.

6:40 End of Day

THURSDAY, SEPTEMBER 22

7:30 am Registration Open and Morning Coffee

NEXT-GENERATION KINASE INHIBITORS

8:30 Chairperson's Remarks

Doriano Fabbro, Ph.D., CSO, PIQUR Therapeutics

» 8:35 KEYNOTE PRESENTATION: FROM SERENDIPITY TO CLINICAL TRIALS: DISCOVERY OF REVERSIBLE COVALENT KINASE INHIBITORS

Jack Taunton, Ph.D., Professor, Cellular and Molecular Pharmacology, UCSF School of Medicine, University of California, San Francisco

We initiated a study of Michael acceptors bearing substituents with increasing electron withdrawing capacity. We were surprised to find that 2-cyanoacrylamides react with simple thiols to form kinetically unstable adducts. We hypothesized that the intrinsically labile nature of the cysteine/cyanoacrylamide bond could be exploited to yield cysteine-targeted, reversible covalent inhibitors. These concepts have led to the design of ultra-selective kinase inhibitors with slow dissociation kinetics.

9:15 Kinetic Selectivity and Target Residence Time Determine Cellular Activity of Kinase Inhibitors

Guido J.R. Zaman, Ph.D., Managing Director & Head of Biology, Netherlands Translational Research Center B.V. (NTRC)

We have developed surface plasmon resonance binding assays for more than 50 different protein tyrosine, serine/threonine, and lipid kinases. Results will be presented on the selectivity profiling and determination of binding kinetics of different PI-3 Kinase inhibitor subclasses, a comparison of reversible and irreversible EGFR inhibitor drugs, and the study of the relationship of kinase protein structure, as determined by x-ray protein crystallography, and target residence time for TTK/Mps1.

9:45 FEATURED PRESENTATION: Crafting Selective Kinase Inhibitors: The Power of a Fully Annotated Kinase Inhibitor Library

Brian Hodous, Ph.D., Director, Medicinal Chemistry, Blueprint Medicines

Blueprint Medicines has developed a proprietary kinase inhibitor library. This collection has been designed, synthesized and fully annotated against a panel of over 400 human wild-type kinases and over 50 clinically relevant mutants. This library has resulted in the identification of exquisitely potent and selective tool compounds, advanced medicinal chemistry starting points, and unique insights into structural features that are drivers of potency and selectivity. Here we present an overview of how this library has been built, analyzed, and applied.

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

11:10 Hit-to-Lead Optimization Guided by Information from Focused Mapping

Istvan Enyedy, Ph.D., Senior Scientist, Drug Discovery, Biogen

Solvent mapping was developed to predict *in silico* where organic solvent molecules would bind to a protein. Later it was found to be useful for identifying "hot spots" corresponding to "druggable" sites by small molecules. Focused mapping is a

method to do a refined exploration of the binding site to highlight key interactions. We evaluated the use of this method for guiding hit-to-lead optimization.

11:40 CASE STUDY: Targeting PLK1 through a Novel Covalent Mechanism

Campbell McInnes, Ph.D., Associate Professor, Drug Discovery & Biomedical Sciences, South Carolina College of Pharmacy, University of South Carolina

We will describe novel inhibitors of PLK1 kinase activity that inhibit through a unique covalent strategy. The discovery and optimization of these inhibitors is described in addition to confirmation of their on-target anti-tumor mode of action through selective PLK1 inhibition.

12:10 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

TARGETING THE UNFOLDED PROTEIN RESPONSE IN CANCER AND NEURODEGENERATIVE DISEASES

2:15 Chairperson's Remarks

Florence Fevrier-Wagner, Ph.D., Senior Group Leader, Medicinal Chemistry, Stanley Center for Psychiatric Research, Broad Institute

2:20 Covalent Inhibitors Allosterically Modulating IRE1 Function

David Thomas, Ph.D., Chair and Professor, Biochemistry, McGill University

This presentation will describe our work on modulators of IRE1 and their biological effects on ER stress and protein trafficking diseases such as cystic fibrosis. Our data on the mechanism of a covalent inhibitor of IRE1 will be described, as will the results with new IRE1 modulators with a different mechanism of action. The link between IRE1 modulators and the correction of trafficking of ER retained mutant proteins will also be described.

2:50 Selected Presentation ~~Discovery of Novel Allosteric IRE1a Inhibitors~~

~~*Dai-Shi Su, Ph.D., Manager, Medicinal Chemistry, Oncology, GlaxoSmithKline*~~

~~This presentation will report the discovery of diazospirodecanes as potent and selective allosteric IRE1a inhibitors. Elucidation of the structure-activity relationship of the structurally novel high-throughput screening (HTS) lead provided potent and selective IRE1a inhibitors. The SAR optimization, first co-crystal structure of a small molecule inhibitor, GSK2850163A, with human IRE1a, and mode of inhibition (MOI) characterization of compounds will also be discussed in the presentation.~~

3:20 Session Break

KINASE INHIBITORS FOR CNS AND NEURODEGENERATIVE DISORDERS

3:30 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.

4:00 Leveraging Pre-Competitive Risk Sharing to Accelerate the Understanding of LRRK2 Kinase Inhibition as a Potential Disease Modifying Treatment for Parkinson's Disease

Matthew Fell, Ph.D., Associate Principal Scientist, Early Neuroscience Discovery, Merck Research Laboratories

Leucine-rich repeat kinase 2 (LRRK2) gain of function mutations are associated with late-onset autosomal dominant Parkinson's disease (PD) and represent the most common known cause of familial PD. In spite of strong genetic evidence for potential disease modification in PD patients, advancement of LRRK2 inhibitors towards the clinic has been hampered by many factors, including perceived on-target toxicology in preclinical species. To further investigate these findings, medicinal chemistry efforts provided a potent, selective, brain-penetrant molecule enabling further investigation of LRRK2 biology both internally and with collaborators via the Michael J. Fox Foundation (MJFF). This molecule has not only been utilized to explore the biological effects of LRRK2 kinase inhibition (including the discovery of bona fide LRRK2 substrates) but also to probe the tolerability of LRRK2 kinase inhibitors. This compilation of preclinical data and will be discussed.

4:30 Use of Exquisitely Selective Inhibitors of the GSK3 Kinase Isoforms for the Treatment of Fragile X Syndrome and Other Psychiatric and Central Nervous System Disorders

Florence Fevrier-Wagner, Ph.D., Senior Group Leader, Medicinal Chemistry, Stanley Center for Psychiatric Research, Broad Institute

We report the discovery of the first isoform selective inhibitors of GSK3α or GSK3β. Exploiting a single amino acid difference within the ATP binding domain, we have developed novel, potent, brain penetrant inhibitors with unprecedented kinome selectivity (>100x selectivity vs. 311 kinases). Our data demonstrate for the first time that the selective inhibition of a single GSK3 isoform is sufficient to rescue three different biochemical or electrophysiological phenotypes in a mouse model of Fragile X.

5:00 Close of Conference

Second Annual | *September 20-21, 2016*

Targeting the Microbiome - PART 1

Redefining Healthcare with Scientific Findings of Microbiome Research

Part One of the Targeting the Microbiome track, taking place September 20-21, 2016, will discuss the underlying mechanisms of the disease. We'll explore scientific-based case studies of the interaction between the microbiome and the immune system, particularly pathways being activated. We will also explore the future of translational medicine as it pertains to the microbiome area and investment/collaboration opportunities.

BEST VALUE:

- September 19 Short Course: Using IP Landscape Studies to Improve Your Confidence While Navigating a Crowded IP and Technology Space
- September 20-21 Conference: Targeting the Microbiome - Part 1
- September 21-22 Conference: Targeting the Microbiome - Part 2

TUESDAY, SEPTEMBER 20

7:00 am Registration Open and Morning Coffee

DYNAMICS OF THE MICROBIOME ON HEALTH AND DISEASE

8:05 Chairperson's Opening Remarks

Deepak K. Rajpal, D.V.M., Ph.D., Director, Computational Biology, GlaxoSmithKline

» 8:20 KEYNOTE PRESENTATION: ELUCIDATING MICROBIOME ROLE AND FUNCTION IN HUMAN HEALTH AND DISEASE USING AN INTEGRATED "-OMICS" APPROACH

Niels Klitgord, Ph.D., Bioinformatician, Human Longevity, Inc.

Human health associations with the microbiome are rampant, finding links in areas ranging from human development to neurology. However, the mechanistic understanding of these associations is mostly lagging, confounding diagnosis and development of treatments. We present an overview of our on-going effort to elucidate microbiome role in human health and disease that is based on whole genome sequencing and analysis of over 3,000 microbiome samples from well phenotyped cohorts.

8:50 Quantitative Prediction of Microbiota Dynamics for Development of Bacteriotherapies

Georg K. Gerber, M.D., Ph.D., MPH, Assistant Professor of Pathology, Harvard Medical School; Co-Director, Massachusetts Host-Microbiome Center; Associate Pathologist, Brigham and Women's Hospital Center for Advanced Molecular Diagnostics

I will present our work on discovery of networks of commensal bacteria protecting against *Clostridium difficile* and prediction of stability of configurations of bacteria in an immune-modulating probiotic cocktail. This work leverages our new computational framework, the Microbial Dynamical Systems INference Engine (MDSINE), which infers dynamical systems models from noisy microbiome sequencing time-series datasets and predicts future behaviors of the microbiota.

9:20 Recurrent Clostridium difficile Infection: Mechanisms of Disease and Emerging Therapeutics

Jessica R. Allegretti, M.D., MPH, Attending Gastroenterologist, Director of Clinical Trials and Director of the Fecal Transplant Program for Recurrent Clostridium Difficile, Brigham and Women's Hospital Crohn's and Colitis Center

9:50 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

10:35 Skin Microbiome Editing by Specific Targeting Probiotic Microbes

Chun-Ming Eric Huang, Ph.D., Professor, Division of Dermatology, University of California San Diego

11:05 Exploring Microbiome in Metabolic Diseases

Deepak K. Rajpal, D.V.M., Ph.D., Director, Computational Biology, GlaxoSmithKline

Metabolic diseases, especially type 2 diabetes and obesity, are growing global healthcare concerns. Various studies have highlighted the role of gastrointestinal microbial communities in metabolic health and disease. We will provide a brief overview of the gut microbiome, its putative role in metabolic diseases and the emerging data in this space.

11:35 Data and Digital Tools for the Microbiome – An Emerging Field in Autoimmune Disease

Bonnie Feldman, D.D.S., MBA, Digital Health Analyst and Chief Growth Officer, DrBonnie360

New research shows an association between changes in the microbiome in Lupus and Rheumatoid arthritis. With the convergence of large population data sets and personal data we are beginning to make progress in research, development and clinical trials in autoimmune disease. This talk will highlight new companies using data and digital tools to improve our understanding and treatment of autoimmunity.

12:05 pm Sponsored Presentation *(Opportunity Available)*

12:35 Session Break

12:45 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Lunch on Your Own**

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

DYNAMICS OF THE MICROBIOME ON HEALTH AND DISEASE

2:05 Chairperson's Remarks

Bonnie Feldman, D.D.S., MBA, Digital Health Analyst and Chief Growth Officer, DrBonnie360

2:15 Metaproteome Display: Identification of Novel Microbiome Derived Immunogenic Proteins

Michael Hust, Ph.D., Professor, Department of Biotechnology, Technische Universität Braunschweig

ORFeome phage display is a novel but already proven approach for the identification of microbial biomarkers which can neither be found by classical MS based proteomics nor by all cDNA based methods. Metaproteome Display allows the selective display of microbiota-derived whole genome ORFs on the surface of phage particles and functional screening for biomarker candidates by affinity binding to antibodies from matching donor sera. By functionally analysing entire ORFeomes, we already discovered novel Biomarkers of a number of microbial pathogens and bowel-disease metagenomes.

2:45 Precise Characterization of and Selective Removal in Bacterial Communities

Bruno Marchon, Ph.D., CTO, EpiBiome

Rich bacterial communities are widespread: Our gut flora is necessary to our well-being, and food preservation has long relied on "good" bacteria to help ward off pathogens. At EpiBiome, we are developing sustainable alternatives to antibiotics, while devising novel technologies to better characterize bacterial populations. These approaches will provide healthcare, agriculture and food producers with better tools to help them deliver better services and products.

3:15 Human Microbiome Research at the NIH: The HMP and Beyond

Lita M. Proctor, Ph.D., Coordinator, NIH Human Microbiome Project

3:45 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

» 4:25 KEYNOTE PRESENTATION: DISCOVERING AND MODELLING PATHOGEN SHARING IN HUMANS, GORILLAS AND LIVESTOCK IN UGANDA

David T.S. Hayman, Ph.D., Senior Lecturer in Veterinary Public Health, Co-Director, mEpiLab, OIE Collaborating Centre Infectious Disease Research Centre, Hopkirk Research Institute, Massey University, New Zealand

How do humans become infected with a virus from another species? The moment of cross species transmission (aka 'spillover') is rarely observed, but culture free next-generation sequencing metagenomic studies allow us new insights into transmission and to test specific hypotheses, including whether pathogen sharing is determined by host relatedness (phylogeny), contact rates, or pathogen traits. Our studies in Africa on people, livestock and wildlife will allow us to address some of these key questions regarding how infections cross the species barriers.

5:25 Welcome Reception in the Exhibit Hall with Poster Viewing

6:25 End of Day

WEDNESDAY, SEPTEMBER 21

7:30 am Registration Open and Morning Coffee

INNOVATION, INVESTMENT, AND COLLABORATION

8:00 Chairperson's Opening Remarks

Keith F. Batchelder, M.D., CEO and Founder, Genomic Healthcare Strategies

8:10 PANEL DISCUSSION: From Microbiome to Market

Keith F. Batchelder, M.D., CEO and Founder, Genomic Healthcare Strategies (Moderator)
Sacha Mann, CEO, Immune Product Services Ltd and Venture Partner, Inventages
Bernat Olle, Ph.D., CEO, Vedanta Biosciences, Inc.
Greg Sieczkiewicz, J.D., Ph.D., Chief IP Council, MPM
Jeremy Springhorn, Ph.D., Partner, Corporate Development, Flagship Ventures
Cameron Wheeler, Ph.D., Principal, Deerfield Management

This Microbiome to Market panel discussion serves as a critical bridge between Part One and Part Two of the Targeting the Microbiome Program. The discussion is appropriate for those working in academic research or science who are thinking about putting a company together or at least thinking about the translation piece. The discussion is also appropriate for companies who have already harnessed microbiome research for a therapeutic area or disease condition to learn the kinds of business and financial models that investors find attractive. Leading investors will gather to discuss the areas of the microbiome they are looking at and why. We will explore the global scope of microbiome and successful collaboration, reimbursement, and business investment models between science, business, healthcare, and government in bringing live microbial products to market. We will also discuss balancing venture activities, external R&D, and long-term market opportunities. Join us for a lively and interactive discussion of the how's and what's of bringing your microbiome product or service to market.

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

10:25 PANEL DISCUSSION: Building Effective Partnership Models in Product Development and Commercialization

Keith F. Batchelder, M.D., CEO and Founder, Genomic Healthcare Strategies (Moderator)
Daria Hazuda, Ph.D., Vice President, Infectious Diseases Discovery and Chief Scientific Officer, Merck Research Laboratories Cambridge Exploratory Science Center
Anu Daniel, Ph.D., Licensing Manager, Innovation, Partners Healthcare
John Hambor, Ph.D., Director, Research Beyond Borders, Boehringer Ingelheim
Matt Adams, Vice President, Technical Operations and Business Development, Rebiotix

Identifying and integrating strategic partnership relationships effectively into your overall business strategy is critical and essential to move the business forward and deliver results. This panel discussion will discuss the skills needed for organizations to collaborate, develop, and commercialize novel therapeutics. Join us for a lively and interactive discussion of the why's and how's in maintaining and expanding a productive alliance in the face of a complex collaboration agreement, organizational and market driven changes.

11:25 Enjoy Lunch on Your Own

12:50 pm Plenary Keynote Program *(See page 3 for details.)*

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

3:20 End of Conference

Second Annual | *September 21-22, 2016*

Targeting the Microbiome - PART 2

Using the Microbiome as a Tool for Therapeutic Development

Part Two of the Targeting the Microbiome track, taking place September 21-22, 2016, features microbiome and biopharma companies discussing the potential of translational interventions and novel therapeutic targets based on microbiome R&D. Case studies will explore how to use the microbiome as a tool for therapeutic, diagnostic and product development. We will also explore issues around microbiome patent eligibility and legal changes that will have a major impact on microbiome research in the next several years.

BEST VALUE:
- September 19 Short Course: Using IP Landscape Studies to Improve Your Confidence While Navigating a Crowded IP and Technology Space
- September 20-21 Conference: Targeting the Microbiome - Part 1
- September 21-22 Conference: Targeting the Microbiome - Part 2

WEDNESDAY, SEPTEMBER 21

11:20 am Conference Registration Open

11:25 Enjoy Lunch on Your Own

12:50 pm Plenary Keynote Program *(See page 3 for details.)*

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

POTENTIAL OF TRANSLATIONAL INTERVENTIONS AND NOVEL THERAPEUTIC TARGETS BASED ON MICROBIOME R&D

3:20 Chairperson's Opening Remarks
Randal Eckert, Ph.D., Senior Director, Preclinical Biology, C3 Jian, Inc.

3:35 Correction of Microbiome Dysbiosis by Specifically-Targeted Antimicrobial Peptides (STAMP)
Randal Eckert, Ph.D., Senior Director, Preclinical Biology, C3 Jian, Inc.
The STAMP platform generates pathogen-specific drugs that target bacteria that drive dysbiosis. Effective elimination of these organisms results in a microbiome reengineered to a healthy ecological state. Dysbiosis of microbiome communities has recently been implicated in several chronic diseases. Animal models and clinical studies have validated the STAMP platform, demonstrating remodeling of microbial communities. Updates to several STAMP development programs will be presented.

4:05 Skin Microbiome
Larry Weiss, M.D., CMO, AOBiome, LLC
AOBiome is exploring the role of Ammonia Oxidizing Bacteria (AOB) as an ancestral human skin commensal. The company is developing live topical therapeutic and cosmetic formulations on *Nitrosomonas Eutropha* for the prevention and treatment of inflammatory disorders of the skin.

4:35 Engineering Synthetic State Machines in Living Cells
Nathaniel Roquet, PhD Graduate Student, Harvard Biophysics Program; Synthetic Biology Group (Professor Timothy Lu), Massachusetts Institute of Technology
State machines are circuits that combine logic and memory to execute complex decision-making, such as producing different outputs based on different orders of inputs. We have engineered state machines in *E. coli* by leveraging recombinases to perform controlled excision and inversion events on DNA. These state machines allow the cell to distinctly record and respond to all permutations of a set of chemical stimuli. We anticipate that our state machine devices may be useful for uncovering the temporal organization of environmental and cellular factors that drive microbial behavior inside the human body.

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

5:40 Rescuing the Infant Gut Microbiome
David Kyle, CEO, Evolve Biosystems, Inc.
From birth to weaning, the natural infant gut microbiome is dominated by *Bifidobacterium infantis*. However, the prevalence of this species has decreased dramatically over the last 50 years due to the unintended consequences of modern medical and nutritional practices, and may have long term health consequences. Here we demonstrate the ability to rescue the natural infant gut microbiome by supplementation with *Bifidobacterium infantis* in breast-fed infants.

6:10 Next Generation Immunotherapeutics from the Microbiome: Amrita Therapeutics' Oncology Peptides
Susan Kling Finston, J.D./M.P.P., CEO, Amrita Therapeutics Ltd.
Amrita Therapeutics is pioneering commercialization of next generation immuno-oncology peptides from the microbiome, with lead candidate drug AT-01C and related SMAR1* biomarker (for precision medicine) heading to the clinic in the next 6 - 9 months. SMAR1 is a DNA binding protein and recognized master regulator with a critical role as a tumor suppressor. Amrita's AT-01C is a p53 tumor suppressor derived from Mycobacterium Tuberculosis (M. bovis) Protein MPT63, also known as ATP-01, one of nearly 4,000 proteins in the bacteria utilized in early immune-oncology therapy BCG for bladder cancer. Amrita Therapeutics is in the vanguard of companies translating microbiome technologies into practical tools to promote human health, with research programs at discovery, early and late preclinical stages. Initially launched in Gujarat, India, Amrita Therapeutics fell outside the scope of American VCs. The company has incorporated in Washington DC in advance of planned human clinical research.

*Scaffold Matrix Attachment Region Binding Protein 1

6:40 End of Day

THURSDAY, SEPTEMBER 22

7:30 am Registration Open and Morning Coffee

POTENTIAL OF TRANSLATIONAL INTERVENTIONS AND NOVEL THERAPEUTIC TARGETS BASED ON MICROBIOME R&D

8:30 Chairperson's Remarks

Susan Kling Finston, J.D./M.P.P., CEO, Amrita Therapeutics Ltd.

8:45 The Gut-Brain-Axis: Neurotransmitter Modulation by the Microbiota

Phil Strandwitz, Ph.D., Postdoctoral Research Associate, The Lewis Lab, Northeastern University Antimicrobial Discovery Center

The gut microbiota has been shown to influence numerous disease of the gastrointestinal system. Surprisingly, recent work has shown the influence of the gut microbiota reaches beyond the gut, and can effect behavior and mental health disorders. In this presentation, several key studies on the gut-brain-axis will be discussed, and new work showing the ability of the microbiota to modulate the neurotransmitter GABA will be reported. Such discoveries will likely have profound implications on how to treat mental health disorders, and pave the way for microbiota-based therapeutics.

9:15 Targeted High Molecular Weight Protein Complexes for Microbiota Engineering

Dean Scholl, Ph.D., Director of Research, AvidBiotics Corporation

Avidocin proteins are engineered high molecular weight bacteriocins targeted to kill chosen bacterial species by manipulating the Avidocin cellular receptor binding motif. *In vivo* data show that Avidocin proteins can remove a targeted bacterial species from the mouse gut without disrupting normal microflora. We are developing these novel antimicrobials for microbiota engineering by selectively removing key species associated with dysbiosis and metabolic disorders.

9:45 Silencing Harmful Bacterial Activity with Non-Antibiotic Drugs

Ward Peterson, Founder & CEO, Symberix, Inc.

The gut microbiome can be pharmacologically targeted to improve human health with a new class of drugs that act on bacteria without killing them. Symberix is targeting the sugar-metabolizing GUS enzyme in gut microbiota that is responsible for causing serious intestinal injuries associated with many pain and cancer drugs. The therapeutic, regulatory and commercialization implications of "drugging the microbiome" will be discussed.

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

11:10 Protection of the Gut Microbiome from Antibiotics

Jean de Gunzburg, Ph.D., CSO, Da Volterra

Antibiotics are life-saving drugs but inflict severe damage to the gut microbiome with short and long term consequences. We have devised a product, DAV132, which delivers a powerful adsorbent to the late ileum of humans, and show in a randomized controlled study on human volunteers that its co-administration with the fluoroquinolone moxifloxacin enables to protect the gut microbiome without jeopardizing the systemic exposure to the antibiotic.

11:40 Precision Medicine and Microbiome Targets: Treatment of IBS-C and Prevention of *C. difficile* Infections

Klaus Gottlieb, M.D., FACG, Vice President, Clinical & Regulatory Affairs, Synthetic Biologics, Inc.

The presentation will discuss two lead candidates in Phase II clinical trials and Phase III program development: 1) SYN-010 intended to reduce the impact of methane producing organisms in the gut microbiome to treat an underlying cause of IBS-C, and 2) SYN-004 designed to protect the gut microbiome from the unintended effects of certain commonly used IV beta-lactam antibiotics for the prevention of *C. difficile* infection and AAD.

12:10 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

POTENTIAL OF TRANSLATIONAL INTERVENTIONS AND NOVEL THERAPEUTIC TARGETS BASED ON MICROBIOME R&D

2:15 Chairperson's Remarks

Susan Kling Finston, J.D./M.P.P., CEO, Amrita Therapeutics Ltd.

2:20 Targeted Delivery of Bacteriophage-Derived Lysins as Microbiome-Sparing Antimicrobials for Gastrointestinal Infection

Gerard Honig, Ph.D., Founder & CEO, Symbiotic Health, Inc.

Symbiotic Health is dedicated to addressing pressing unmet medical needs by combining insights from microbiome biology with innovative drug delivery engineering. Our lead candidate, SHP-01, is an ultra-targeted, ultra-rapid antimicrobial against C.difficile infection. Conventional antibiotic treatments for C.difficile infection injure and deplete the healthy gut bacterial ecosystem of the gut, increasing the risk of infection recurrence. SHP-01 is an engineered bacteriophage-derived lysin enzyme; lysins target carbohydrate cell wall structures which are highly pathogen-specific. As a result, lysin-based antimicrobials have the potential to eradicate pathogens with exceptional speed while sparing healthy gut microbiota. In order to address challenges which have limited the development of orally administered recombinant proteins, SHP-01 incorporates a novel polymer-based platform technology for delivery of proteins and bacterial cells to the lower gastrointestinal tract for local therapeutic action. The development of SHP-01 is an opportunity to demonstrate the general potential of an innovative and disruptive therapeutic strategy with applications in infectious disease and gastrointestinal pathologies.

2:50 Developing a Room Temperature Stable, Orally Delivered Microbiota-Based Drug for the Prevention of Recurrent *C. difficile* Infection

Matt Adams, Vice President, Technical Operations and Business Development, Rebiotix

Disruption of the intestinal microbiota has been implicated in *C. difficile* (CDI). Fecal microbiota transplantation (FMT) has demonstrated high efficacy for preventing recurrence but has limitations. This talk discusses the delivery of an oral room-temperature stable microbiota-based drug that may provide a number of advantages in terms of dosing and therapy access and updates on a clinical study program encompassing CDI and other indications.

3:20 Session Break

3:30 Catalyzing Safe Fecal Microbiota Transplantation: From Current Practices to Future Therapies

Zain Kassam, M.D., MPH, FRCPC, CMO, OpenBiome; Gastroenterologist, Epidemiologist and Research Affiliate, MIT Center for Microbiome Informatics & Therapeutics

Fecal microbiota transplantation (FMT) is a promising emerging therapy for the treatment of recurrent *C. difficile* infections (rCDI). FMT has already advanced significantly from a DIY therapy using minimally screened individual donors to a highly standardized process, using universal donors subject to rigorous screening. As an example of this transformation, OpenBiome, the first public stool bank, has delivered over 11,000 treatments to over 600 hospitals in 7 countries, with less than 3% of prospective donors passing the 178-point clinical assessment and 30-item laboratory screening panel required for enrollment. The field continues to evolve rapidly with new synthetic microbial therapies under development for rCDI, and a wide range of new indications emerging as targets for microbial engineering.

KEYNOTE SESSION: MICROBIOME-PATENT ELIGIBILITY

4:00 The Changing Legal Landscape for Microbiome Research

John M. Conley, J.D., Ph.D., William Rand Kenan, Jr. Professor of Law, University of North Carolina, Chapel Hill; Counsel, Robinson Bradshaw & Hinson

This presentation will review three sets of legal changes that will have a major impact on microbiome research in the next several years. These changes are occurring in patent law, making it much harder to get and enforce patents on both biological substances and analytic methods; in the Common Rule for protecting human research subjects; and in the U.S. and international law of privacy.

4:30 Microbiome, Industrial Product Development and Their Patent Protection: Key Emerging Issues

Ananda Chakrabarty, Ph.D., Department of Microbiology & Immunology, University of Illinois College of Medicine

Many microbiome-related inventions may fall under legal limitations and prevent their marketing because of lack of patent protection, as illustrated by the recent CAFC decision on Sequenom v. Ariosa Diagnostics. This talk will deal with such issues to sensitize both academic/industrial researchers and entrepreneurs on the limits of patent protection for many microbiome inventions of great practical and industrial importance.

5:00 Q&A Discussion: Patent Eligibility Issues of Microbiome Innovations

This interactive discussion will provide attendees an opportunity to explore direct questions regarding patent eligibility of microbiome innovations and IP issues involved.

5:15 Close of Conference

Eleventh Annual | *September 20-21, 2016*

GPCR-Based Drug Discovery - PART 1

Screening and Structure-based Approaches

Recent advances in biophysical approaches to studying GPCRs have enabled progress in both structure-based design of ligands for GPCRs and new screening methods, which though not as high throughput as traditional cell-based assays, allow receptors to be studied in more relevant cellular contexts.

RECOMMENDED ALL ACCESS PACKAGE:

- September 19 Short Course: GPCR Structure-Based Drug Discovery
- September 20-21 Conference: GPCR-Based Drug Discovery - Part 1
- September 21-22 Conference: GPCR-Based Drug Discovery - Part 2
- September 21 Short Course: Introduction to Allosteric Modulators

TUESDAY, SEPTEMBER 20

7:00 am Registration Open and Morning Coffee

BIOPHYSICAL APPROACHES FOR STUDYING GPCRS

8:05 Chairperson's Opening Remarks

Andrew Alt, Ph.D., Senior Research Investigator, Lead Discovery, Bristol-Myers Squibb

» 8:10 KEYNOTE PRESENTATION: NMR AND ALLOSTERIC SIGNAL TRANSDUCTION NETWORKS IN THE β1-ADRENERGIC RECEPTOR

Gebhard F.X. Schertler, Ph.D., Professor, Head of Biology and Chemistry, Paul Scherrer Institute

By combined analysis of chemical shift changes from GPCR point mutations in a thermostabilized mutant of the turkey β1-adrenergic receptor (β1AR) with ligand responses to the mutated receptors, we were able to identify crucial connections in the allosteric activation pathway of the receptor. This approach represents a general experimental method to delineate signal transmission networks at high resolution in GPCRs.

8:50 GPCR Dynamics as Revealed by NMR

Matthew Eddy, Ph.D., Postdoctoral Fellow, Ray Stevens Laboratory, The Bridge Institute, University of Southern California

To understand the function of G Protein-Coupled Receptors (GPCRs), deeper insight is needed into the role of conformational dynamics in molecular recognition and activation. Nuclear magnetic resonance (NMR) is uniquely suited to deliver information about dynamics at atomic resolution and over a large range of time scales. However, application of NMR to study GPCRs has so far been very challenging. I will present advances in the field that address some of these challenges and reveal initial insights into mechanisms of GPCR activation.

9:20 Combining Biophysical Techniques to Identify and Optimize New Chemical Entities in Targeted GPCR Drug Discovery

Daniel Mattle, Ph.D., Roche Postdoctoral Research Fellow, Roche Pharma Research and Early Development (pRED), Roche Innovation Center Basel

We investigate new small molecular therapeutics to treat autosomal dominant retinitis pigmentosa (RP) caused by the GPCR rhodopsin. Our effort focuses on a combination of virtual screening, *in vitro* biophysical binding assays and structure determination of rhodopsin-ligand complex. Our tool platform enables fast and reliable identification and optimization of new hits towards leads for rhodopsin caused RP and any other GPCR involved in diseases.

9:50 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

10:35 Nanobody-Enabled Fragment Screening on GPCRs

Jan Steyaert, Ph.D., Vice-Director, Structural Biology Research Center, Vlaams Instituut voor Biotechnologie and Senior Advisor, ConFoTherapeutics

Progress in GPCR drug discovery has been disappointing. New compounds need to target the correct receptor, but the drugs must also exhibit the appropriate efficacy profile: (inverse) agonist, antagonist or biased ligand. We present a nanobody-enabled fragment screening approach to identify fragments that exclusively bind to particular functional conformations of the receptor allowing us to triage hits according to efficacy profile and potency.

11:05 A2AR Ligand Binding Kinetics Using Fluorescence Anisotropy: Determining Binding Rates in the Ligand Depletion Regime

Anne Robinson, Ph.D., Professor and Chair, Chemical & Biomolecular Engineering, Tulane University

We have developed a system to measure kinetics (on and off rates for different ligands/drugs) based on fluorescence anisotropy that allows label-free comparison of potential novel drugs. Here, ligand binding kinetics of the full-length human A2AR reconstituted in detergent micelles were measured using a fluorescently labeled ligand and fluorescence anisotropy. This approach, and the implications for drug discovery, will be described.

11:35 The Influence of Local Ligand Concentration on Observed Receptor Binding Kinetics: Measuring Drug Concentration Where it Matters

Steven Charlton, Ph.D., Professor, Molecular Pharmacology, University of Nottingham

Most current pharmacological approaches assume the interacting molecules are homogeneously distributed in solvent, but this is not necessarily the case for GPCRs where the membrane provides an additional compartment into which drugs may partition. This talk will discuss biophysical approaches to measure

local drug concentrations at a sub-cellular level and explore the effects on observed receptor binding kinetics, building "micro PK/PD relationships" for receptor ligands.

12:05 pm Harnessing TruBind™ Technology to Enable Label-Free, Solution-Based Affinity Measurements for GPCR Target Engagement and MOA Studies

Sponsored by MOLECULAR SENSING

Richard Isaacs, Ph.D., Applied Research Sciences Manager, Molecular Sensing, Inc.

GPCRs are critical targets for drug discovery but present a host of challenges to the characterization of their binding affinity for small molecules. Verification of target engagement by putative GCPR ligands and further determination of mechanism of action for agonist/antagonist/allosteric compounds is especially valuable and extremely challenging information to obtain by established binding assay platforms, but can be addressed through the label-free solution-based TruBind platform based on back-scattering interferometry.

12:35 3DM Protein Family Analysis System Applied to the GPCR Protein Family

Sponsored by bio-prodict

Henk-Jan Joosten, Ph.D., CEO, Bio-Prodict

Proteins often fall in large protein families (e.g 65.000 GPCR sequences are available). 3DM systems contain huge amounts of data (sequence-, structure-, mutation-, literature-, patent-, and binding data) for complete protein-families. 3DMs analysis suite (structure visualization-, literature/patent analysis-, correlated mutation-, mutation prediction-) connect all data/tools enabling state-off-the-art analysis.

12:50 Not All Cell Lines Are Created Equal - Developing and Validating GPCR Assays for Screening

Sponsored by MULTISPAN

Lisa Minor, Ph.D., Business Development Consultant, Multispan, Inc.

GPCRs are one of the most pharmaceutically proven targets in drug discovery. There are several ways to screen for activity against GPCRs, calcium mobilization, receptor binding, cAMP increases etc. One unifying feature of these screens is the requirement for reproducible and reliable expression of the receptor in native or transfected cells. At Multispan, we have developed a robust platform for the development and production of stably transfected GPCR expressing cells. In our efforts, we have come to realize that the level of expression of the receptors affects the ability to measure activity such as partial or full agonist, and so it is critical to evaluate multiple cell clones to ensure that the screen identifies compounds of interest. In this talk, we will share our screening platform and results using cells that deferentially express receptors to show how critical the selection of clones can impact outcome.

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

GPCR STRUCTURAL INSIGHTS

2:05 Chairperson's Remarks

Samantha J. Allen, Ph.D., Senior Scientist, Emerging Science& Innovation, Janssen Research Labs

2:15 The Changing Landscape in GPCR-Targeted Drugs

Andrew Tebben, Ph.D., Senior Principal Scientist, Molecular Structure and Design, Bristol Myers Squibb Co.

2:45 GPCR Structural Biology for Drug Discovery: Through the Protein Science Lens

Sujata Sharma, Ph.D., Director, Screening and Protein Science, Merck and Company

3:15 Studying GPCRs with AMRIs Conventional and Next-Generation Screening Technologies

Sponsored by AMRI

Rory Curtis, Ph.D., Vice President & Site Head, AMRI Buffalo, Discovery & Development, AMRI

AMRI, with investment from the State of New York and in collaboration with PerkinElmer, has state-of-the-art screening platform and cloud-based data analytics solutions. We have capabilities for high-throughput screening of GPCRs and other targets in multiple formats and readout, including screening by mass spectrometry and high-content imaging.

3:30 Modern Drug Research Informatics Applications to CNS, Infectious, Neglected, Rare, and Commercial Diseases

Sponsored by CDD VAULT

Barry Bunin, Ph.D., CEO, Collaborative Drug Discovery

Collaborative innovation is uniquely able to realize the economics of well-integrated specialization required for chemical biology and drug discovery. Recent results shared publicly for Neglected Disease applications amply demonstrate these bold suppositions are true and general. Since collaborative technology is "therapeutic area agnostic" it has general been proven equally applicable for commercial applications.

3:45 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

4:25 Kratom derived orally active analgesic with G-protein biased mu opioid agonism and delta opioid antagonism

Susruta Majumdar PhD, Assistant Attending Chemist, Department of Neurology, Memorial Sloan-Kettering Cancer Center

Mitragynine pseudoindoxyl (MP), a kratom-derived alkaloid is a G-protein biased mu opioid agonist with delta antagonist. It is a potent analgesic in mice, which exhibited no reward, attenuated respiratory depression, and constipation compared to morphine similar to most G-protein biased mu agonists. In addition, MP showed slower development of tolerance and minimal physical dependence owing to its delta antagonism. It is the first molecule engaging two pathways namely G-protein mu opioid biased agonism and delta antagonism.

4:55 Mutation-Guided Unbiased Modeling of the Fat Sensor GPR119 for High-Yield Agonist Screening

Thomas M.Frimurer, Ph.D., Associate Professor, The Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Denmark

Recent assessment studies have demonstrated difficulties in accurate modeling of receptor-ligand complexes. We present an unbiased mutation-guided protein-ligand optimization protocol with full ligand and receptor flexibility, which in contrast to conventional derived models could explain SAR and proved successful in separating active ligands from decoys in large-scale virtual screening - directly related to drug discovery applications when applied to the fat censor GPR119 as a case study.

5:25 Welcome Reception in the Exhibit Hall with Poster Viewing

6:25 End of Day

WEDNESDAY, SEPTEMBER 21

7:30 am Registration Open and Morning Coffee

'SEEING' GPCRS AND NEW DISCOVERY STRATEGIES

8:00 Chairperson's Opening Remarks

Adam Weinglass, Ph.D., Director, Cell Pharmacology, In Vitro Pharmacology, Merck Research Laboratories

8:10 Revealing the Structural Basis for GPCR Drug Action through Atomic-Level Simulation

Ron Dror, Ph.D., Associate Professor of Computer Science and, by courtesy, Molecular and Cellular Physiology, Stanford University

We have used molecular dynamics simulations to capture in atomic detail the processes by which drugs bind to GPCRs, by which GPCRs transition between active and inactive states, and by which GPCRs stimulate G proteins. Our results, together with complementary experimental data, suggest opportunities for the design of drugs that achieve greater specificity and control receptor signaling more precisely.

8:40 Negative Allosteric Modulators of the LPA1 Receptor: Using Backscattering Interferometry to Probe Compound Binding

Jonathan Ellery, Ph.D., Director, Pharmacology, Takeda

The LPA1 receptor has attracted considerable interest as a drug target for the treatment of a range of fibrotic conditions. Several pharmaceutical companies have progressed compounds into the clinic. Here we investigate two compounds that have advanced into the clinic alongside a Takeda compound and show evidence to suggest that one is an orthosteric antagonist whilst the others act as negative allosteric modulators.

9:10 PANEL DISCUSSION: Phenotypic v. Target-Based Screening for GPCRs

Moderator: Andrew Alt, Ph.D., Senior Research Investigator, Lead Discovery, Bristol-Myers Squibb

Panelists:

Samantha J. Allen, Ph.D., Senior Scientist, Emerging Science& Innovation, Janssen Research Labs

Laura M. Bohn, Ph.D., Professor, Departments of Molecular Therapeutics & Neuroscience, The Scripps Research Institute

Jonathan Ellery, Ph.D., Director, Pharmacology, Takeda

Adam Weinglass, Ph.D., Director, Cell Pharmacology, In Vitro Pharmacology, Merck Research Laboratories

- Rationale for phenotypic v. target-based screening approaches
- Native v. recombinantly expressed receptor systems for target-based screening
- "But what will we miss?" - case studies
- Deconvolution strategies for phenotypic screening hits

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

10:25 Probing the Functional and Therapeutic Significance of GPCR Oligomerization at the Nano-Scale via Super-Resolution Imaging

Aylin Hanyaloglu, Ph.D., Senior Lecturer, Institute of Reproductive and Developmental Biology, Imperial College London

Organization of GPCRs into dimers and oligomers represents a key mechanism in pleiotropic signaling and has received significant attention for its ability to impact receptor pharmacology and signaling *in vivo*. Our latest application of super-resolution imaging approaches has unveiled the molecular intricacies of GPCR oligomers and how it defines receptor activity that, in turn, may pave the way for novel avenues in intelligent drug design.

10:55 GPCR Drug Discovery at the Single Molecule Level

Tim Kaminski, Ph.D., Postdoctoral Fellow, Biophysics/Discovery Sciences, AstraZeneca

I am converting single molecule microscopy, a method primarily used in academia, into a versatile tool for drug discovery. We aim to address shortcomings of established biophysical methods such as tight binding limit, working with GPCRs and higher throughput. Additionally we are able to extract kinetic profiling of inhibition reactions in solution by observing the association and dissociation of thousands of molecules in parallel with a surface-based single molecule platform.

11:25 Enjoy Lunch on Your Own

12:50 pm Plenary Keynote Program *(See page 3 for details.)*

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

3:20 End of Conference

Fourth Annual | *September 21-22, 2016*

GPCR-Based Drug Discovery - PART 2

Signaling and Pharmacological Complexities

This meeting explores the unique aspects of G-protein coupled receptor (GPCR) signaling that make the receptors such challenging yet fruitful targets by offering multiple avenues for pharmacological modulation. Insights on receptor trafficking, modifications, desensitization and selective/biased coupling and how that impacts design of GPCR-targeted compounds will also be discussed.

RECOMMENDED ALL ACCESS PACKAGE:

- September 19 Short Course: GPCR Structure-Based Drug Discovery
- September 20-21 Conference: GPCR-Based Drug Discovery - Part 1
- September 21-22 Conference: GPCR-Based Drug Discovery - Part 2
- September 21 Short Course: Introduction to Allosteric Modulators

WEDNESDAY, SEPTEMBER 21

11:20 am Conference Registration Open

11:25 Enjoy Lunch on Your Own

12:50 pm Plenary Keynote Program *(See page 3 for details.)*

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

GPCR COMPLEXITIES: ALLOSTERISM, BIASED SIGNALING AND MORE

3:20 Chairperson's Opening Remarks
Annette Gilchrist, Ph.D., Professor, Pharmacology, Midwestern University

3:35 Directing Opioid Receptor Signaling to Improve Analgesic Therapies
Laura M. Bohn, Ph.D., Professor, Departments of Molecular Therapeutics & Neuroscience, The Scripps Research Institute
GPCRs propagate signals via interactions with multiple effectors, including G proteins and {beta}arrestins. GPCRs in different contexts, such as different neuronal populations or different cellular compartments, can couple to different effectors. We are finding that opioid receptor ligands that promote signaling towards G protein signaling over {beta}arrestin recruitment *in vitro* can be used to dissociate from analgesic responses and certain side effects *in vivo*.

4:05 GPCR-Mediated G Protein Activation
Heidi Hamm, Ph.D., Professor, Department of Pharmacology, Vanderbilt University Medical Center
GPCR mediated heterotrimeric G protein activation is an obligate step in signal transduction. Our laboratory has used biophysical approaches to show that GPCRs open up a binding site during activation that interacts with Gα's alpha 5 (α5) helix leading to a rigid body rotation and translation of this helix. The repositioned α5 helix changes its hydrophobic interactions with the core of the protein, leading to allosteric changes, nucleotide release and G protein activation.

Sponsored by PerkinElmer For the Better

4:35 360 Degree Characterization of GPCR Function through Ligand Binding, Functional and Phenotypic Analyses
Roger Bosse, Ph.D., Senior Market Segment Leader, PerkinElmer
We will present several examples showing how combining ligand binding, functional and phenotypic analyses, leads to the discovery and development of an entirely new generation of GPCR drugs including allosteric regulators, inverse agonists and drugs targeting hetero-oligomeric complexes.

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

5:40 Positive Allosteric Modulators of mGlu4 for the Treatment of Parkinson's Disease: From HTS to Pre-Clinical Leads
Corey R. Hopkins, Ph.D., Research Assistant Professor, Vanderbilt Center for Neuroscience Drug Discovery
Disorders of the CNS remain some of the most elusive targets for the pharmaceutical industry and academic researchers to tackle. Although Parkinson's disease (PD) is the second most common neurodegenerative disease, no effective long term treatment or cure has been developed. Utilizing a functional HTS and medicinal chemistry approach, we have discovered a novel series of PAMs of the metabotropic glutamate receptor 4 (mGlu4).

6:10 Structural Basis of Allostery in Chemokine Receptors
Irina Kufareva, Ph.D., Project Scientist, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego
Interaction of chemokines with 7TM receptors on cell surface drives cell migration in the context of development, immunity, inflammation, and cancer, making it an attractive therapeutic target. However, therapeutic development has been hindered by the pharmacological complexities of receptor:chemokine system and by the inherently limited druggability of receptor:chemokine interfaces. Allosteric regulators may be a new word in the discovery of anti-chemokine receptor therapeutics. Using molecular modeling, biophysical and functional experiments, and X-ray crystallography, we obtained first insights into the structural basis of allostery in CXCR4, CCR2, and CCR5.

6:40 End of Day

THURSDAY, SEPTEMBER 22

7:30 am Registration Open and Morning Coffee

GPCRS IN DISEASE

8:30 Chairperson's Remarks
Jeffrey L. Benovic, Ph.D., Professor and Chair, Department of Biochemistry & Molecular Biology, Thomas Jefferson University

8:45 FEATURED PRESENTATION: GPCRs in Cancer: An Untapped Opportunity

Paul Insel, M.D., Distinguished Professor, Pharmacology and Medicine, University of California San Diego

GPCRs are the most common drug targets but have largely been ignored as therapeutic targets in cancer, other than endocrine-driven tumors, even though GPCRs can regulate many features of the malignant phenotype. Thus, GPCRs may be useful targets directed at cancer cells themselves but in addition, in cells of the tumor microenvironment—including in pancreatic cancer, a tumor in desperate need of new therapies.

9:15 Desensitization of Cardiac Adrenergic Receptor Signaling through Receptor Cross-Talk

Kevin Xiang, Ph.D., Professor, Pharmacology, University of California Davis

A growing list of cell receptors, including GPCRs, RTKs, and cytokine receptors, impair cardiac adrenergic receptor via both GRKs and second messenger-dependent kinases. Here, I will focus on the impacts of hyperinsulinemia on development of cardiac dysfunction associated with Type-2 diabetes and obesity, and discuss the phosphodiesterase 4D in the cross talk between insulin receptor and adrenergic receptor in heart.

9:45 Selected Poster Presentations

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

11:10 Discovery of the First Orally Bioavailable GPR39 Agonists

Vidya Kunjathoor, Ph.D., Scientist, Cardiovascular & Metabolic Disease Area, Novartis Institutes for BioMedical Research, Inc.

We report on the identification of highly potent and orally bioavailable GPR39 agonists in mice. The compound was found in a phenotypic screening campaign and was transformed into compound 2 with good activity on both the rat and human GPR39 receptor. This compound was further optimized to improve ligand efficiency and pharmacokinetic properties to yield GPR39 agonists for the potential oral treatment of type 2 diabetes.

11:40 CXCR4 Cyclic Peptide Antagonists for Cancer

Sheng Bin Peng, Ph.D., Group Leader and Senior Research Advisor, Eli Lilly & Co.

We present on our anti-CXCR4 cyclic peptide inhibitor that is now in Phase 2 clinical studies for human hematological malignancies.

12:10 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

GPCR COMPLEXITIES: ALLOSTERISM, BIASED SIGNALING AND MORE

2:15 Chairperson's Remarks

Thomas J. Gardella, Ph.D., Associate Professor, Medicine, Massachusetts General Hospital, Harvard

2:20 FEATURED PRESENTATION: Arrestin/Rhodopsin Crystal Structure and Implications for Drug Design

H. Eric Xu, Ph.D.,Professor, Cancer Research, Van Andel Institute (VAI)

I present the work of our team on using SLAC's Linac Coherent Light Source (LCLS), the world's first hard X-ray free electron laser, to generate the first three-dimensional map of arrestin while it was linked with a GPCR. This capability allowed us to create a three-dimensional image of the arrestin-rhodopsin complex at an atomic level—a much higher resolution than is possible with conventional X-ray technology.

2:50 Biasing Beta2-Adrenergic Receptor Signaling

Jeffrey L. Benovic, Ph.D., Professor and Chair, Department of Biochemistry & Molecular Biology, Thomas Jefferson University

GPCRs interact with three families of proteins in a ligand-dependent manner: G proteins, GRKs and arrestins. These interactions play an essential role in regulating GPCR signaling, trafficking and degradation. I will discuss recent strategies that we have used to bias b2-adrenergic receptor signaling to promote Gs bias to regulate airway function and arrestin bias to regulate cardiovascular function.

3:20 Session Break

3:30 Late Breaking Presentation: SCFA Receptors are Novel Mediators of Pancreatic β Cell Function

Brian Layden, M.D., Ph.D., Associate Professor, Department of Medicine, University of Illinois at Chicago

Nutrient sensing receptors are key metabolic mediators. Two nutrient sensing receptors, short chain fatty acid (SCFA) receptors (FFA2 and FFA3) are uniquely responsive to gut microbiota derived nutrients (such as acetate, propionate, and butyrate). Recent studies have investigated their role in pancreatic ß cell biology. Through a combination of studies, we have helped define their role in ß cell function, revealing new therapeutic opportunities for type 2 diabetes.

4:00 Small Molecule Targeting of G Protein β/γ Subunit Signaling

Alan V. Smrcka, Ph.D., Professor, Pharmacology and Physiology, University of Rochester School of Medicine

Our laboratory has identified a number of small molecules that inhibit various aspects of G β/γ subunit function. This presentation will discuss the biochemical basis for the mechanism of action of these compounds, their pharmacological efficacy in various preclinical models of disease, and their utility in the dissection of GPCR signaling pathways.

4:30 Extended cAMP GPCR-Generated Signaling

Thomas J. Gardella, Ph.D., Associate Professor, Medicine, Massachusetts General Hospital, Harvard

5:00 Close of Conference

Thirteenth Annual | *September 20-21, 2016*

Advances in Gene Editing and Gene Silencing - PART 1

Utilizing CRISPR and RNAi to Identify New Drug Targets and Therapies

The two-part conference on Advances in Gene Editing and Gene Silencing will cover the latest in the use of CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)/Cas9-based gene editing and RNA interference (RNAi) for use in drug discovery and for developing novel drug therapies. Part 1 will cover the use of CRISPR/Cas9 and RNAi for identifying new drug targets and therapies. It will bring together experts from all aspects of basic science and clinical research to talk about how and where gene editing and RNAi can be best applied. Scientists and clinicians from pharma/biotech as well as from academic and government labs will share their experiences leveraging the utility of gene editing for target discovery, disease modeling, and for creating cell and viral therapies.

RECOMMENDED ALL ACCESS PACKAGE:

- September 19 Short Course: Introduction to Gene Editing
- September 19 Symposium: Understanding CRISPR: Mechanisms and Applications
- September 20-21 Conference: Advances in Gene Editing and Gene Silencing - Part 1
- September 21-22 Conference: Advances in Gene Editing and Gene Silencing - Part 2
- September 21 Short Course: Functional Screening Strategies Using CRISPR and RNAi

TUESDAY, SEPTEMBER 20

7:00 am Registration Open and Morning Coffee

KEYNOTE SESSION: GENOME EDITING FOR *IN VIVO* APPLICATIONS

8:05 Chairperson's Opening Remarks

Bryan R. Cullen, Ph.D., James B. Duke Professor of Molecular Genetics and Microbiology and Director, Center for Virology, Duke University

8:20 AAV for Gene Therapy and Genome Editing

James Wilson, M.D., Ph.D., Professor, Department of Pathology and Laboratory Medicine, Perelman School of Medicine; Director, Orphan Disease Center and Director, Gene Therapy Program, University of Pennsylvania

In vivo delivery of nucleic acid therapeutics remains the primary barrier to success. My lab has focused on the use of vectors based on adeno-associated virus (AAV) for achieving success in pre-clinical and clinical applications of gene replacement therapy. Most of the current academic and commercial applications of *in vivo* gene replacement therapy are based on endogenous AAVs we discovered as latent viral genomes in primates. These vectors are reasonably safe and efficient for application of gene replacement therapy. The emergence of genome editing methods has suggested more precise and effective methods to treat inherited diseases in which genes are silenced or mutations are corrected. AAV vectors have been the most efficient platform for achieving genome editing *in vivo*. We will review our attempts to achieve therapeutic genome editing in animal models of liver disease using AAV.

9:20 Using CRISPR/Cas to Target and Destroy Viral DNA Genomes

Bryan R. Cullen, Ph.D., James B. Duke Professor of Molecular Genetics and Microbiology and Director, Center for Virology, Duke University

A number of pathogenic human DNA viruses, including HBV, HIV-1 and HSV1, cause chronic diseases in humans that remain refractory to cure, though these diseases can be controlled by antivirals. In addition the DNA virus HPV causes tumors that depend on the continued expression of viral genes. Here, I will present data demonstrating that several of these viruses can be efficiently cleaved and destroyed using viral vectors that express Cas9 and virus-specific guide RNAs, thus providing a potential novel approach to treatment.

9:50 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

10:35 Targeted Endonucleases as Antiviral Agents: Promises and Pitfalls

Keith R. Jerome, M.D., Ph.D., Member, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center; Professor and Head, Virology Division, Department of Laboratory Medicine, University of Washington

Genome editing offers the prospect of cure for infections such as HIV, hepatitis B virus, herpes simplex, and human papillomavirus, by disruption of essential viral nucleic acids or the human genes encoding receptors needed for viral entry. This talk will highlight the most recent laboratory data and the challenges still ahead in bringing this technology to the clinic.

11:05 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

High throughput, combinatorial approaches have revolutionized small molecule drug discovery. Here we describe our 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 applications for the treatment of genetic diseases, viral infections and cancers.

11:35 PANEL DISCUSSION: CRISPR/Cas: A Realistic and Practical Look at What the Future Could Hold

Moderator: Bryan R. Cullen, Ph.D., James B. Duke Professor of Molecular Genetics and Microbiology and Director, Center for Virology, Duke University

Participants: Session Speakers

Each speaker will spend a few minutes sharing their viewpoints and experiences on where things stand with using the CRISPR/Cas system for *in vivo* applications. Attendees will have an opportunity to ask questions and share their opinions.

12:05 pm CRISPR/Cas9 for the Screening of the Human Kinome – A Pilot Study in an Aggressive Pediatric Cancer Cell Line

Sponsored by ThermoFisher SCIENTIFIC

Simone T. Sredni, M.D., Ph.D., Research Assistant Professor, Neurological Surgery, Northwestern University Feinberg School of Medicine, Ann and Robert H. Lurie Children's Hospital of Chicago

The CRISPR-Cas9 system for genome editing is a powerful tool to identify genes involved in vital biological processes. A systematic functional screening of the human kinome has the potential to reveal molecules that are essential for tumor survival, growth and migration. We will describe our experience using the Invitrogen LentiArray™ CRISPR library to mutate 160 kinases in a highly malignant pediatric tumor cell line. We will discuss our approach for the screening, monitoring the stably mutated cells lines, and validate our findings. The CRISPR/Cas9 genome editing technology can help identifying new potential therapeutic targets for cancer.

12:35 Session Break

12:45 Luncheon Presentation: Building a Better Research Story: Screening with shRNA and CRISPR

Sponsored by MilliporeSigma

Ryan Raver, Ph.D., Global Product Manager, Functional Genomics, MilliporeSigma

Parallel RNAi and CRISPR-Cas9 screens have opened up new opportunities for assay development, screening and validation. In partnership with the Wellcome Trust Sanger Institute, MilliporeSigma has developed the first whole genome arrayed CRISPR library. Topics include evaluation of complementary shRNA and CRISPR screens, and the efficacy of each. As each technology has distinct biological processes, the advantages and disadvantages of each for uncovering novel targets will be discussed in detail.

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

COMPLEMENTING THE USE CRISPR & RNAi FOR DISEASE MODELING

2:05 Chairperson's Remarks

Ralph Garippa, Ph.D., Director, RNAi & Gene Editing Core Facility, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center

2:15 Use of CRISPR and Other Genomic Technologies to Advance Drug Discovery

Namjin Chung, Ph.D., Head, Functional Genomics Platform, Discovery Research, AbbVie, Inc.

Advances in CRISPR gene editing and genomics technologies are rapidly changing biopharmaceutical R&D landscape, from target ID and validation, to drug mechanism of action, and to translational science. We will use vignettes of various genomics research applications within AbbVie R&D environment as a witness to this paradigm shift currently ongoing in the drug industry.

2:45 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

The combination of human stem cell retinal modeling, CRISPR/Cas9 genome editing, and high content screening technology provides unparalleled opportunities for the study of retinal biology, disease modeling, drug screening, and the development of novel gene therapy-based treatment approaches. The use of these technologies to model and identify new targets for diseases involving retinal ganglion cells, photoreceptors, and retinal pigment epithelial cells will be discussed.

3:15 Sponsored Presentation *(Opportunity Available)*

3:45 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

4:25 Comparing Arrayed siRNA and CRISPR Approaches Towards Functional Genomics Screening

Scott Martin, Ph.D., Group Lead, Functional Genomics, Genentech Inc.

RNAi has been a workhorse for loss-of-function screening. Although powerful, RNAi is hampered by false positives. New screening technologies based on CRISPR/Cas9 appear less prone to off-target effects. CRISPR/Cas9 screens are conducted in pooled formats. However, this format is not amenable to many assays. In an effort to expand its utility, we explored the use of arrayed CRISPR/Cas9 screening with synthetic CRISPR RNAs.

4:55 Technology Panel: Trends in CRISPR & RNAi Technologies

Moderator: Ralph Garippa, Ph.D., Director, RNAi & Gene Editing Core Facility, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center

Panelists: Opportunity Available for Sponsoring Companies

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

5:25 Welcome Reception in the Exhibit Hall

6:25 End of Day

WEDNESDAY, SEPTEMBER 21

7:30 am Registration Open and Morning Coffee

EXPLORING THE VERSATILITY OF CRISPR/Cas9

8:00 Chairperson's Opening Remarks
Geoffrey Bartholomeusz, Ph.D., Associate Professor and Director, Target Identification and Validation Program, Department of Experimental Therapeutics, Division of Cancer Medicine, The University of Texas M.D. Anderson Cancer

8:10 Functional Genomics Using CRISPR-Cas9: Technology and Applications
Neville Sanjana, Ph.D., Core Faculty Member, New York Genome Center and Assistant Professor, Department of Biology & Center for Genomics and Systems Biology, New York University
The easy programmability of CRISPR/Cas9 suggests a new way to interrogate gene function at the DNA level instead of the transcript level. By combining genome engineering with functional genomic screens, we have developed genome-wide libraries for negative and positive selection screening in human and mouse cells. In addition, we have developed techniques for adapting CRISPR screens into noncoding regions of the genome, where it can be challenging to identify functional elements.

8:40 Therapeutic Gene Editing With CRISPR/Cas9
TJ Cradick , Ph.D., Head of Genome Editing, CRISPR Therapeutics
CRISPR-Cas9 systems are programmable nucleases that can be designed to precisely edit the genome to correct disease-causing mutations. CRISPR/Cas systems have enabled a wide range of editing methods in humans and also have enabled genome editing in a long list of plant and animal species. CRISPR/Cas systems are being optimized to drive gene editing. Bioinformatics and design strategies are used to improve and ensure specificity. We will also discuss the use of new CRISPR ortholog systems.

9:10 Towards Combinatorial Drug Discovery: Mining Heterogenous Phenotypes from Large Scale RNAi/Drug Perturbations
Arvind Rao, Ph.D., Assistant Professor, Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center
In this talk, we will outline methodologies and share our experiences for the interpretation of cellular phenotypes obtained via high throughput microscopy on drug screens in patient-derived glioma cell lines as well as of Triple negative breast tumors, in 3D culture. The large volume and heterogeneity in cellular phenotypes across the population make this a challenging task. We will also describe frameworks to quantitatively interpret such heterogeneity and prioritize hits (genes from RNAi, drugs from screens).

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

10:25 CRISPR in Stem Cell Models of Eye Disease
Alexander Bassuk, M.D., Ph.D., Associate Professor of Pediatrics, Department of Molecular and Cellular Biology, University of Iowa
Induced pluripotent stem cells (iPSCs) generated from patient fibroblasts could potentially be used as a source of autologous cells for transplantation in retinal disease. Patient-derived iPSCs, however, would still harbor disease-causing mutations. To generate healthy patient-derived cells, we used CRISPR/Cas9 to precisely repair a point mutation that causes retinal degeneration. This important proof-of-concept finding supports the development of personalized iPSC-based transplantation therapies for retinal disease.

10:55 CRISPR in Mouse Models of Eye Disease
Vinit Mahajan, M.D., Ph.D., Assistant Professor of Ophthalmology and Visual Sciences, University of Iowa College of Medicine
Massive parallel sequencing enables identification of numerous genetic variants, but determining pathogenicity of any one mutation is daunting. The most commonly studied preclinical model of retinal degeneration is homozygous for two different mutations in the same gene. We used the CRISPR/Cas9 gene editing system to identify the causative variant and rescue neurofunction. This is among the first examples of CRISPR-mediated repair in a sensory system.

11:25 Enjoy Lunch on Your Own

12:50 pm Plenary Keynote Program *(See page 3 for details.)*

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

3:20 End of Conference

Thirteenth Annual | *September 21-22, 2016*

Advances in Gene Editing and Gene Silencing - PART 2

Improving CRISPR and RNAi Technology for Functional Screening

The two-part conference on Advances in Gene Editing and Gene Silencing will cover the latest in the use of CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)/Cas9-based gene editing and RNA interference (RNAi) for use in drug discovery and for developing novel drug therapies. Part 2 will cover the latest in the use of CRISPR/Cas9 and RNAi for functional screening. It will cover everything from assay design to data analysis when conducting low and high throughput screens and generating cellular models, both ***in vitro*** and ***in vivo***, using CRISPR/Cas9, siRNA (small interfering RNA), and shRNA (short hairpin RNA). Speakers will share their experiences leveraging the utility of these diverse screening platforms for a wide range of applications.

RECOMMENDED ALL ACCESS PACKAGE:

- September 19 Short Course: Introduction to Gene Editing
- September 19 Symposium: Understanding CRISPR: Mechanisms and Applications
- September 20-21 Conference: Advances in Gene Editing and Gene Silencing - Part 1
- September 21-22 Conference: Advances in Gene Editing and Gene Silencing - Part 2
- September 21 Short Course: Functional Screening Strategies Using CRISPR and RNAi

WEDNESDAY, SEPTEMBER 21

11:20 am Conference Registration Open

11:25 Enjoy Lunch on Your Own

12:50 pm Plenary Keynote Program *(See page 3 for details.)*

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

INTERPRETING & PRIORITIZING DATA FROM CRISPR/RNAi SCREENS

3:20 Chairperson's Opening Remarks

Eugen Buehler, Ph.D., Group Leader, Informatics, National Center for Advancing Translational Sciences, National Institutes of Health

3:35 Differences between CRISPR/RNAi Necessitate Re-Thinking Analysis Algorithms

Eugen Buehler, Ph.D., Group Leader, Informatics, National Center for Advancing Translational Sciences, National Institutes of Health

Recent CRISPR screens illustrate their low rate of false positives. Although initial CRISPR screens published have been analyzed using methods developed first for RNAi screening, the data is distinctly different. We will quantify the differences in false positives between the two screening modalities and suggest how analysis methods can be better tailored to CRISPR screens.

4:05 CARD: An Interactive Web-Based Application for Comprehensive Analysis of RNAi-Screen Data

Bhaskar Dutta, Ph.D., Principal Biomedical Informatics Scientist, AstraZeneca

Screen data can be susceptible to myriad of experimental biases, many of which can be corrected by computational analysis. We have developed a web-based platform for integrated analysis and visualization of RNAi screen data, named CARD. CARD allows the user to seamlessly carry out sequential steps, including normalization, off-target analysis, integration of gene expression data, optimal thresholds for hit selection and network/pathway analysis.

4:35 Sponsored Presentation *(Opportunity Available)*

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

5:40 Extracting Novel Insight from Genome-Scale Genetic Screens through Integrated Iterative Analysis

Iain Fraser, Ph.D., Investigator, Laboratory of Systems Biology, National Institute of Allergy and Infectious Diseases, National Institutes of Health

The interpretation of genome-wide screens through annotated databases of known molecular processes has been shown to increase the validation rates and the interpretability of those screens, yet these approaches come at a cost of missing novel, non-annotated hits. We will present an approach that integrates the advantages of annotated databases with statistical and network corrections allowing novel hits to still emerge.

6:10 PANEL DISCUSSION: Strategies to Interpret and Prioritize Data from CRISPR and RNAi Screens

Moderator: Eugen Buehler, Ph.D., Group Leader, Informatics, National Center for Advancing Translational Sciences, National Institutes of Health

Panelists: Session Speakers

Each speaker will spend a few minutes sharing their ideas and experiences on tools and techniques for handling data analysis. Attendees will have an opportunity to ask questions and share their opinions.

6:40 End of Day

THURSDAY, SEPTEMBER 22

7:30 am Registration Open and Morning Coffee

USING CRISPR/RNAi FOR TARGET DISCOVERY & PATHWAY ANALYSIS

8:30 Chairperson's Remarks

John Doench, Ph.D., Associate Director, Genetic Perturbation Platform, Broad Institute of Harvard and MIT

8:45 Strategies and Applications Using shRNA and CRISPR Technology for Identification of New Druggable Targets

Donald Apanovitch, Ph.D., Director, Functional Genomics (Oncology), Pfizer Research

Application of RNAi loss of function negative selection screens is a well-documented platform for identification of essential gene function regulating oncogenic pathways and tumorigenesis. In collaboration with the Cold Spring Harbor and the IBB group of Pfizer Oncology we have designed and validated druggable and target specific lentiviral shRNA libraries. Overview of our mir-based libraries and screening strategy will be presented along with CRISPR applications as an orthogonal tool to characterize differences in shRNA rescue experiments.

9:15 High Throughput Phenotypic Screening in Drug Discovery Using the CRISPR-Cas9 System

Greg Hoffman, Ph.D., Investigator III, Developmental & Molecular Pathways Department, Novartis Institutes for Biomedical Research

The CRISPR-Cas9 system has revolutionized high throughput forward genetics in mammalian cells. I will present our work applying CRISPR screening for the discovery of novel targets in complex models of human disease using FACS based assays. I will describe results of a systematic comparison of pooled CRISPR and shRNA libraries, insights on improving gRNA activity, and methods for validation of hits from CRISPR screens.

9:45 CRISPR Libraries for Functional Genomics: Optimizing On-Target Activity and Avoiding Off-Target Effects

John Doench, Ph.D., Associate Director, Genetic Perturbation Platform, Broad Institute of Harvard and MIT

The use of more active and specific CRISPR libraries is critical for maximizing the productivity of genetic screens. Here I will discuss considerations for genome-wide pooled screens using conventional CRISPR knockout libraries using Cas9 from S. pyogenes. I will also discuss the use of other Cas9 proteins for this purpose, as well as orthogonal approaches, such as CRISPRa and CRISPRi technologies.

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

11:10 A High Throughput Functional Genomics Screening Approach to Identify Modulators of Nonsense-Mediated mRNA Decay to Treat Mendelian Disorders

Madhu Lal-Nag, Ph.D., Group Leader, Trans-NIH RNAi Facility, National Center for Advancing Translational Sciences, National Institutes of Health

Many genetic disorders are attributed to a premature termination codon (PTC), and cells have evolved a surveillance pathway called nonsense-mediated mRNA decay (NMD) to eliminate PTC-containing transcripts. Identification of regulatory effectors could help manipulate the NMD machinery, allowing targeted interventions for PTC-associated diseases. A genome-wide RNAi screen identified known and novel players of the NMD pathway, and the top hits were validated with CRISPR to determine the extent of pathological phenotypes for NMD.

11:55 Associating Tumor Phenotype with Genomics across Biological Scale

Arvind Rao, Ph.D., Assistant Professor, Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center

Sponsored by Dharmacon™ part of GE Healthcare

12:10 pm Arrayed CRISPR Screening with Synthetic crRNA Libraries for High-Throughput Loss-of-Function Studies

Louise Baskin, Senior Product Manager, Dharmacon, GE Healthcare

While pooled lentiviral sgRNAs screens have demonstrated utility for loss-of-function studies, there are limitations in the assay types that can be utilized. Arrayed screens offer the advantage of more sophisticated assays, such as high-content microscopy. High-throughput synthesis allows rapid generation of large collections of CRISPR RNAs (crRNAs) in arrayed formats. We will demonstrate the application of arrayed screening with synthetic crRNA libraries across multiple assay types, and present considerations for experimental success.

12:40 Session Break

Sponsored by CELLECTA Discovery is *Yours*.

12:50 Optimizing CRISPR for *in vitro* and *in vivo* Pooled Functional Genetic Screens

Paul Diehl, Ph.D., Director, Business Development, Cellecta, Inc.

Well-designed pooled lentiviral-based CRISPR/Cas9 libraries provide an efficient tool for genome-wide loss-of-function genetic screening to identify genes required for biological responses or disease pathologies. Generating robust screening results with complex heterogeneous pools of sgRNA, however, requires effective and efficient targeted gene interruption. We will review improvements we have discovered that produce more consistent results with stronger signals, and show how these enhancements provide better results in both *in vitro* and *in vivo* pooled CRISPR screens.

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

CRISPR-BASED FUNCTIONAL SCREENING FOR ONCOLOGY

2:15 Chairperson's Remarks

Roderick Beijersbergen, Ph.D., Group Leader, Netherlands Cancer Institute and Head, NKI Robotics and Screening Center

2:20 Large Scale CRISPR Screens for Discovery of Genotype Specific Combination Therapies

Roderick Beijersbergen, Ph.D., Group Leader, Netherlands Cancer Institute and Head, NKI Robotics and Screening Center

The complexity and heterogeneity of cancer, the extensive crosstalk between pathways and unanticipated feedback control are underlying the limited long-

term success of targeted therapeutics in the clinic. We use large-scale functional genomic screening technologies including shRNA/CRISPR-based gene editing in combination with (clinically) relevant screening models for the identification of dependencies in the context of specific genetic alterations. Using this platform we have identified novel effective drug combinations that are currently in the clinic.

2:50 GPCR-Mediated cAMP as an Immune Checkpoint in Cancer Identified by RNAi Screening

Tillmann Michels, Head of Research Group, Immune Checkpoint Inhibitors, Department of Interventional Immunology, Regensburg Center for Interventional Immunology; Member, Department of Translational Immunology, German Cancer Research Center

Immune checkpoint blockade has revolutionized cancer therapy. Our group screened several tumor entities in conjunction with tumor-infiltrating lymphocytes (TILs) for novel immune modulators. We found that many immune checkpoints are tumor-restricted but the underlying mechanisms are shared between tumor entities. These mechanism range from inhibition of TIL-mediated apoptosis to cAMP-mediated inhibition of TILs.

3:20 Session Break

4:00 Applying Functional Genomics in Mouse Models of Human Cancer

Yejing Ge, Ph.D., Postdoctoral Fellow, Laboratory of Dr. Elaine Fuchs, Department of Mammalian Cell Biology and Development, Rockefeller University

Using skin as paradigm, we describe the first panoramic view of microRNAs during the development, homeostasis and malignant transformation of skin epithelium. We devised lentiviral microRNAs expression platform and conducted pooled *in vivo* functional screens for oncomiRs in mice. Empowered by mouse genetics and high throughput approaches, we unveiled a rich set of putative microRNAs that drive skin malignancy, and their oncogenic targets.

4:30 A CRISPR/Cas9 System to Increase Homologous Recombination Repair

Ciro Bonetti, Ph.D., Postdoctoral Scientist, Laboratory of Dr. Andrea Ventura, Memorial Sloan-Kettering Cancer Center

CRISPR/Cas9 genome editing technology has been shown to be very effective to perform inactivation or activation of specific genes. However, engineering precise genomic modifications remains a challenge due to the low efficiency of repair of the double strand breaks through the homologous recombination pathway. Here, I will discuss a novel method to skew the repair away from non-homologous end-joining towards homologous repair pathway.

5:00 Close of Conference

Second Annual | *September 20-21, 2016*

Gene Therapy Breakthroughs

Novel Approaches and Techniques Enabling Better and Safer Therapies

While the challenges and risks associated with gene therapy 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 is once again being embraced with renewed hope and enthusiasm. Cambridge Healthtech Institute's conference on Gene Therapy Breakthroughs will bring together experts who will discuss the recent progress in gene therapy and how it can be applied. The conference will highlight scientific breakthroughs, use of innovative technologies, novel approaches to tackle gene delivery, emerging translational challenges, and will bring together the right people to discuss expected pitfalls and existing opportunities in this field.

RECOMMENDED ALL ACCESS PACKAGE:

- September 19 Symposium: Strategies for Tackling Rare Genetic Diseases
- September 20-21 Conference: Gene Therapy Breakthroughs
- September 21-22 Conference: Advances in Gene Editing and Gene Silencing - Part 2

TUESDAY, SEPTEMBER 20

7:00 am Registration Open and Morning Coffee

KEYNOTE SESSION: GENOME EDITING FOR IN VIVO APPLICATIONS

8:05 Chairperson's Opening Remarks

Bryan R. Cullen, Ph.D., James B. Duke Professor of Molecular Genetics and Microbiology and Director, Center for Virology, Duke University

8:20 AAV for Gene Therapy and Genome Editing

James Wilson, M.D., Ph.D., Professor, Department of Pathology and Laboratory Medicine, Perelman School of Medicine; Director, Orphan Disease Center and Director, Gene Therapy Program, University of Pennsylvania

In vivo delivery of nucleic acid therapeutics remains the primary barrier to success. My lab has focused on the use of vectors based on adeno-associated virus (AAV) for achieving success in pre-clinical and clinical applications of gene replacement therapy. Most of the current academic and commercial applications of *in vivo* gene replacement therapy are based on endogenous AAVs we discovered as latent viral genomes in primates. These vectors are reasonably safe and efficient for application of gene replacement therapy. The emergence of genome editing methods has suggested more precise and effective methods to treat inherited diseases in which genes are silenced or mutations are corrected. AAV vectors have been the most efficient platform for achieving genome editing *in vivo*. We will review our attempts to achieve therapeutic genome editing in animal models of liver disease using AAV.

9:20 Using CRISPR/Cas to Target and Destroy Viral DNA Genomes

Bryan R. Cullen, Ph.D., James B. Duke Professor of Molecular Genetics and Microbiology and Director, Center for Virology, Duke University

A number of pathogenic human DNA viruses, including HBV, HIV-1 and HSV1, cause chronic diseases in humans that remain refractory to cure, though these diseases can be controlled by antivirals. In addition the DNA virus HPV causes tumors that depend on the continued expression of viral genes. Here, I will present data demonstrating that several of these viruses can be efficiently cleaved and destroyed using viral vectors that express Cas9 and virus-specific guide RNAs, thus providing a potential novel approach to treatment.

9:50 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

10:35 Targeted Endonucleases as Antiviral Agents: Promises and Pitfalls

Keith R. Jerome, M.D., Ph.D., Member, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center; Professor and Head, Virology Division, Department of Laboratory Medicine, University of Washington

Genome editing offers the prospect of cure for infections such as HIV, hepatitis B virus, herpes simplex, and human papillomavirus, by disruption of essential viral nucleic acids or the human genes encoding receptors needed for viral entry. This talk will highlight the most recent laboratory data and the challenges still ahead in bringing this technology to the clinic.

11:05 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

High throughput, combinatorial approaches have revolutionized small molecule drug discovery. Here we describe our 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 applications for the treatment of genetic diseases, viral infections and cancers.

11:35 PANEL DISCUSSION: CRISPR/Cas: A Realistic and Practical Look at What the Future Could Hold

Moderator: Bryan R. Cullen, Ph.D., James B. Duke Professor of Molecular Genetics and Microbiology and Director, Center for Virology, Duke University

Participants: Session Speakers

Each speaker will spend a few minutes sharing their viewpoints and experiences on where things stand with using the CRISPR/Cas system for *in vivo* applications. Attendees will have an opportunity to ask questions and share their opinions.

12:05 pm Sponsored Presentation *(Opportunity Available)*

12:35 Session Break

12:45 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Lunch on Your Own**

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

NEW STRATEGIES FOR BETTER SPECIFICITY AND DELIVERY

2:05 Chairperson's Remarks

Joseph D. Gold, Ph.D., Director, Manufacturing, Center for Biomedicine and Genetics, Beckman Research Institute

2:15 Large-Scale Production of Cell Therapies for Regenerative Medicine

Joseph D. Gold, Ph.D., Director, Manufacturing, Center for Biomedicine and Genetics, Beckman Research Institute

There are multiple key decisions to be made in the course of conceptualizing and producing a stem cell-derived therapeutic with profound implications for every step from cell choice to eventual use in clinical trials. I will present lessons learned in the ongoing process of designing a large-scale stem cell-based therapy for heart disease that are relevant to other disease targets and cell sources as well.

2:45 Directed Evolution of New Viruses for Therapeutic Gene Delivery

David Schaffer, Ph.D., Professor of Chemical and Biomolecular Engineering, Bioengineering, Molecular and Cell Biology, and Neuroscience; Director, Berkeley Stem Cell Center, University of California, Berkeley

Adeno-associated viral (AAV) vectors have been increasingly successful in clinical trials; however, viruses face many delivery barriers that limit their efficacy for most disease targets. We have developed directed vector evolution – the iterative genetic diversification of a viral genome and functional selection for desired properties – to engineer novel, optimized AAV vectors for efficient, selective delivery for a range of tissue and disease targets.

3:15 Sponsored Presentation *(Opportunity Available)*

3:45 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

4:25 Lentiviral Vectors for Gene Therapy

Manjunath N. Swamy, M.D., Professor of Biomedical Sciences and Co-Director of the Center of Emphasis in Infectious Diseases, Paul L Foster School of Medicine, Texas Tech University Health Sciences Center

Lentiviral vectors allow transduction of mediators of RNAi and gene editing in a wide variety of cells. We have designed lentiviral vectors to 1) express virtually unlimited numbers of microRNA mimicking shRNAs (shRNA-miRs) using minimal flanking sequence from multiple endogenous miRNAs, 2) transiently express zinc finger nucleases using integrase-deficient vectors and 3) pre-pack Cas9 protein in the viral particles for safer gene editing.

4:55 AAV Caspid Engineering

Miguel Sena Esteves, Ph.D., Associate Professor, Department of Neurology, Gene Therapy Center, University of Massachusetts Medical School

Adeno-associated virus vectors have become the leading platform for development of *in vivo* gene therapies for neurological diseases. We have developed new AAV vectors for widespread gene delivery to the CNS through vascular infusion in adult animals through peptide grafting and *in vivo* library selection. These new neurotropic AAVs have achieved CNS-wide silencing of gene expression using gene-specific microRNAs.

5:25 Welcome Reception in the Exhibit Hall with Poster Viewing

6:25 End of Day

WEDNESDAY, SEPTEMBER 21

7:30 am Registration Open and Morning Coffee

USE OF NOVEL TOOLS AND METHODOLOGIES

8:00 Chairperson's Opening Remarks

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

8:10 Gene Editing Technologies for the Treatment of Liver Diseases

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

Efforts have been intensified to develop liver-targeted approaches using novel gene editing technologies, including ZFN, TALEN, CRISPR/Cas and PITCh. While each of these methods utilizes a distinct mechanism at the genomic level, they all are dependent on an efficient delivery system to the target site within the host cell. Clinical trials for liver gene therapy have entered an exciting era and are already showing promise with the development of novel technologies and delivery options.

8:40 Gene Editing for Generating Exogenic Organs and Cells

Walter C. Low, Ph.D., Professor and Associate Head for Research, Department of Neurosurgery, Stem Cell Institute, University of Minnesota Medical School

A major goal of stem cell research is generating organs and cells for repair and replacement in degenerative disorders. Recent advances in gene editing and stem cell biology have converged to demonstrate generating specific organs and types of cells. We have used gene editing technologies to knockout key genes required for the development of the pancreas, liver, skeletal muscle, kidney, and lungs, as well as specific types of neurons, and immune cells. Stem cell complementation in knockout blastocysts for generating targeted organs and cells is discussed.

9:10 Novel *in vivo* Genome Editing Technology and Application for Gene Therapy

Keiichiro Suzuki, Ph.D., Research Associate, Laboratory of Dr. Juan Carlos Izpisua Belmonte, Gene Expression Laboratory, The Salk Institute for Biological Studies

Non-dividing cells, the major constituents of adult tissues, are inaccessible for targeted knock-in with current technologies. We have developed a robust homology-independent targeted integration (HITI) strategy that allows for efficient targeted knock-in in both dividing and non-dividing cells *in vitro* and *in vivo*. Using this method, we achieved the therapeutic efficacy of a rat model of blindness retinitis pigmentosa *in vivo*.

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

10:25 CRISPR in Stem Cell Models of Eye Disease

Alexander Bassuk, M.D., Ph.D., Associate Professor of Pediatrics, Department of Molecular and Cellular Biology, University of Iowa

Induced pluripotent stem cells (iPSCs) generated from patient fibroblasts could potentially be used as a source of autologous cells for transplantation in retinal disease. Patient-derived iPSCs, however, would still harbor disease-causing mutations. To generate healthy patient-derived cells, we used CRISPR/Cas9 to precisely repair a point mutation that causes retinal degeneration. This important proof-of-concept finding supports the development of personalized iPSC-based transplantation therapies for retinal disease.

10:55 CRISPR in Mouse Models of Eye Disease

Vinit Mahajan, M.D., Ph.D., Assistant Professor of Ophthalmology and Visual Sciences, University of Iowa College of Medicine

Massive parallel sequencing enables identification of numerous genetic variants, but determining pathogenicity of any one mutation is daunting. The most commonly studied preclinical model of retinal degeneration is homozygous for two different mutations in the same gene. We used the CRISPR/Cas9 gene editing system to identify the causative variant and rescue neurofunction. This is among the first examples of CRISPR-mediated repair in a sensory system.

11:25 Enjoy Lunch on Your Own

12:50 pm Plenary Keynote Program *(See page 3 for details.)*

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

3:20 End of Conference

Inaugural | *September 21-22, 2016*

Translating Cancer Genomics

Exploring Ways to Use Genomic Data to Reveal New Targets and Therapies

Cancer Genomics is set to greatly impact oncology, both from a drug discovery and therapeutic standpoint. With improvements in sequencing, transcriptomics and data analysis accelerating the growth of knowledge and scientific discovery, cancer genomics can now be used more widely and effectively. Cancer genomic data coupled with the right functional screening tools, can be exploited to reveal new disease biology and new drug targets for intervention. This conference on Translating Cancer Genomics brings together experts from academia and industry to share ideas and strategies on how to further explore the promise of cancer genomics.

RECOMMENDED ALL ACCESS PACKAGE:

- September 19 Symposium: NK Cell-Based Cancer Immunotherapy
- September 20-21 Conference: Advances in Gene Editing and Gene Silencing - Part 1
- September 21-22 Conference: Translating Cancer Genomics
- September 21 Short Course: Functional Screening Strategies Using CRISPR and RNAi

WEDNESDAY, SEPTEMBER 21

11:20 am Conference Registration Open

11:25 Enjoy Lunch on Your Own

12:50 pm Plenary Keynote Program *(See page 3 for details.)*

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

CANCER GENOMICS FOR DISEASE BIOLOGY AND TARGET DISCOVERY

3:20 Chairperson's Opening Remarks

Arthur L. Shaffer, III, Ph.D., Staff Scientist, Laboratory of Dr. Louis Staudt, Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health

3:35 Revealing Cancer Landscape by Sequencing Single Cells and Cell-free DNA

J. Christopher Love, Ph.D., Associate Member, Broad Institute; Associate Professor, Chemical Engineering, Koch Institute for Integrative Cancer Research at MIT; and Associate Member, Ragon Institute of MGH, MIT, and Harvard

Metastatic cancer remains a significant cause of mortality. Limited access to lesions and sparse samples have hindered genomic analyses of this stage of disease. This talk will describe advances in whole-exome sequencing from single cells and circulating tumor DNA and computational analysis for detecting somatic mutations, indels, and copy number alterations. These methods may complement tumor biopsies for both translational studies and precision medicine.

4:20 Single-Cell Analysis Reveals Enriched EMT Pathway in Castration Resistant Prostate Cancer and CTCs Affected by Enzalutamide and Abiraterone

Chun-Liang Chen, Ph.D., Assistant Professor, Molecular Medicine, University of Texas Health Science Center at San Antonio

Single cell qRT-PCR and RNA sequencing show that epithelial-to-mesenchymal transition (EMT) gene expression is unregulated in castration resistant prostate cancer cells and circulating tumor cells. We explored the effects of emalutaminde and arbiraterone on EMT molecular profiling and aggressive behaviors of castration resistant cancer cells. The data are consistent with our previous study of EMT expression in circulating tumor cells indicating that high EMT gene expression is a biomarker for castration resistance and a potential therapeutic target.

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

5:40 Cancer Mutations of the SMARCA4 ATPase Domain Lead to Altered Polycomb Activity

Benjamin Stanton, Ph.D., Research Associate, Laboratory of Dr. Gerald Crabtree, Stanford University School of Medicine and Howard Hughes Medical Institute; Laboratory of Dr. Keji Zhao, Laboratory of Epigenome Biology, NHLBI, National Institutes of Health

Genetic alterations of the subunits of the mammalian SWI/SNF (mSWI/SNF or BAF) complex contribute to a wide range of human cancers. We sought to examine defects of Brg (SMARCA4), where mutations observed in cancer cluster at highly conserved regions. We characterized many interesting downstream effects of mSWI/SNF ATPase mutations, including alterations in Polycomb activity.

6:10 Untangling Bad Wiring: Using CRISPR/Cas9 to Understand Lymphoma

Arthur L. Shaffer, III, Ph.D., Staff Scientist, Laboratory of Dr. Louis Staudt, Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health

CRISPR/Cas9 technology is a powerful tool that permits the easy exploration of human genetics using cell line models. Our lab focuses on understanding the wiring of lymphoma cells in an effort to discover essential signaling pathways, leading to new therapeutic options. I will relate some of our recent successes with CRISPR/Cas9 in the study of lymphoma.

6:40 End of Day

THURSDAY, SEPTEMBER 22

7:30 am Registration Open and Morning Coffee

EFFECTIVELY COUPLING GENOMIC DATA WITH FUNCTIONAL SCREENING

8:30 Chairperson's Remarks

Jeff MacKeigan, Ph.D., Associate Professor, Innovation and Integration Program, Center for Cancer and Cell Biology, Van Andel Research Institute

8:45 Therapeutic Targets and the Genomic Landscape in a Rare Pediatric Tumor Syndrome

Jeff MacKeigan, Ph.D., Associate Professor, Innovation and Integration Program, Center for Cancer and Cell Biology, Van Andel Research Institute

Tuberous sclerosis complex (TSC) is a rare disease, characterized by mutations in TSC1 or TSC2, two tumor suppressor genes located in the mTOR pathway. Often diagnosed during childhood, the disease causes benign tumors in major organs including the brain, kidneys, skin, and heart. We will present our latest data on new and existing therapeutic targets along with the genomic landscape of this disease.

9:15 Optimized Synthetic Lethal Screening Approaches for Drug Target Discovery

Benjamin Housden, Ph.D., Post-Doctoral Fellow, Laboratory of Dr. Norbert Perrimon, Department of Genetics, Harvard Medical School

Synthetic lethal screens represent a promising approach to identify candidate drug targets for tumorigenic diseases. However, detection of robust synthetic lethal interactions has proved challenging with existing screening methods. We have developed an optimized approach combining CRISPR and RNAi in cross-species screens. I will describe these new methods and their application to identify candidate drug targets for TSC deficient tumors.

9:45 Super Enhancing Precision Medicine by Integrating Genomic, Epigenetic and Functional Screen Data

Berkley E. Gryder, Ph.D., Research Scientist, Laboratory of Dr. Javed Khan, Genetics Branch, National Cancer Institute, National Institutes of Health

Precision medicine hopes to succeed in treating diseases individually by leveraging patient-specific genomics and targeted therapy, but most cancers lack highly recurrent and therapeutically actionable protein-coding alterations. Studying childhood cancers, we show that despite genomic heterogeneity, epigenetic landscapes are highly consistent among patients. Translating epigenetic knowledge into biological vulnerabilities, by overlaying high-throughput drug and functional genomics datasets, is promising new avenues of therapy which are being pursued.

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

11:10 Using Data Visualization for Discovery and Subtype Characterization

Nils Gehlenborg, Ph.D., Assistant Professor, Department of Biomedical Informatics, Harvard Medical School

Studies like The Cancer Genome Atlas are providing the biomedical community with multidimensional datasets that offer a comprehensive view on cancer. I will present visualization approaches that enable researchers to gain deeper insights into populations of cancer patients by integrating multiple such datasets and multiple visualizations within a single user interface. I will also show how algorithmic analysis can efficiently be linked with visual analysis.

11:55 Associating Tumor Phenotype with Genomics across Biological Scale

Arvind Rao, Ph.D., Assistant Professor, Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center

With the availability of large public repositories of cancer genomics and phenotype (pathology, radiology) data, there is an unprecedented opportunity to link cancer-induced phenotype with cancer genomic data. This permits the inference of the phenotypic basis of cancer, in terms of the molecular characteristics of the disease. In this talk, we'll focus on methods and results intended to understand the genomic-phenomic confluence, using Gliomas as a case study.

12:40 Lunch on Your Own

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

CRISPR-BASED FUNCTIONAL SCREENING FOR ONCOLOGY

2:15 Chairperson's Remarks

Roderick Beijersbergen, Ph.D., Group Leader, Netherlands Cancer Institute and Head, NKI Robotics and Screening Center

2:20 Large-Scale CRISPR Screens for Discovery of Genotype Specific Combination Therapies

Roderick Beijersbergen, Ph.D., Group Leader, Netherlands Cancer Institute and Head, NKI Robotics and Screening Center

The complexity and heterogeneity of cancer, the extensive crosstalk between pathways and unanticipated feedback control are underlying the limited long-term success of targeted therapeutics in the clinic. We use large-scale functional genomic screening technologies including shRNA/CRISPR-based gene editing in combination with (clinically) relevant screening models for the identification of dependencies in the context of specific genetic alterations. Using this platform we have identified novel effective drug combinations that are currently in the clinic.

2:50 GPCR-Mediated cAMP as an Immune Checkpoint in Cancer Identified by RNAi Screening

Tillmann Michels, Head of Research Group, Immune Checkpoint Inhibitors, Department of Interventional Immunology, Regensburg Center for Interventional Immunology; Member, Department of Translational Immunology, German Cancer Research Center

Immune checkpoint blockade has revolutionized cancer therapy. Our group screened several tumor entities in conjunction with tumor-infiltrating lymphocytes (TILs) for novel immune modulators. We found that many immune checkpoints are tumor-restricted but the underlying mechanisms are shared between tumor entities. These mechanisms range from inhibition of TIL-mediated apoptosis to cAMP-mediated inhibition of TILs.

3:20 Session Break

3:30 CRISPR-Based Mutagenesis Approach for Cancer Drug Target Identification

Junwei Shi, Ph.D., Assistant Professor, Department of Cancer Biology, University of Pennsylvania School of Medicine

CRISPR-Cas9 genome editing technology provides high-throughput genetic knockout screening strategies for cancer therapeutic target identification. We recently reported a domain-focused CRISPR screening approach to nominate protein domains that would sustain cancer cell growth and are suitable for drug targeting. Here, I will present an optimized CRISPR system, which could achieve robust genome editing efficiency in a broad variety of human cancer cell lines.

4:00 Applying Functional Genomics in Mouse Models of Human Cancer

Yejing Ge, Ph.D., Postdoctoral Fellow, Laboratory of Dr. Elaine Fuchs, Department of Mammalian Cell Biology and Development, Rockefeller University

Using skin as paradigm, we describe the first panoramic view of microRNAs during the development, homeostasis and malignant transformation of skin epithelium. We devised lentiviral microRNAs expression platform and conducted pooled *in vivo* functional screens for oncomiRs in mice. Empowered by mouse genetics and high throughput approaches, we unveiled a rich set of putative microRNAs that drive skin malignancy, and their oncogenic targets.

4:30 A CRISPR/Cas9 System to Increase Homologous Recombination Repair

Ciro Bonetti, Ph.D., Postdoctoral Scientist, Laboratory of Dr. Andrea Ventura, Memorial Sloan-Kettering Cancer Center

CRISPR/Cas9 genome editing technology has been shown to be very effective to perform inactivation or activation of specific genes. However, engineering precise genomic modifications remains a challenge due to the low efficiency of repair of the double strand breaks through the homologous recombination pathway. Here, I will discuss a novel method to skew the repair away from non-homologous end-joining towards homologous repair pathway.

5:00 Close of Conference

Fourth Annual | *September 20-21, 2016*

Antibodies Against Protein Membrane Targets - PART 1

Antigen Optimization and Antibody Discovery

The first meeting in the set, Antigen Optimization and Antibody Generation, offers a comprehensive examination of state-of-the-art approaches for producing high quality membrane protein antigens and the display and immunization strategies that can be applied to discover binders with functional activity against GPCR and ion channel targets.

RECOMMENDED ALL ACCESS PACKAGE:

- September 19 Short Course: Targeting of GPCRs with Monoclonal Antibodies
- September 20-21 Conference: Antibodies Against Membrane Protein Targets - Part 1
- September 21-22 Conference: Antibodies Against Membrane Protein Targets - Part 2

TUESDAY, SEPTEMBER 20

7:00 am Registration Open and Morning Coffee

8:05 Chairperson's Opening Remarks
Lili Huang, M.D., Ph.D., Principal Research Scientist, AbbVie

» 8:10 KEYNOTE PRESENTATION: MEMBRANE PROTEINS AS TARGETS FOR THERAPEUTIC ANTIBODY DISCOVERY

David R. Buckler, Ph.D., Director, Therapeutic Proteins, Regeneron Pharmaceuticals

Membrane proteins constitute a challenging class of targets for antibody discovery since they must remain membrane-associated to maintain their native conformation. However, an expanding number and variety have been successfully isolated in native form for structural studies, and these advances can be leveraged for antibody discovery. Examples from the recent literature and where Regeneron's VelocImmune antibody discovery platform has been applied to GPCR and ion channel targets will be presented.

EXPRESSION AND PRODUCTION OPTIMIZATION OF MEMBRANE PROTEIN ANTIGENS

8:50 Design of Water-Soluble Variants of Membrane Proteins
Jeffery G. Saven, Ph.D., Professor, Chemistry, University of Pennsylvania

Recent theoretical and computational methods can identify the properties of amino acid sequences consistent with targeted structures and functions. Such methods address the structural complexity of proteins and their many possible amino acid sequences. Computational redesign of membrane proteins has yielded variants that retain structure and functionally related properties.

9:20 Stabilization of Functional Membrane Proteins Using Lipid-Like Self-Assembling Peptides
Sotirios Koutsopoulos, Ph.D., Research Scientist, Center for Biomedical Engineering, Massachusetts Institute of Technology

Membrane proteins are integral proteins of the cell membrane and are directly involved in the regulation of many biological functions and in drug targeting. However, our knowledge of membrane proteins is limited due to difficulties in producing sufficient quantities of soluble, functional, and stable receptors. Designer, surfactant-like peptides may be used to extract the protein from the cell membrane and stabilize the protein outside the membrane bilayer for further studies.

9:50 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

10:35 Strategies and Methods to Deliver Ion Channel Reagents for Antibody Discovery
Michael Mullin, Ph.D., Investigator, Protein Cellular and Structural Sciences, RD Platform Technology and Science, GlaxoSmithKline, United Kingdom

Antibody discovery relies on the generation of high quality reagents ranging from cell lines to purified proteins. Many therapeutically relevant targets are difficult to express membrane proteins and production of appropriate reagents is both challenging and time-consuming. Using inducible mammalian cell-based systems combined with membrane tagging strategies, we present a unique method to improve the expression and detection of complex membrane proteins such as ion channels for antibody discovery.

11:05 Streamlining Integral Membrane Protein Antigen Production for Biologics Discovery
Pravien Abeywickrema, Associate Principal Scientist, Screening and Protein Sciences, Merck & Co., Inc.

Integral membrane proteins represent more than 60% of current drug targets. Despite the clinical significance, therapeutic antibodies against membrane proteins have been difficult to develop. One major challenge in this field is the difficulty in producing antigens in their native form to identify conformation-specific functional antibodies. We present here strategies we developed to streamline the design, production and characterization of membrane protein antigens to enable therapeutic antibody discovery.

11:35 A Saposin-Based Nanoparticle System for Stabilization of Membrane Proteins

Jens Frauenfeld, Ph.D., CEO, Salipro Biotech AB, Sweden

We present a saposin-lipoprotein nanoparticle system, which allows for the reconstitution of membrane proteins in a lipid environment. We demonstrate the applicability of the method on purified membrane proteins as well as by the direct solubilization and nanoparticle incorporation of membrane protein complexes from the virus membrane. The Salipro system allows for high-resolution cryo-EM of membrane proteins and is applicable for the development of novel drugs, vaccines and therapeutic antibodies.

12:05 pm New Approaches for mAb Discovery against GPCRs, Ion Channels, and Transporters

Sponsored by integral

Ross Chambers, Ph.D., Director, Antibody Discovery, Integral Molecular, Inc.

Integral Molecular has developed new approaches to elicit, characterize, and engineer mAbs against challenging membrane proteins using its MPS Discovery Engine®. Robust immune responses are generated against native antigens using Lipoparticles (high-concentration membrane proteins) and DNA immunization. Chickens are used because most membrane proteins are highly conserved, while both phage display and B-cell cloning are used for isolation. MAbs are engineered using high-throughput Shotgun Mutagenesis and profiled for specificity using a comprehensive membrane proteome array.

12:35 Immunization Strategies for Difficult Membrane Proteins

Sponsored by ANTIBODY SOLUTIONS

John Kenney, Ph.D., President, Antibody Solutions

Multi-pass transmembrane and multi-meric membrane proteins, targets for therapeutic monoclonal antibody development, are often difficult to express in a native, bio-active state with appropriate structure. We will present results using surrogate antigen strategies such as DNA, transfected cells, viral lipoparticles and nanodiscs for antibody generation and screening against such targets.

12:50 Session Break

12:55 Luncheon Presentation: Affimers-Next Generation Affinity Tools

Sponsored by Avacta LIFE SCIENCES

Martin Michel, Ph.D. Candidate - MRC Cambridge, Avacta Life Sciences

The Affimer protein scaffold is a biologically inert, biophysically and biochemically stable scaffold capable of presenting a range of designed or random binding surfaces for highly specific, high affinity interactions with a wide range of targets. Affimers are designed to work in the same way as the very best antibodies. Loop lengths can be varied to change the size or shape of the recognition surface.

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

ANTIBODY GENERATION AND ENGINEERING STRATEGIES

2:05 Chairperson's Remarks

Andrew Nixon, Ph.D., Independent Consultant

2:15 Generation of Synthetic Antibodies to Trap Functional Intermediates of Membrane Proteins

Tony Kossiakoff, Ph.D., Professor, Biochemistry, Molecular Biology and the Institute for Biophysical Dynamics, University of Chicago

A high throughput phage display pipeline has been established to generate Fab-based synthetic antibodies to trap conformational states of membrane proteins to facilitate probing both their static and dynamic features, as well as the transitions between states. A key component of the system is the use of lipid-filled nanodiscs to provide membrane-like environments for the proteins during phage display selections. Our results demonstrate that in many cases detergents induce conformational states that are incompatible with true membrane environments.

2:45 Generation of Functional Antibodies Against the P2X3 Ion Channel

Lili Huang, M.D., Ph.D., Principal Research Scientist, AbbVie

Targeting ion channels with antibody approaches has been challenging and largely unsuccessful due to the difficulties in generating proteins in appropriate forms for antibody generation and establishing assays for screening. We will present the discovery of functional mAbs targeting P2X3 ligand-gated ion channel as a testament of a successful antibody approach for ion channels. We will also discuss lessons learned that can be applied to other difficult multi-spanning membrane protein targets.

3:15 A Novel Approach for the Generation and Affinity Maturation of Fully Human Antibodies to Natively Expressed GPCRs

Sponsored by INNOVATIVE TARGETING SOLUTIONS

Michael Gallo, Ph.D., President, Research, Innovative Targeting Solutions Inc.

A novel mammalian display system incorporating V(D)J recombination for the generation of fully human antibodies to GPCRs is described. This *in vitro* system is capable of simultaneously evaluating the binding of billions of monoclonal antibodies to identify binders to a GPCR target in its native and functional confirmation expressed in the cell membrane. Application of V(D)J recombination to the affinity maturation of antibodies to GPCRs will also be presented.

3:45 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

4:25 Inducible GPCR Cell Lines for Antibody Characterization

Eric Grazzini, Ph.D., Team Leader Rapid Protein Production, Senior Research Officer, Biologics, National Research Council of Canada, Canada

National Research Council Canada (NRC) has a strong track record in target discovery and monoclonal antibody production. Among the most interesting and well-known therapeutic targets identified, GPCRs proteins represent a challenge and an opportunity to develop and characterize mAbs. Cells expressing GPCRs of interest can be used for immunization and/or screening purposes. To this end, we have developed the proprietary cumate-inducible CHOBRI cell line for stable and modulated gene expression.

4:55 Generation of Functional mAbs Targeting GPCRs for Fibrosis and Autoimmune Disease Indications

Kiyoshi Takayama, Ph.D., President, Research Center, NB Health Laboratory Co., Ltd., Japan

MoGRAA is a new biotherapeutic concept for a GPCR targeted drug. Using the MoGRAA discovery engine, we discovered mAbs targeting a chemokine GPCR involved in the fibrosis pathway. The mAb exerts a therapeutic effect by shutting down chemokine-induced GPCR signaling. Using the surrogate mAb for the rat

target GPCR, we proved the therapeutic concept of the antibody treatment in a lung fibrosis model, with superiority over the existing drug.

5:25 Welcome Reception in the Exhibit Hall with Poster Viewing

6:25 End of Day

WEDNESDAY, SEPTEMBER 21

7:30 am Registration Open and Morning Coffee

NEW TECHNOLOGIES FOR DISCOVERY OF ANTIBODIES AGAINST MEMBRANE PROTEIN TARGETS

8:00 Chairperson's Opening Remarks
John Kenney, Ph.D., President, Antibody Solutions

8:10 Strategies to Target Cell Surface Peptide-HLA Complexes as Cancer Antigens
David M. Kranz, Ph.D., Professor, Biochemistry, University of Illinois, Urbana-Champaign
T cells, via their T-cell receptors (TCRs), evolved to target intracellular peptides as cell-surface complexes with MHC products (HLA in humans). Many cancer-associated peptides have now been identified. These peptide-HLA complexes provide a vast source for next generation targets. Strategies to target them, including engineering high-affinity TCRs or antibodies that can be formatted as soluble therapeutics or as receptors in adoptive T cell therapies, will be discussed.

8:40 New Strategies and Technologies for Ab Discovery without Purified Proteins
JT Koerber, Ph.D., Scientist, Antibody Engineering, Genentech
The generation of high quality, natively folded proteins can often limit antibody discovery efforts. Therefore, robust alternative antigen formats to recombinant antigens are highly desired. I will discuss our optimization and comparison of several different DNA immunization technologies in both mice and rats. I will also present a case study highlighting the quality of mAbs generated via DNA immunization compared to mAbs generated with recombinant protein.

9:10 Strategies to Identify High Potency Therapeutic Antibodies for Multi-TM Targets
Martin J. Scott, Ph.D., Investigator, Biopharm Molecular Discovery, GlaxoSmithKline, United Kingdom
Cellular targets such as G-protein coupled receptors (GPCRs) are typically very challenging for therapeutic antibody discovery due to their complex nature and limited antigen availability. This presentation will describe the strategies implemented by GSK to successfully identify high potency neutralizing antibodies for such targets, using both *in vitro* display technologies and *in vivo* immunization approaches.

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

10:25 Generating Synthetic Nanobodies against Purified Membrane Proteins
Roger Dawson, Ph.D., Principal Scientist, Roche Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Switzerland
Nanobodies are versatile binding proteins receiving increasing attention in drug discovery. The considerable track record of camelid nanobodies from assay development to therapeutic applications has led us to combine the benefits of this natural scaffold with the advantages of synthetic libraries and *in vitro* display technologies. Using the example of a purified transporter, we explain a novel workflow used to create nanobodies for structural studies.

10:55 G Protein-Coupled Receptor Antibody-Ligand Identification by Directed Evolution
John Burg, Ph.D., Head, Biochemistry, Ab Initio Biotherapeutics
G protein coupled receptors (GPCRs) are critical mediators of signaling for both endogenous ligands and therapeutics. Despite their diversity in function, GPCRs signal through a conserved mechanism where agonist binding on the extracellular receptor face stabilizes active receptor conformations to enable cytoplasmic G-protein binding and downstream signaling. Leveraging this information, we have developed selection methodologies to isolate agonist antibodies and other biologics.

11:25 Enjoy Lunch on Your Own

12:50 pm Plenary Keynote Program *(See page 3 for details.)*

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

3:20 End of Conference

Fourth Annual | *September 21-22, 2016*

Antibodies Against Protein Membrane Targets - PART 2

Structural Analysis, Characterization and Development

The second conference, Structural Analysis, Characterization and Development, explores new developments in structural biology, screening campaigns and characterization assays used to support research against these challenging targets. This segment then examines progress in biotherapeutic development, new scaffold constructs, other membrane protein target classes and solutions to unique problems with membrane bound targets.

RECOMMENDED ALL ACCESS PACKAGE:

- September 19 Short Course: Targeting of GPCRs with Monoclonal Antibodies
- September 20-21 Conference: Antibodies Against Membrane Protein Targets - Part 1
- September 21-22 Conference: Antibodies Against Membrane Protein Targets - Part 2
- September 21 Short Course: Introduction to Allosteric Modulators

WEDNESDAY, SEPTEMBER 21

11:20 am Conference Registration Open

11:25 Enjoy Lunch on Your Own

12:50 pm Plenary Keynote Program *(See page 3 for details.)*

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

STRUCTURAL BIOLOGY STUDIES FOR DEVELOPMENT OF ANTIBODIES AGAINST MEMBRANE PROTEIN TARGETS

3:20 Chairperson's Opening Remarks

Debra T. Hansen, Ph.D., Associate Research Professor, Center for Applied Structural Discovery, Arizona State University

» 3:25 KEYNOTE PRESENTATION: PRODUCTION OF HUMAN MEMBRANE PROTEINS FOR ANTIBODY GENERATION, X-RAY AND SERIAL FEMTOSECOND CRYSTALLOGRAPHY, AND ELECTRON MICROSCOPY

Liz Carpenter, Ph.D., Professor, Structural Genomics Consortium, Oxford University, United Kingdom

For human integral membrane proteins (IMPs), producing the protein samples is often the limiting factor for structural and functional studies, and for antibody generation. The SGC has created a pipeline for human IMPs production that has allowed us to solve structures of seven human IMPs, using a range of structure determination techniques. We use these methods to produce and study proteins that are identified as genetic hits for human diseases.

4:05 Conformational Dynamics of a Neurotransmitter Sodium Symporter (NSS) in a Membrane Bilayer

Satinder Kaur Singh, Ph.D., Assistant Professor, Cellular & Molecular Physiology, Yale University School of Medicine

Neurotransmitter sodium symporters are dynamic proteins that exploit pre-existing ion gradients to transport a diverse array of substrates across the lipid bilayer. Eukaryotic members are established targets of multiple psychoactive agents, and their dysfunction has been implicated in numerous neuropsychiatric diseases. We applied a novel biophysical approach to dissect the conformational behavior of NSS members in customizable lipid microdomains (nanodiscs), allowing us to probe global conformational changes induced by mutations and/or ligand binding.

4:35 Computational Advances in Antibody Design: Toward Improved Optimization, Selection and Formulation

Sponsored by SCHRÖDINGER. BIOLOGICS

David Pearlman, Ph.D., Senior Principal Scientist, Schrödinger

Recent computational advances hold significant promise both for improved prediction of antibody structure from sequence, and for the ability to precisely calculate physically relevant properties such as affinity and stability. When combined with additional theoretical approaches to identify liabilities such as aggregation propensity and immunogenicity, we can use these tools to variously optimize a lead antibody candidate, triage among multiple potential leads, and improve the formulation process.

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

5:40 Speaker has cancelled. ~~Delegates may attend sessions of concurrent meetings.~~ Visualization Functional Motions of Membrane Transporters Using Advanced Simulation Technologies

~~*Emad Tajkhorshid, Ph.D., Professor, Biophysics, Biochemistry, and Pharmacology, Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign*~~

~~Describing structural changes of membrane transporters continues to pose a major challenge to both experimental and computational approaches. I will describe recently developed methodologies in our lab, and their application to structurally and mechanistically diverse membrane transporters. We can not only capture inter-conversion of major functional states, but also successfully characterize how chemical details such as ion/substrate binding modulate the associated free energy landscapes.~~

6:10 Speaker has cancelled. Delegates may attend sessions of concurrent meetings.

6:40 End of Day

THURSDAY, SEPTEMBER 22

7:30 am Registration Open and Morning Coffee

SCREENING AND CHARACTERIZATION

8:30 Chairperson's Remarks

Joseph Rucker, Ph.D., Vice President, Research and Development, Integral Molecular, Inc.

8:45 Assay Development for High Throughput and Biased Agonist Screening of GPCR Targets

Patricia McDonald, Ph.D., Associate Scientific Director, Translational Research Institute, The Scripps Research Institute

The development of an autocrine-based assay system for the selection of GPCR agonists from large intracellular combinatorial peptide libraries is described. One out of ~108 different peptides and a GPCR are co-localized in the plasma membrane. When the co-localized peptide activates the neighboring receptor a fluorescent signal is generated and each cell becomes a reporter unto itself. The system was validated by selection of highly potent agonists for the GLP-1R.

9:15 Cell-Based Characterization of a Conformationally and Topologically Sensitive Epitope of Human Gpr34: Implications for GPCR Immunogen Design

Haruki Hasegawa, Ph.D., Principal Scientist, Therapeutic Discovery - Biologics, Amgen, Inc.

We identified and characterized an epitope that reports the correct conformation, membrane topology, and cell surface trafficking competency of GPR34. The epitope formation required the oxidation of four cysteine residues located individually in the four separate extracellular regions of GPR34. The underlying biochemical properties of the conformational epitope not only illustrated the intrinsic challenges of raising mAbs against GPCRs, but also suggested preferred strategies for GPCR antigen design.

9:45 Speaker has cancelled - delegates may attend sessions of concurrent meetings

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

11:10 New Technologies to Determine Specificity of mAbs Targeting Complex Membrane Proteins

Joseph Rucker, Ph.D., Vice President, Research and Development, Integral Molecular, Inc.

Integral Molecular has developed a panel of complementary technologies for detailed specificity and epitope profiling of therapeutic antibodies targeting complex membrane proteins. We have developed the Membrane Proteome Array™ to profile antibody binding across 4,500 membrane proteins, providing identification of off-target interactions, target deconvolution and detailed comparison of biosimilars. In addition, we have used a high-throughput comprehensive mutagenesis platform for high-resolution mapping of over 500 antibody epitopes on complex targets.

11:40 Single Domain Antibodies Targeting Complex Membrane Proteins Identified by Phage Display Screening

Mick Foley, Ph.D., CSO, AdAlta, Australia

Identifying monoclonal antibodies to complex membrane proteins such as GPCRs and ion channels is a notoriously difficult undertaking. By screening a large phage library displaying single domain antibodies (i-bodies), high affinity i-bodies specific for CXCR4 and TRPV4 were obtained. These binders have been shown to have valuable biological functions *in vitro* and *in vivo*. Indeed we are progressing the CXCR4 single domains as a treatment for fibrosis.

12:10 pm High Throughput Single Cell Antibody Discovery from Natural Immune Repertoires Against Membrane Proteins

Sponsored by AbCellera

Veronique Lecault, Ph.D., Co-Founder, AbCellera

12:40 Session Break

12:50 Hu-mAb Chickens: A New Path for Therapeutic Antibody Discovery

Sponsored by Crystal Bioscience

William Harriman, Ph.D., MBA, CSO, Crystal Bioscience

Crystal Bioscience has developed a line of genetically engineered chickens containing human V genes that have been targeted into the chicken immunoglobulin loci. Upon immunization hu-mAb chickens generate affinity matured human sequence chimeric antibodies that can be recovered through the GEM single-B cell cloning technology. Fully human recombinant antibodies from hu-mAb chickens are shown to bind therapeutic targets with the high affinities and diverse epitope coverage that is characteristic of wild-type chicken mAbs.

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

PROBLEM SOLVING AND BIOTHERAPEUTIC DEVELOPMENT

2:15 Chairperson's Remarks

Xin Huang, Ph.D., Principal Scientist and Group Leader, Molecular Engineering, Amgen

2:20 Efficiency of Genetic Immunization for the Generation of Antibodies Against Membrane Proteins

Debra T. Hansen, Ph.D., Associate Research Professor, Center for Applied Structural Discovery, Arizona State University

We describe the first report of the efficiency of a DNA-based immunization approach to generate antibodies against membrane proteins. Genetic immunization relies on the immunized host to express, fold, and modify the antigen. We used micronanoplex gene gun immunization of mice to generate antibodies against BSL3 pathogens and a novel *in vitro* expression method that purifies the antigen. We will discuss method development and applications.

2:50 Structural Studies of Human Glycine Receptors

Xin Huang, Ph.D., Principal Scientist and Group Leader, Molecular Engineering, Amgen

Glycine receptors (GlyRs) mediate inhibitory neurotransmission in the central nervous system. Selective activation of GlyRs has been hypothesized as an alternative approach to treat neuropathic pain. Here we present crystal structures of GlyRa3 with both positive and negative modulators. Our structures provide new insights into molecular recognition of these modulators and their modulation mechanisms. These results also offer promise of rational structure-based design of new classes of GlyR modulators.

3:20 Session Break

3:30 Modulation of P2X3 and P2X2/3 Receptors by Monoclonal Antibodies

Anatoly Shcherbatko, Ph.D., Associate Research Fellow, Rinat Laboratories, Pfizer, Inc.

Monoclonal antibodies inhibited P2X3 after short-term exposure binding to the inactivated state of the channel and potentiated the heteromeric P2X2/3 channel. Extending the duration of exposure resulted in a profound inhibition of both homomeric P2X3 and heteromeric P2X2/3 receptors by efficient antibody-induced internalization of the channel from the plasma membrane. The efficacy in the visceral hypersensitivity model indicates that antibodies against P2X3 may have therapeutic potential in visceral pain indications.

4:00 Harnessing Venomics for Ion Channel Drug Discovery

Hongkai Zhang, Ph.D., Senior Scientist, Lerner Laboratory, The Scripps Research Institute

Animal venoms represent a rich source of active peptides for ion channel and GPCR drug targets. However, a challenge remains with the slow pace at which venom peptides are discovered and refined. Combining autocrine-based selection with proximity-based assay provides a robust and user-friendly solution. The talk will include discovery of novel Kv1.3 blockers from natural venom peptide library and selection of refined venom peptides from combinatorial library.

4:30 Discovery, Generation, and Development of Therapeutic mAb Candidates against GPCR Targets

Shuqian Jing, Ph.D., Founder and CEO, Gmax Biopharm, LLC, China

Gmax Biopharm focuses on discovery and development of novel antibody therapeutics targeting GPCRs. Using our proprietary technologies, we have successfully generated functional mAbs against a number of GPCR targets, including endothelin receptor A (ETa), GLP-1 receptor (GLP-1R), and glucagon receptor (GCGR), etc. The most advanced programs of our GPCR mAb therapeutic development have reached various clinical or preclinical stages.

5:00 Close of Conference

Inaugural | *September 20-21, 2016*

Targeting Cardio-Metabolic Diseases

With a Focus on the Fatty Liver

This conference focuses on new cardiometabolic drug targets and the connections between cardiometabolic disease and liver metabolism. New approaches for targeting PCSK9, a protein in the liver that effects cholesterol metabolism will be covered. Another featured topic will be NASH (Non-Alcoholic SteatoHepatitis), a disease of the fatty or metabolically-impaired liver.

RECOMMENDED ALL ACCESS PACKAGE:
- September 19 Symposium: Autoimmunity – Small Molecule Approaches
- September 20-21 Conference: Targeting Cardio-Metabolic Diseases
- September 21-22 Conference: Metabolomics in Drug Discovery

TUESDAY, SEPTEMBER 20

7:00 am Registration Open and Morning Coffee

NEW CARDIOMETABOLIC DRUG TARGETS AND PCSK9

8:05 Chairperson's Opening Remarks
H. James Harwood, Ph.D., Delphi BioMedical Consultants, LLC

8:20 FEATURED PRESENTATION: PCSK9 (Proprotein Convertase Subtilisin Kexin): From Gene to Therapy
Jay D. Horton, M.D., Professor, Internal Medicine and Molecular Genetics; Chair, Obesity and Diabetes; Chief of Division of Digestive and Liver Diseases, UT Southwestern Medical Center
Proprotein convertase subtilisin-like kexin type 9 (PCSK9) is a serine protease that is secreted into the blood and controls levels of LDL cholesterol. Here data will be presented that defines the mechanism of PCSK9's action, explores the relationship between PCSK9 levels and plasma LDL cholesterol concentrations, and that describes new therapeutic strategies to block the activity of PCSK9.

8:50 New CETP Inhibitor K-312 Suppresses PCSK9 Production and Atherosclerosis
Masanori Aikawa, M.D., Ph.D., Director, Center for Interdisciplinary Cardiovascular Sciences, Brigham and Women's Hospital and Associate Professor of Medicine, Harvard Medical School
The novel CETP inhibitor K-312 raises HDL- and lowers LDL-cholesterol levels in animals. K-312 also decreases PCSK9 expression in cultured hepatocytes, seemingly via CETP-independent mechanisms. K-312 administration to cholesterol-fed rabbits raises HDL, decreases LDL, and attenuates atherosclerosis. In addition, K-312 reduces PCSK9 in the circulating blood of rabbits (high-sensitivity mass spectrometry). K-312 represents novel strategies to reduce residual global burden of cardiovascular disease.

9:20 Peptide Inhibitors of PCSK9 Derived from Phage Display
Yingnan Zhang, Ph.D., Scientific Manager, Department of Early Discovery Biochemistry, Genentech
PCSK9 is a negative regulator of hepatic LDL receptor. We developed two types of peptide inhibitors of PCSK9 using phage display: an engineered calcium-independent EGF(A) domain of LDLR and a 13-amino acid linear peptide Pep2-8, both with Kd ~ 0.7 μM and could fully restored LDL receptor surface levels in PCSK9-treated HepG2 cells. The mechanism of inhibition for Pep2-8 was clearly defined by structure.

9:50 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

10:35 Small Molecule PCSK9 Binders and Allosteric Modulation of PCSK9 Function
Yusheng Xiong, Ph.D., Director, Exploratory Chemistry, Merck Research Laboratories
Screening of the Merck sample collection identified a small molecule PCSK9 binder of 20 uM affinity. The X-ray structure revealed that it binds at the junction between the catalytic domain and C-terminal domain of PCSK9. This binding site is close to multiple loss-of-function natural mutation sites, and therefore we hypothesized that a potent binder may have the potential of modulating PCSK9 function either intra- or extracellularly. This talk will present our effort in improving this class of binders in terms of binding affinity, selectivity, and cell permeability to interrogate the potential of modulating PCSK9 function.

11:05 Protection from Cardiac Ischemia by Inhibiting Phosphorylation of a Specific PKC Substrate
Nir Qvit, Ph.D., Postdoctoral Fellow, Department of Chemical and Systems Biology, Stanford University
Delta protein kinase C (delta-PKC) activation after a heart attack leads to cardiac damage. To determine if of the many substrates of delta-PKC, PDK is the substrate that mediates this injurious effect in the heart, we designed a short protein-protein interaction inhibitory peptide (PPIIP) to selectively inhibit delta-PKC phosphorylation of PDK. The peptide selectively inhibited phosphorylation of PDK without affecting phosphorylation of several other delta-PKC substrates. Further, PDK/delta-PKC PPIIP treatment led to a 50% reduction in infarct size, in release of cardiac enzyme and in JNK phosphorylation, all markers of cardiac injury.

11:35 GPR40 Full Agonists for Type 2 Diabetes
Sanath Meegalla, Ph.D., Principal Scientist, Cardiovascular and Metabolic Therapeutic Area, Janssen Research & Development, LLC
The medicinal chemistry efforts that led to the discovery of a series of GPR40 full agonists and its biological activities will be the focus of this presentation. The structure activity relationships, G-protein signaling due to the engagement of the GPR40 receptor, insulin secretion from human islets and rat oral glucose tolerance test results of a full agonist series will be presented.

12:05 pm Sponsored Presentation *(Opportunity Available)*

12:35 Session Break

12:45 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Lunch on Your Own**

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

NASH: NON-ALCOHOLIC STEATOHEPATITIS AND CARDIOMETABOLISM

2:05 Chairperson's Remarks
Weilin Xie, Ph.D., Senior Principal Scientist, Biotherapeutics, Celgene Corp.

2:15 Challenges and Opportunities in NASH Therapy Development
Weilin Xie, Ph.D., Senior Principal Scientist, Biotherapeutics, Celgene Corp

2:45 Inhibiting ASK1 and Implications for Liver Disease
Frank Lovering, Ph.D., Associate Research Fellow, World Wide Medicinal Chemistry, Pfizer
Apoptosis signal-regulating kinase 1 (ASK1), a member of the MAP3K kinase family, plays a role in activating c-Jun N-terminal kinase (JNK) and p38 MAP kinase signaling pathways in response to various stress stimuli including reactive oxygen species (ROS) and endoplasmic stress. Inhibition of ASK1 is expected to have implications in a number of pathological situations including COPD, diabetic nephropathy and NASH.

3:15 Advances in Preclinical Models for Cardio-Metabolic and Liver Disease
Sponsored by CrownBio
Amar Thyagarajan, Ph.D., Associate Director Product Marketing, Crown Bioscience

3:30 Sponsored Presentation *(Opportunity Available)*

3:45 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

4:25 FXR Agonist, Obeticholic Acid, Attenuates Fibrosis Development in a More Translational NASH Mouse Model
Martine Morrison, Ph.D., Research Scientist, Metabolic Health Research, The Netherlands Organization of Applied Scientific Research (TNO)
While obeticholic acid treatment has shown promising results in clinical studies, currently most data available on the effects of obeticholic acid and FXR activation in the liver are derived from animal models that have limited translational value to the human situation. The LDLr-/-.Leiden mouse is a translational, diet-inducible model for non-alcoholic steatohepatitis (NASH) with associated fibrosis, which displays many clinically relevant features of NASH.

4:55 Presentation to be Announced

5:25 Welcome Reception in the Exhibit Hall with Poster Viewing

6:25 End of Day

WEDNESDAY, SEPTEMBER 21

7:30 am Registration Open and Morning Coffee

8:00 Chairperson's Opening Remarks
Rebecca Taub, M.D., Ph.D., CEO, Madrigal Pharmaceuticals

8:10 FEATURED PRESENTATION: The Epidemic of Fatty Liver Disease: Silent, Serious, and Still Growing?
Lee Kaplan, M.D., Ph.D., Director, Obesity, Metabolism and Nutrition Institute, Massachusetts General Hospital, Harvard Medical School

8:40 Non-Alcoholic Steatohepatitis and Cardiovascular Disease: Modulation by Novel PPAR Agonists
Bart Staels, Ph.D., Professor, University of Lille, France
Peroxisome proliferator-activated receptors (PPARs) are ligand-activated nuclear receptors which regulate lipid and glucose metabolism as well as inflammation. In this presentation, we will review recent findings on the pathophysiological role of PPARs in the different stages of non-alcoholic fatty liver disease (NAFLD), from steatosis development to steatohepatitis and fibrosis, as well as the preclinical and clinical evidences for potential therapeutical use of PPAR agonists in the treatment of NAFLD. PPARs play a role in modulating hepatic triglyceride accumulation, a hallmark of the development of NAFLD. Moreover, PPARs may also influence the evolution of reversible steatosis towards irreversible, more advanced lesions. Large controlled trials of long duration to assess the long-term clinical benefits of PPAR agonists in humans are ongoing.

9:10 PANEL DISCUSSION: Liver Fibrosis and NASH Targets
H. James Harwood, Ph.D., Delphi BioMedical Consultants, LLC
- FDA's view on surrogate endpoints
- Biomarkers of NASH
- Translational animal models

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

10:25 Targeting Fibroblast Activation Protein (FAP) and FGF21 to Treat Fatty Liver Disease
Diana Ronai Dunshee, Ph.D., Department of Molecular Biology, Senior Scientific Researcher, Genentech, Inc.
FGF21 is a hormone with anti-obesity and hepatoprotective properties. However, the beneficial effects of FGF21 are limited by a relatively short half-life in circulation. We discovered that fibroblast activation protein (FAP), an endopeptidase overexpressed in liver with cirrhosis, cleaves and inactivates FGF21. Pharmacological inhibition of FAP increases endogenous levels of active FGF21, thus making FAP a promising target for the treatment of non-alcoholic-steatohepatitis (NASH).

10:55 Thyroid Hormone Receptor Beta (THR-ß) Agonist for NASH: Correcting a Primary Deficiency in NASH Livers
Rebecca Taub, M.D., Ph.D., CEO, Madrigal Pharmaceuticals
NASH patients typically have metabolic syndrome including diabetes, dyslipidemia, obesity, and primarily die of cardiovascular disease. Hypothyroidism at the level of the thyroid gland and liver-specific hypothyroidism are common in NASH. Based on clinical and preclinical data, Thyroid receptor beta agonists decrease insulin resistance, reduce LDL-C, triglycerides fatty liver, inflammation and fibrosis in NASH. The target will also provide CV benefit to patients with NASH. MGL-3196 is a highly THR-ß selective liver-directed once daily oral medication that has shown excellent safety and lipid-lowering efficacy in humans; unlike prior thyroid receptor agonist(s), no cartilage findings in chronic toxicology or ALT increases in human studies. MGL-3196 is being advanced in Phase II studies in patients with genetic dyslipidemia or NASH.

11:25 Enjoy Lunch on Your Own

12:50 pm Plenary Keynote Program *(See page 3 for details.)*

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

3:20 End of Conference

Inaugural | *September 21-22, 2016*

Metabolomics in Drug Discovery

Applications to Cancer Metabolism and More

A few introductory type presentations will explain the current state of the field and its major technologies then the focus will turn to applications of metabolomics to drug discovery research. Case-studies will be mostly from cancer metabolism.

BEST VALUE:
- September 20-21 Conference: Targeting Cardio-Metabolic Diseases
- September 21-22 Conference: Metabolomics in Drug Discovery
- September 21 Short Course: Cancer Metabolism

WEDNESDAY, SEPTEMBER 21

11:20 am Conference Registration Open

11:25 Enjoy Lunch on Your Own

12:50 pm Plenary Keynote Program *(See page 3 for details.)*

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

METABOLOMICS OVERVIEW AND TECHNOLOGIES

3:20 Chairperson's Opening Remarks
Edward Driggers, CSO, General Metabolics

3:35 Understanding Disease Mechanisms through LC/MS-Based Metabolomics
Elizaveta Freinkman, Ph.D., Research Scientist and Manager, Metabolite Profiling Facility, Whitehead Institute, MIT
Liquid chromatography–mass spectrometry (LC/MS) is the most versatile analytical technique for metabolomics. Drawing on the past several years of research at the Whitehead Institute Metabolite Profiling Core Facility, this presentation will provide an overview of current LC/MS technologies. Sample preparation, method development, data analysis, and quality control will be discussed in the context of specific metabolomic experiments and the biological insights that they enabled.

4:05 Translating Inhibitors of Mutant IDH into the Clinic for Myeloid Malignancies
Eytan M. Stein, M.D., Assistant Attending Physician, Department of Medicine, Memorial Sloan Kettering Cancer Center
Mutations in the conserved enzymatic active sites of Isocitrate Dehydrogenase isoforms 1 and 2 (IDH1 and IDH2) lead to novel enzymatic activity that catalyzes the conversion of α-ketoglutarate to α-hydroxyglutarate (2-HG) and a block in cellular differentiation. Inhibitors of mutant IDH, both alone and in combination with standard-of-care therapy are in early and advanced clinical studies and show remarkable efficacy.

4:35 Using Metabolomics to Discern New Target Opportunities from Established Models
Kirk Beebe, Ph.D., Director, Application Science, Metabolon
Although 'omic technologies have matured to the point that targets can potentially be mined directly from human cohorts, model systems continue and will remain an important avenue for probing disease mechanisms and efficacy of novel molecules. Through providing a functional assessment of the phenotype, we will discuss how metabolomics offers a mechanism to more fully interrogate the functional traits of model systems to identify new target opportunities.

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

5:40 Separating Metabolites Based on Their Structural Properties – A Case Study in Central Carbon Metabolome and a Path to Metabolite Molecular Structure Digitization
Gang Xing, Ph.D., Principal Scientist, CVMET Department, Pfizer Biomedical Institute
Cellular metabolites consist of vastly diverse chemical structures that can be described by structural templates and functional groups. A mixed mode LC strategy was developed to separate central carbon metabolites basing on their molecular structure properties, with a prediction algorithm for extension to other molecular families. Integrated with HRAM-QExactive plus Mass Spectrometry, stable isotope labeling and modeling, its application to derive biological insight will be shown.

6:10 6:10 Application of Stable Isotope Labels and Flux Analysis in Drug Discovery
Thomas Roddy, Ph.D., Senior Director, Cellular Metabolism, Agios Pharmaceuticals, Inc.

6:40 End of Day

THURSDAY, SEPTEMBER 22

7:30 am Registration Open and Morning Coffee

DISEASE-FOCUSED RESEARCH STEMMING FROM METABOLOMIC ANALYSIS

8:10 Chairperson's Remarks
Peter Juhasz, Ph.D., Director, Mechanisms and Pathways, Biogen

8:15 Using Metabolomics to Discern New Target Opportunities from Established Models
Kirk Beebe, Ph.D., Director, Application Science, Metabolon
Although 'omic technologies have matured to the point that targets can potentially be mined directly from human cohorts, model systems continue and will remain an important avenue for probing disease mechanisms and efficacy of

novel molecules. Through providing a functional assessment of the phenotype, we will discuss how metabolomics offers a mechanism to more fully interrogate the functional traits of model systems to identify new target opportunities.

8:45 KEYNOTE PRESENTATION: IDENTIFICATION OF METABOLIC INDICATORS OF DISEASE AND DRUG ACTIVITY USING METABOLOMICS

Clary B. Clish, Ph.D., Director, Metabolite Profiling, Broad Institute of MIT and Harvard

Metabolomics is powerful tool to study metabolic perturbations associated with both disease and drug activity. The presentation will highlight recent efforts to identify a plasma metabolic signature of pancreatic cancer in human cohorts years before clinical diagnosis of disease as well as an example of an effort to elucidate the molecular mechanism of action of the MS therapeutic dimethylfumarate.

9:15 Identifying Inhibitors of Oncology Target, Phosphoglycerate Dehydrogenase, with Metabolite Profiling

Michael Pacold, Ph.D., Postdoctoral Research Fellow, Sabitini Lab, MIT

In the canonical glucose-derived serine synthesis pathway, Homo sapiensphosphoglycerate dehydrogenase (PHGDH) catalyzes the first, rate-limiting step. Genetic loss of PHGDH is toxic towards PHGDH-overexpressing breast cancer cell lines even in the presence of exogenous serine. We have used a quantitative high-throughput screen to identify small molecule PHGDH inhibitors, and validated these compounds using metabolite profiling. I will discuss the role of metabolomics in validating these compounds

9:45 Metabolomic Analysis and CardioMetabolic Drug Development

Stephen F. Previs, Ph.D., Senior Scientist, Translational Biomarker - CardioMetabolic Disease, Merck & Co.

The presentation will consider the combined use of isotopic flux data and concentration profiling to elucidate if and how one has modulated carbon-energy flow. We will also consider the impact of sub-cellular compartmentation and metabolic heterogeneity on the data interpretation.

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

11:10 Genetic and Metabolomic Dissection of One-Carbon Metabolism

Gregory Ducker, Ph.D., Postdoctoral Research Fellow, Rabinowitz Laboratory, Princeton University

One-carbon metabolism is the most consistently upregulated metabolic pathway in cancer. Integrating genetic and metabolomic methods, we investigated the compartment specific roles for this metabolism in cancer initiation and proliferation. In most cancers, 1C units are produced in the mitochondria together with glycine, NADPH and NADH. Loss of the mitochondrial pathway, slows, but does not inhibit tumor growth, which is now supported by the cytosolic pathway.

11:40 Panel Discussion: Challenges in Metabolomic Applications

Moderator:

Peter Juhasz, Ph.D., Director, Mechanisms and Pathways, Biogen

Panelists:

Clary B. Clish, Ph.D., Director, Metabolite Profiling, Broad Institute of MIT and Harvard

Elizaveta Freinkman, Ph.D., Research Scientist and Manager, Metabolite Profiling Facility, Whitehead Institute, MIT

Stephen F. Previs, Ph.D., Senior Scientist, Translational Biomarker - CardioMetabolic Disease, Merck & Co.

Thomas Roddy, Ph.D., Senior Director, Cellular Metabolism, Agios Pharmaceuticals, Inc.

- Metabolic profiling – targeted or untargeted?
- Software tools and strategies for untargeted data processing
- Pathway analysis: making sense of metabolic profiling
- Analyzing polar metabolites
- Questions from audience

12:10 pm Late Breaking Presentation

12:40 Session Break

Sponsored by METABOLON

12:50 Luncheon Presentation: Atlas of the Human Metabolome "A New Avenue for Target Discovery and Validation"

John Ryals, Ph.D., President and CEO, Metabolon

Metabolomics has evolved to accompany tools like genomics in the quest to unlock human health and disease. The ability to collect so much data directly on human subjects offers the potential to deliver new targets that will have unequivocal relevance to human disease. By producing a comprehensive read-out of a living system's metabolic profile, we will discuss how metabolomics is creating an "atlas" by which new targets have the potential to be discerned.

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

CANCER METABOLISM

2:15 Chairperson's Remarks

Francesco Parlati, Ph.D., Senior Director, Biology, Calithera Biosciences

2:20 Targeting Glycolysis in Cancer: Opportunities and Challenges

Raju Pusapati, Ph.D., Scientist, Ribon Therapeutics; formerly Postdoctoral Research Fellow, Discovery Oncology, Genentech

Although glycolysis is substantially elevated in many tumors, therapeutic targeting of glycolysis in cancer patients has not yet been successful, potentially reflecting the metabolic plasticity of tumor cells. Employing metabolomics approaches, we identified the nature of the metabolic plasticity in cancer cells that promote escape from glycolytic dependency. These findings reveal novel combinatorial therapeutic strategies to realize the potential benefit from targeting the Warburg effect.

2:50 Hyperpolarized Metabolic MRI in Drug Discovery and Development

John Kurhanewicz, Ph.D., Professor, Pharmaceutical Chemistry, University of California San Francisco

The characteristic features of tumor metabolism have provided opportunities to detect and grade disease and in measuring therapeutic response using metabolic imaging techniques. This lecture will focus on imaging tumor metabolism before and after therapy using hyperpolarized 13C-labeled cell substrates, in which hyperpolarization of the 13C nucleus increases its sensitivity by more than 5-orders of magnitude, and the translation of this technique into the clinic.

3:20 Session Break

3:30 The First Small Molecule Inhibitors and Co-Crystal Structures of PHGDH

Scott Cowen, Ph.D., Discovery Sciences, AstraZeneca R&D Boston

The conversion of 3-phosphohydroxyglycerate to 3-phosphohydroxypyruvate catalyzed by 3-phosphohydroxyglycerate dehydrogenase (PHGDH) is the first and rate-limiting step in serine biosynthesis in humans. A number of studies have implicated PHGDH in tumorigenesis and tumor proliferation. Using a dual fragment and HTS based screening approach, we were able to generate what we believe to be the first potent series of small molecule inhibitors of PHGDH.

4:00 Targeting Amino Acid Metabolism for Cancer Treatment

Ethan Emberley, Ph.D., Scientist II, Biology, Calithera Biosciences

CB-839 is an orally-bioavailable glutaminase inhibitor that blocks the ability of tumors to use glutamine as a nutrient source. CB-839 has antitumor activity in a number of tumor models by reducing levels of key metabolites including TCA cycle intermediates, glutathione and nucleotides. Genomic, proteomic and metabolomics analysis has identified biomarkers and combination partners for CB-839 that are under investigation in ongoing Phase 1 clinical studies.

4:30 A Novel Oncology Candidate Selectively Attacks Cancer Mitochondrial Metabolism

Paul M. Bingham, Ph.D., Vice President, Research, Cornerstone Pharmaceuticals and Professor, Biochemistry and Cell Biology, Stony Brook University

CPI-613, a non-redox active lipoate analog, represents a first-in-class group of drugs attacking core mitochondrial metabolism selectively in tumor cells. This drug is producing striking clinical results in several cancers, including AML and PDAC. CPI-613's unprecedented MOA also renders it a powerful probe of the details of cancer metabolism, revealing clinically relevant features of the altered anabolism and catabolism in tumor cells.

5:00 Close of Conference

Fourth Annual | *September 20-21, 2016*

Targeting Ocular Disorders

The Latest Targets, Pathways and Drug Delivery Methods

With its complex structure and the breadth of ocular disorders, the eye presents unique challenges to drug discovery. Cambridge Healthtech Institute's fourth annual Targeting Ocular Disorders conference provides a platform to discuss novel targets and disease pathways, the latest drug delivery methods, and the most promising emerging therapies. A special focus will be on gene therapy, stem cell therapies, and treatments outside of the well-established anti-VEGF therapies. The event will cover a broad range of diseases including but not limited to glaucoma, wet and dry age related and diabetic macular degeneration, retinopathy and retinitis pigmentosa.

BEST VALUE:

- September 20-21 Conference: Targeting Ocular Disorders
- September 21-22 Conference: Advances in Gene Editing and Gene Silencing - Part 2

TUESDAY, SEPTEMBER 20

7:00 am Registration Open and Morning Coffee

STEM CELLS FOR OCULAR DISORDERS

8:05 Chairperson's Opening Remarks

Jason Slakter, CEO, Ohr Pharmaceutical, Inc.

8:20 Translating Genomics and Stem Cell Technology into Therapy for Major Blinding Diseases

Kang Zhang, M.D., Ph.D., Professor of Ophthalmology, Chief of Ophthalmic Genetics at University of California San Diego

Stem cell research shows great promise in modeling disease *in vitro*, and for treating blinding degenerative diseases of the eye, including age-related macular degeneration (AMD) and glaucoma (Zhu, et al, Cell Stem Cell, 2010; Li et al, PNAS, 2010; Zhang and Ding, NEJM, 2010; Skowronska et al, Mol Cell, 2015). Limbal stem cell (LSC) deficiency causes corneal surface disease, which leads to blindness in millions of people world-wide. We established an *in vitro* feeder-free LSC expansion/3-D corneal differentiation system and show transplantation of LSCs in animal models and humans can replenish the LSC pool and restore corneal transparency (Ouyang et al, Nature, 2014). We have also shown that lanosterol is essential for prevention of protein aggregation and can reverse cataract (Zhao et al., Nature, 2015). We also demonstrated regeneration of a functional human lens using endogenous stem cells, with gain of visual function, in human infants with cataract (Lin, et al Nature, 2016). Furthermore, epigenetics contributes to the progression of aging and age related diseases (Hannum et al, Mol Cell, 2013; Skowronska et al, Mol Cell, 2015). The recent advances in genetic and stem cell therapies of the eye will allow for identification of the high risk patients for personalized intervention and treatment in the near future (Zhang, et al, Nature Review Drug Discovery, 2016).

8:50 Palucorcel for the Treatment of Geographic Atrophy in AMD

James S. Baldassarre, M.D., Head, Clinical Development, Janssen

Human umbilical tissue cells (hUTC; palucorcel) produce a number of trophic factors which may favorably influence various retinal cell types in AMD and have the potential to reverse visual impairment. They appear to be well tolerated when confined to the subretinal space, but accurate delivery has been a technical challenge. This talk will discuss the potential of palucorcel in GA, and the evolution of a novel subretinal delivery approach.

9:20 Stem Cell-Derived Retinal Pigment Epithelium for Treatment of Retinal Degeneration

Irina Klimanskaya, Ph.D., Senior Director of Translational Development, Astellas Institute for Regenerative Medicine (AIRM)

Health and efficiency of photoreceptor cells depend on Retinal Pigment Epithelium (RPE) which plays an essential role in photoreceptor maintenance. RPE malfunction can result in photoreceptor loss and subsequent blindness. RPE generated from human embryonic stem cells is the first differentiated derivative of pluripotent cells that entered clinical trials for age-related macular degeneration and Stargardt's disease. Development of this cell replacement therapy will be discussed.

9:50 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

GENE THERAPY FOR RETINAL DISEASES

10:35 AAV2 Rep-1 Gene Therapy in the Treatment of Choroideremia

David Fellows, CEO, NightstaRx

Choroideremia is an X linked recessive retinal disease that leads to blindness. Nightstar's lead program AAV2 Rep-1, administered through sub-retinal injection has been evaluated in a series of phase I/II trials in the treatment of choroideremia. The current status of the AAV2 Rep-1 program will be discussed.

11:05 Novel Optogenetic Approach to Vision Restoration in Retinal Degenerative Conditions

Sean Ainsworth, CEO, RetroSense

Optogenetics refers to genetic delivery of optically-sensitive proteins, i.e., opsins. RetroSense is applying the approach to retinal neurons, which remain intact after photoreceptor degeneration, enabling them to directly respond to light stimuli and send a visual signal to the brain. The safety and efficacy of the approach has been well established in several animal models. RetroSense has secured exclusive intellectual property rights from Wayne State University and Massachusetts General Hospital covering the use of a broad range of opsins in vision restoration.

11:35 Novel Gene Therapy to Treat Diabetic Retinopathy and Wet Macular Degeneration

R. Michael Burr, MS, MBA, Vice President, Product Development, iVeena, Inc.

iVeena has three gene therapy pipeline products in preclinical development. Flt23k nanoparticles for intravenous delivery and AAV2-Flt23k for sub-retinal delivery regress CNV in mice and monkeys. Comp-ANG1 is a soluble construct of angiopoetin-1 targeting the tie-2 receptor that prevents vision loss and restores vascular function in diabetic mice. iVeena intends to do first-in-human work with these products in 2017.

Sponsored by PharmOptima

12:05 pm Ligand Binding Assay Development and Troubleshooting

Phil Zaworski, M.S., Senior Research Scientist, Biochemistry, PharmOptima LLC

12:20 Sponsored Presentation *(Opportunity Available)*

12:35 Session Break

12:45 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Lunch on Your Own**

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

GENE THERAPY FOR RETINAL DISEASES (CONT.)

2:05 Chairperson's Remarks

Ken Mandell, President and CEO, LayerBio, Inc.

2:15 Gene Therapy for Retinal Diseases

Abraham Scaria, Ph.D., Senior Scientific Director, Ophthalmology, Genzyme, a Sanofi Company

Over the past two decades several studies have demonstrated the utility of Adeno associated viral (AAV) vectors for gene delivery to the retina based on the non-pathogenic nature of AAV and due to its ability to transduce a variety of different cell types in the retina. Different routes of AAV delivery to retina and the use of different AAV serotypes lead to transduction of different cell types. Results will be presented from studies aimed at developing gene therapies for wet-AMD and LCA-1.

INNOVATIVE DRUG DELIVERY METHODS FOR OCULAR DISORDERS

2:45 Novel Drug Delivery Platform and Polymer for Treating Ocular Diseases

Barbara Wirostko, M.D., CMO, EyeGate Pharmaceuticals, Inc.

EyeGate is a late-stage specialty pharmaceutical and drug delivery company focused on developing and commercializing therapeutics and drug delivery mechanisms for treating diseases of the eye. EyeGate recently acquired Jade Therapeutics developing a novel crosslinked Hyaluronic acid polymer platform. HA has a long history of being an ocular lubricant, capable of wound healing systemically, provides an extracellular matrix for stem cell delivery and regenerative medicine, and can deliver drugs in a sustained release manner.

Sponsored by oculis

3:15 Nanoparticle Eye-Drops Deliver Drugs to Retina in Human Patients

Einar Stefansson, M.D., Ph.D., FARVO, Chairman, Co-Founder, Oculis

Oculis' solubilizing nanoparticle (SNP) eye drops deliver drugs to retina in animals and humans. Four clinical trials have shown effect in DME and posterior uveitis. Various SNP eye drops have been successfully tested for anterior and posterior segment use.

Sponsored by RXi Pharmaceuticals

3:30 Self-Delivering RNAi Compounds (sd-rxRNA™) for the Treatment of Ocular Disorders

Michael Byrne, Ph.D., Director, Pharmacology, RXi Pharmaceuticals

RXi developed novel self-delivering RNAi compounds (sd-rxRNA®) with drug-like properties. RXI-109, is in a Phase 1/2 clinical trial for the treatment of subretinal fibrosis in patients with late-stage AMD. An overview of sd-rxRNA delivery and efficacy in the retina and cornea will demonstrate sd-rxRNA's utility for treatment of ocular disorders.

3:45 Refreshment Break in the Exhibit Hall with Poster Viewing and Poster Competition Winner Announced

4:25 Current Trends in Ocular Drug Delivery

Ken Mandell, President and CEO, LayerBio, Inc.

An overview of current approaches to ocular drug delivery will be presented with examples from various ophthalmic indications, including dry eye syndrome, uveitis, postoperative inflammation, glaucoma and retinal diseases.

» 4:55 KEYNOTE PRESENTATION: THE DAWN OF NANOTECHNOLOGY IN OCULAR THERAPEUTICS

Justin Hanes, Ph.D., Lewis J. Ort Professor; Director, The Center for Nanomedicine at the Wilmer Eye Institute, Johns Hopkins University School of Medicine; Founder, Kala Pharmaceuticals and GrayBug Vision

Vision loss due to ocular disease is prevalent and devastating to those affected and their families. The worldwide economic burden is also enormous. This talk will provide an overview of two technologies that are being commercialized as methods to provide more effective drug delivery to the eye: (1) mucus-penetrating particles (MPP) composed of nearly pure drug particles suspended in topical eye drops; MPP are currently being evaluated in Phase II and III clinical trials for treatment of various diseases that affect the front or back of the eye, and (2) non-inflammatory injectable polymer microparticles that provide effective and long-lasting treatments for major eye disease.

5:25 Welcome Reception in the Exhibit Hall with Poster Viewing

6:25 End of Day

WEDNESDAY, SEPTEMBER 21

7:30 am Registration Open and Morning Coffee

INNOVATIVE DRUG DELIVERY METHODS FOR OCULAR DISORDERS (CONT.)

8:00 Chairperson's Opening Remarks

Thomas A. Ciulla, M.D., MBA, Vice President, Clinical Strategy, Ophthotech

8:10 Intraocular Implant Technology Providing Sustained Delivery of a Therapeutic Protein to Treat Back of the Eye Disorders

Konrad Kauper, MSc, Vice President, Core Technology Development, Neurotech Pharmaceuticals, Inc.

This presentation will review the manufacturing, regulatory and pre-clinical development of Encapsulated Cell Therapy (ECT) delivery of ciliary neurotrophic factor (CNTF) and discuss preliminary data from two completed Neurotech clinical trials. Data from both macular telangiectasias and glaucoma clinical trials suggest that sustained, intraocular delivery of CNTF may arrest retinal disease progression and prevent vision loss in both diseases, providing a novel therapy for patients currently without effective treatment options.

NOVEL TARGETS AND DISEASE PATHWAYS OUTSIDE OF CONVENTIONAL ANTI-VEGF MONOTHERAPIES

8:40 Innovation Theory Applied to AMD Therapy Development: The Innovators' DNA, Dilemma, and Prescription

Thomas A. Ciulla, M.D., MBA, Vice President, Clinical Strategy, Ophthotech

This talk reviews innovation therapy at a personal level, technology level, and health care system level. It reviews the sweeping innovations in AMD therapies over the past two decades and identifies trends that are predicted by innovation theory. It reviews the discovery skills of an innovator, contrasting them with the delivery skills of an executive. It contrasts the differences between sustaining innovation and disruptive innovation, with particular emphasis on AMD therapy development. Finally, it reviews innovation theory as it applies to the health care system as a whole, with emphasis on business model innovation and value networks. It discusses these concepts as they apply to the delivery of AMD therapies.

9:10 Squalamine Lactate Ophthalmic Solution: A Topical Approach to Combination Therapy for AMD

Jason Slakter, CEO, Ohr Pharmaceutical, Inc.

Squalamine lactate ophthalmic solution is a topically delivered multi-target anti-angiogenic agent. Squalamine used in combination with ranibizumab demonstrated greater visual acuity benefits over ranibizumab monotherapy in patients with neovascularization due to age-related macular degeneration (AMD) in an exploratory Phase 2 clinical trial. A global Phase 3 program will enroll 1,300 patients with treatment naïve, neovascular AMD with lesion characteristics that demonstrated the strongest treatment benefit with the combination therapy in the phase 2 study.

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

10:25 Treating Diabetic Eye Disease via Activation of Tie2 by AKB-9778: Results of a Phase II Clinical Study

Mitchell Brigell, Ph.D., Vice President, Clinical Development, Aerpio Therapeutics

AKB-9778 is a small molecule inhibitor of vascular endothelial protein tyrosine phosphatase (VE-PTP) that stimulates phosphorylation of Tie2 in vascular endothelial cells. Activation of Tie2 is necessary for vascular integrity, and is reduced by angiopoietin2 (Ang2) in disease states such as diabetic macular edema (DME) and diabetic retinopathy (DR). In this talk I will summarize the DME and DR results of TIME-2, a phase 2a study in 144 patients with DME randomized to receive 3 months of treatment with AKB-9778 monotherapy, ranibizumab monotherapy, or combination AKB-9778 + ranibizumab therapy.

10:55 Single Domain Antibodies Against CXCR4 as a Potential Therapy in Retinal Vascular Disease

Mick Foley, Ph.D., CSO, Biochemistry, AdAlta, Australia

The chemokine receptor CXCR4 has been implicated in a number of ocular diseases including aberrant choroidal neovascularization and it has been suggested that antagonizing this receptor may be a promising therapy for ocular diseases. We have identified a human single domain "i-body" against CXCR4 and shown that upon intravitreal administration, this antagonist can reduce retinal scarring and tissue contraction in a laser induced mouse model of choroidal neovascularization.

11:25 Enjoy Lunch on Your Own

12:50 pm Plenary Keynote Program *(See page 3 for details.)*

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

3:20 Close of Conference

CONFERENCE PRICING

	Commercial	Academic, Government, Hospital-affiliated
ALL ACCESS *(Includes access to 2 Short Courses or 1 Symposium and 2 Conferences and/or Training Seminar)*		
Registration after September 9, 2016	$3,299	$1,999
STANDARD PACKAGE *Includes access to 2 Conferences and/or Training Seminar, (excludes Short Courses and Symposia)*		
Registration after September 9, 2016	$2,849	$1,379
SINGLE CONFERENCE PRICING *Includes access to 1 Conference or Training Seminar, (excludes Short Courses and Symposia)*		
Registration after September 9, 2016	$1,929	$1,049

September 20-21	September 21-22
(T1A) Targeting Histone Methyltransferases and Demethylases	(T1B) Targeting Epigenetic Readers and Chromatin Remodelers
(T2A) Targeting the Ubiquitin Proteasome System	(T2B) Kinase Inhibitor Discovery
(T3A) Targeting the Microbiome - Part 1	(T3B) Targeting the Microbiome - Part 2
(T4A) GPCR-Based Drug Discovery - Part 1	(T4B) GPCR-Based Drug Discovery - Part 2
(T5A) Advances in Gene Editing and Gene Silencing - Part 1	(T5B) Advances in Gene Editing and Gene Silencing - Part 2
(T6A) Gene Therapy Breakthroughs	(T6B) Translating Cancer Genomics
(T7A) Antibodies Against Membrane Protein Targets - Part 1	(T7B) Antibodies Against Membrane Protein Targets - Part 2
(T8A) Targeting Cardio-Metabolic Diseases	(T8B) Metabolomics in Drug Discovery
(T9A) Targeting Ocular Disorders	(TS1) Training Seminar: Data Visualization

SYMPOSIUM PRICING

Monday, September 19	Commercial	Academic, Government, Hospital-affiliated
(S1) Next-Generation Histone Deacetylase Inhibitors	$999	$699
(S2) Strategies for Tackling Rare Genetic Diseases		
(S3) Understanding CRISPR: Mechanisms and Applications		
(S4) Autoimmunity – Small Molecule Approaches		
(S5) NK Cell-Based Cancer Immunotherapy		

CONFERENCE DISCOUNTS

Poster Submission - Discount ($50 Off): Poster abstracts are due by August 5, 2016. 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.

REGISTER 3 - 4th IS FREE: Individuals must register for the same conference or conference combination and submit completed registration form together for discount to apply.

Alumni Discount: Cambridge Healthtech Institute (CHI) appreciates your past participation at Discovery On Target. As a result of the great loyalty you have shown us, we are pleased to extend to you the exclusive opportunity to save an additional 20% off the registration rate.

**Alumni, Twitter, LinkedIN, Facebook or any other promotional discounts cannot be combined. Discounts not applicable on Event Short Courses.*

Group Discounts and NIH/Government Discounts Available! Special rates are available for multiple attendees from the same organization and for NIH/ Government employees. For more information on group and government discounts contact Bill Mote at 781-972-5479

** Separate registration required for Short Courses, Symposia, Training Seminar*

Registration details continued on next page.

Registration details continued from previous page.

SHORT COURSES

Add a Short Course to your Conference Registration, SAVE $100	Commercial	Academic, Government, Hospital-affiliated
One short course	$699	$399
Two short courses	$999	$699
Three short courses	$1,199	$899
Registered Conference Delegates SAVE $100	-$100	-$100

Monday, September 19, 8-11:00 am
SC1: Immunology Basics for Chemists
SC4: Medical Dermatology Therapeutic R&D and Technical Innovation - Part 1
Monday, September 19, 12-3:00 pm
SC5: GPCR Structure-Based Drug Discovery
SC6: RNA as a Small Molecule Drug Target
SC7: Using IP Landscape Studies to Improve Your Confidence While Navigating a Crowded IP and Technology Space
SC8: Medical Dermatology Therapeutic R&D and Technical Innovation - Part 2
Monday, September 19, 3:30-6:30 pm
SC9: Targeting of GPCRs with Monoclonal Antibodies
SC12: Introduction to Gene Editing

Monday, September 19, 7:00-9:30pm (Dinner provided)
SC13: Convergence of Immunotherapy and Epigenetics for Cancer Treatment
Wednesday, September 21, 7-9:30 pm (Dinner provided)
SC14: Cancer Metabolism: Pathways, Targets and Clinical Updates
SC15: Introduction to Allosteric Modulators
SC16: Functional Screening Strategies Using CRISPR and RNAi

** Separate registration required for Short Courses, Symposia, Training Seminar*

TRAINING SEMINAR

Each CHI Training Seminar offers 1.5 Days of instruction with start and stop times for each day shown above and on the Event-at-a-Glance published in the onsite Program & Event Guide. Training Seminar will include morning and afternoon refreshment breaks, as applicable, and lunch will be provided to all registered attendees on the full day of the class. Each person registered specifically for the training seminar will be provided with a hard copy handbook for the seminar in which they are registered. A limited number of additional handbooks will be available for other delegates who wish to attend the seminar, but after these have been distributed no additional books will be available.

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