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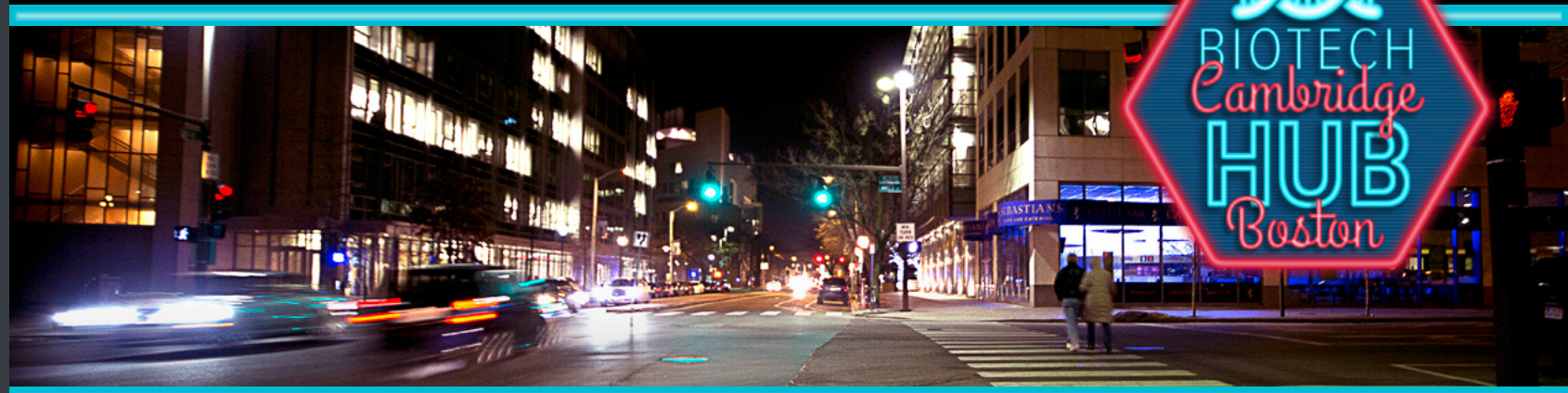

12th ANNUAL

Discovery on TARGET

The Industry's Preeminent Event on Novel Drug Targets

OCTOBER 8 - 10, 2014 | WESTIN BOSTON WATERFRONT | BOSTON MA

October 8 – 9

Targeting Epigenetic Readers and Chromatin Remodelers
Targeting the Ubiquitin Proteasome System
Big Data Analytics and Solutions – *NEW!*
GPCR-Based Drug Discovery
RNAi for Functional Genomics Screening - Part 1
Protein-Protein Interactions as Drug Targets – *NEW!*
Antibodies Against Membrane Protein Targets - Part 1

October 9 – 10

Targeting Histone Methyltransferases and Demethylases
Screening Drug Transporter Proteins – *NEW!*
Maximizing Efficiency in Discovery – *NEW!*
GPCR-Targeted Therapeutics
Genome Editing for Functional Genomics Screens - Part 2
Cancer Metabolism
Antibodies Against Membrane Protein Targets - Part 2

PLENARY KEYNOTE PROGRAM

Chas Bountra, Ph.D., *Professor of Translational Medicine & Head, Structural Genomics Consortium, University of Oxford*

Andrew L. Hopkins, *D.Phil., FRSC, FSB, Chair of Medicinal Informatics and SULSA Research Professor of Translational Biology, Division of Biological Chemistry and Drug Discovery, College of Life Sciences, University of Dundee*

Martin Tolar, M.D., Ph.D., *Founder, President & CEO, Alzheon, Inc.*

SYMPOSIUM
EIGHTH ANNUAL
Next Generation Histone Deacetylase Inhibitors

EVENT FEATURES

14 Conferences
13 Short Courses
1 Symposium
40+ Exhibitors
50+ Posters
40+ Interactive Breakout Discussion Groups
Plenary Keynote Speakers

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CONFERENCE-AT-A-GLANCE*

Tuesday October 7	Pre-Conference Short Courses* and 1-day Symposium: Next Generation Histone Deacetylase Inhibitors*						
Wednesday October 8	1A: Targeting Epigenetic Readers and Chromatin Remodelers	2A: Targeting the Ubiquitin Proteasome System	3A: Big Data Analytics & Solutions	4A: GPCR-Based Drug Discovery	5A: RNAi for Functional Genomics Screening – Part 1	6A: Protein-Protein Interactions as Drug Targets	7A: Antibodies Against Membrane Protein Targets – Part 1
Thursday October 9	1A: Targeting Epigenetic Readers and Chromatin Remodelers	2A: Targeting the Ubiquitin Proteasome System	3A: Big Data Analytics & Solutions	4A: GPCR-Based Drug Discovery	5A: RNAi for Functional Genomics Screening – Part 1	6A: Protein-Protein Interactions as Drug Targets	7A: Antibodies Against Membrane Protein Targets – Part 1
	1B: Targeting Histone Methyltransferases and Demethylases	2B: Screening Drug Transporter Proteins	3B: Maximizing Efficiency in Discovery	4B: GPCR-Targeted Therapies	5B: Genome Editing for Functional Genomics Screens – Part 2	6B: Cancer Metabolism	7B: Antibodies Against Membrane Protein Targets – Part 2
Thursday October 9 7:00–10:00 pm	Dinner Short Courses*						
Friday October 10	1B: Targeting Histone Methyltransferases and Demethylases	2B: Screening Drug Transporter Proteins	3B: Maximizing Efficiency in Discovery	4B: GPCR-Targeted Therapies	5B: Genome Editing for Functional Genomics Screens – Part 2	6B: Cancer Metabolism	7B: Antibodies Against Membrane Protein Targets – Part 2

Separate registration required for Short Courses and Symposium

Cambridge Healthtech Institute will host its *12th Annual* **Discovery on Target** event showcasing current and emerging "hot" targets for the pharmaceutical industry October 8 – 10, 2014 in Boston, MA. Spanning three days, the meeting attracts 900+ attendees (from 24 countries), composed of scientists/technologists, executives, directors, and managers from biopharma, academic, and healthcare organizations. In 2014 the event is comprised of 14 meeting tracks which include Epigenetic Readers, Ubiquitin Proteasome, Big Data Discovery, GPCR Drug Discovery, RNAi-Screens-Functional-Genomics, PPI Targets, Protein-Targets, Histone-Methyltransferases-Demethylases, Drug Transporters, Maximizing Efficiency, GPCR Therapeutics, Genomics Screening, Cancer Metabolism and Membrane Production. The 2014 event offers 200+ scientific presentations across these 14 conference tracks, 1 Symposium and 13 conference short courses, 40+ interactive breakout discussion groups, an exhibit hall of 40+ companies, and dedicated poster viewing and networking sessions. The *12th Annual* **Discovery on Target** assembles an impressive group of 195+ distinguished speakers who look forward to sharing their knowledge, best practices, and expertise with all attendees.

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SHORT COURSES*

TUESDAY, OCTOBER 7

Afternoon Courses | 12:00 pm – 3:00 pm

SC2: Approaches for Biologically-Relevant Chemical Diversity

Todd Wenderski, Ph.D., Research Fellow, Molecular Pharmacology & Chemistry Program, Sloan-Kettering Institute for Cancer Research, Memorial Sloan-Kettering Cancer Center

Matthew Clark, Ph.D., Senior Vice President, Research, X-Chem, Inc.

Tim Briggs, Ph.D., Scientist, Medicinal Chemistry, Ensemble Therapeutics

Small bioactive molecules are the starting point for any discovery program, yet despite the vast chemical space available for generation of novel chemical matter, existing small-molecule drugs address only a very small subset of protein targets. To address this disconnect, a resurgence of interest in pharmacognosy, using "privileged" natural products along with the utilization of diversity oriented synthesis (DOS), and DNA-templated organic synthesis as a starting point for translation into chemical libraries are being recognized as important strategies to guide design and generation of novel compound collections. This workshop will discuss modern approaches for the synthesis of novel, diverse, and biologically-relevant chemical collections.

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

Caroline Shamu, Ph.D., Director, ICCB-Longwood Screening Facility, Harvard Medical School

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

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

Scott Martin, Ph.D., Team Leader, RNAi Screening, NIH Chemical Genomics Center, National Center for Advancing Translational Sciences, National Institutes for Health

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

SC4: Targeting Protein-Protein Interactions

Daniel A. Erlanson, Ph.D., Co-Founder and President, Carmot Therapeutics, Inc.

Edward R. Zartler, Ph.D., President & CSO, Quantum Tessera Consulting

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

SC5: GPCR Structure-Based Drug Discovery

Vsevolod (Seva) Katritch, Ph.D., Assistant Professor, Integrative Structural and Computational Biology, The Scripps Research Institute

Jan Steyaert, Ph.D., Director, Structural Biology Brussels Research Center, Vrije University Brussels

This course will review the new structural knowledge now available for many G Protein-Coupled Receptors (GPCRs) based on their recently elucidated crystal structures. The instructors will explore with participants, how new findings are impacting rational drug design approaches for GPCRs. There will also be a focus on tools now showing progress against GPCRs such as fragment-based approaches and using antibodies to probe GPCR structure for extracting information that enables the medicinal chemist to more efficiently design GPCR-targeted ligands.

Evening Courses | 3:45 pm – 6:45 pm

SC7: Targeting of GPCRs with Monoclonal Antibodies

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

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

SC8: A Primer to Gene Editing: Tools and Applications

Neville Sanjana, Ph.D., Simons Postdoctoral Fellow, Laboratory of Dr. Feng Zhang, Broad Institute and the Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology

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

Benjamin Housden, Ph.D., Postdoctoral Fellow, Laboratory of Dr. Norbert Perrimon, Department of Genetics, Harvard Medical School

Florian T. Merkle, Ph.D, Postdoctoral Fellow, Departments of Stem Cell and Regenerative Biology and Molecular and Cellular Biology, Harvard University, Harvard Stem Cell Institute and Broad Institute of Harvard and MIT

This course will help attendees understand the fundamentals of gene editing and the various tools available. The instructors will compare and contrast the use of CRISPR/Cas9 system with meganucleases, zinc-finger nucleases, and transcription activator-like effector nucleases (TALENs) highlighting the best use of each system for various applications. Tools and methods for setting up CRISPR-based genetic screens using Drosophila and mammalian cell systems will be discussed in great detail.

** Separate registration required; see website for complete course details*

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SHORT COURSES*

SC9: Introduction to Targeted Covalent Inhibitors

Mark Schnute, Ph.D., Associate Research Fellow, Biotherapeutics Chemistry & Immunoscience Research, Pfizer Global R&D

Christoph Zapf, Ph.D., Principal Scientist, Worldwide Medicinal Chemistry, Pfizer Research Labs

Covalent inhibitors of kinases have re-emerged as a drug design strategy due to more examples of their safety and efficacy in patients. Covalent inhibitors have the advantage of increased selectivity and longer action of duration but there are still important issues about their design and application that need to be better understood. This course will cover practical as well as theoretical issues that a medicinal chemist needs to keep in mind in developing covalent inhibitors.

THURSDAY, OCTOBER 9

Dinner Courses | 7:00 pm – 10:00 pm

SC10: Setting Up Effective Functional Screens Using 3D Cell Cultures

Sophie Lelièvre, DVM, LLM, Ph.D., Associate Professor, Department of Basic Medical Sciences and Associate Director, Discovery Groups, NCI-designated Purdue Center for Cancer Research, Purdue University

Geoffrey A. Bartholomeusz, Ph.D., Assistant Professor and Director, siRNA Core Facility, Department of Experimental Therapeutics, Division of Cancer Medicine, The University of Texas M.D. Anderson Cancer Center

Arvind Rao, Ph.D., Assistant Professor, Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center

SC12: Introduction to Allosteric Modulators and Biased Ligands of GPCRs

Michel Bouvier, Ph.D., Professeur, Department of Biochemistry, University of Montréal

Stephan Schann, Ph.D., Head, Research, Domain Therapeutics SA

Allosteric modulators and biased ligands of G protein-coupled receptors (GPCRs) represent new therapeutic paradigms for achieving more selective activation of cellular responses. However the identification and characterization of such GPCR-targeted compounds using standard functional assays remain elusive due to the'context-dependent phenomena' of GPCRs. This course will discuss important aspects of hit identification and validation of allosteric modulators and biased ligands in GPCR research activity.

** Separate registration required; see website for complete course details*

Next Generation Histone Deacetylase Inhibitors Symposium*

Promising New Chemistries and Biological Strategies for Targeting HDACs

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 in 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. However, much remains to be elucidated about the functional implications of modulating HDACs and understanding the signaling pathways that can cause adverse cellular effects and unwanted toxicity. Cambridge Healthtech Institute's eighth annual event on Next Generation Histone Deacetylase Inhibitors, tracks both the scientific and clinical progress being made to better understand the cellular function of this complex drug target family.

Suggested Event Package

October 7 Symposium: Next Generation Histone Deacetylase Inhibitors

October 8-9 Conference: Targeting Epigenetic Readers and Chromatin Remodelers

October 9-10 Conference: Targeting Histone Methyltransferases and Demethylases

New HDAC Chemistries and Screening Approaches

8:00 Chairperson's Opening Remarks

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

8:10 HDAC6 Inhibitor Platform: Therapeutic Applications in Charcot-Marie-Tooth (CMT) and Rett Syndrome

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

HDAC6 is one of the key enzymes that regulates the acetylation state of the microtubule protein a-tubulin, and microtubule-dependent transport rates are more efficient along acetylated a-tubulin than deacetylated a-tubulin. In addition to facilitating anterograde transport of new cargo to synaptic zones, acetyl-tubulin also increases the ability of damaged organelles or misfolded proteins to leave synaptic zones. This may be very important for Rett Syndrome as well as other conditions, as damaged mitochondria and elevated levels of improperly spliced mRNA transcripts have been noted in MeCP2-deficient neurons. The design, synthesis, assay, and application of HDAC6 inhibitors to various therapeutic areas will be covered.

8:40 Defining the Structural Requirements for the Design of Inter-Class Selective HDAC Inhibitors

Edward Holson, Ph.D., Director, Medicinal Chemistry, Stanley Center for Psychiatric Research and Director of Chemistry, Chemical Biology Platform, Broad Institute

I will describe the minimal structural requirements necessary for the potent and selective inhibition of HDAC6 achieved through the careful choice of linker element only. We extend these design considerations to the design of the first inhibitors capable of potently and selectively inhibiting both HDAC6 and HDAC8 despite the fact that these isoforms belong to distinct phylogenetic classes within the HDAC family of enzymes. Our biochemical and computational data provide evidence that evolutionary relationships between HDACs cannot always predict molecular recognition or ligand binding similarities.

9:10 Engaging Nuclear Receptors for Targeted Histone Deacetylase Inhibition

Adeboyega "Yomi" Oyelere, Ph.D., Associate Professor, School of Chemistry and Biochemistry, Georgia Institute of Technology

Histone deacetylase (HDAC) inhibition is a clinically validated strategy for cancer treatment. Despite promises in preclinical studies, HDAC inhibitors (HDACi) have been less efficacious in treating solid tumors. To address this problem, my lab has designed HDACi equipped with secondary pharmacophores to facilitate selective accumulation in malignant cells. In this presentation, I will discuss the discovery and SAR studies on new class of HDACi compounds targeted to breast and prostate tumors by equipping them with the additional ability to bind to the estrogen receptor (ER) and androgen receptor (AR) respectively.

9:40 Coffee break

10:00 Discovery of the First N-Hydroxycinnamamide-Based Histone Deacetylase 1/3 Dual Inhibitors with Potent Oral Antitumor Activity

Yingjie Zhang, Ph.D., Lecturer, Department of Medicinal Chemistry, School of Pharmaceutical Sciences, Shandong University

A novel class of N-hydroxycinnamamide-based HDACs inhibitors was designed and synthesized. *In vitro* activity evaluation of these compounds showed excellent HDACs inhibition and potent growth inhibition in multiple tumor cell lines. Relative to the approved HDACs inhibitor SAHA, our compound 11r exhibited comparable even more potent oral anticancer activity in a human leukemic monocyte lymphoma (U937) xenograft model. Most importantly, our compounds exhibited marked dual HDAC1/3 selectivity over other Class I isoforms (HDAC2 and HDAC8), Class IIa representative isoform HDAC4, Class IIb representative isoform HDAC6 and Class IV isoform HDAC11.

10:30 Imaging HDAC Density and Drug Inhibition in the Human Brain

Jacob Hooker, Ph.D., Assistant Professor, Radiology, Harvard Medical School

Histone deacetylases have shown broad potential in treatments against cancer and emerging data supports HDAC-targeting in the context of cardiovascular disease and CNS dysfunction. Development of a radiotracer for non-invasive imaging will elucidate the distribution and functional roles of HDACs in human and accelerate medical research and drug discovery in this domain. We have developed an HDAC imaging agent, [11C]Martinostat for imaging HDACs in the brain, heart, kidney, pancreas and spleen to realize these goals.

*Separate Registration Required for Next Generation Histone Deacetylase Inhibitors Symposium

Next Generation Histone Deacetylase Inhibitors Symposium*

Promising New Chemistries and Biological Strategies for Targeting HDACs

11:00 Enjoy Lunch on Your Own

Exploring HDAC Biology

12:00 pm Chairperson's Remarks

Wayne W. Hancock, M.D., Ph.D., Professor of Pathology and Chief of Transplant Immunology, Children's Hospital of Philadelphia and University of Pennsylvania

12:10 Chemogenomic Approaches to Spatiotemporal Regulation of HDAC Activity

Ralph Mazitschek, Ph.D., Assistant Professor, Center for Systems Biology, Chemical Biology Platform, Massachusetts General Hospital

HDACs are master regulators of chromatin structure and function. Beyond modulating histones acetylation they are recognized as regulators of non-histone proteins. HDAC inhibitors have been used as tool compounds to study basic biology and recognized as promising therapeutics. However, systemic exposure is often not well tolerated, or does not provide the required resolution in biological model systems. To address these shortcomings we have developed a new approach to control HDAC activity with greater spatial and temporal resolution.

12:40 Characterization of HDAC Inhibitors: From Structural Analysis to Cell Function

Pascal Steiner, Ph.D., Scientist, Department of Neuroscience, Genentech, Inc.

A detailed understanding of how HDAC inhibitors with different pharmacological properties affect biological functions *in vitro* and *in vivo* is still missing. I will present our recent findings showing the evaluation of HDAC inhibitors potency *in vitro* using recombinant proteins and of their pharmacodynamic properties as measured with histone acetylation are insufficient to predict their functional consequences on biological activity such as gene expression and cell viability and therefore might be misleading in identifying useful HDACi.

1:10 Immuno-Modulatory Function of HDAC6 and Tubulin Acetylation

Tso-Pang Yao, Ph.D., Associate Professor, Department of Pharmacology and Cancer Biology, Duke University

HDAC inhibitors show an anti-inflammatory activity. The underlying mechanism is not well understood. The potential toxicity associated with pan-HDAC inhibitors also presents a barrier for their chronic use in inflammatory disease. We will discuss different anti-inflammatory phenotypes induced by HDAC inhibitors and offer mechanistic basis for differential therapeutic effects and opportunities for targeting selective HDAC members.

1:40 Coffee break

2:00 The Roles of Class I HDACs in Alzheimer's Disease

Li-Huei Tsai, Ph.D., Professor of Neuroscience, Department of Brain and Cognitive Sciences and Director, Picower Institute for Learning and Memory, Massachusetts Institute of Technology

Impaired genome integrity has been implicated in aging and in neurodegenerative diseases such as Alzheimer's disease (AD). Our work suggests that the accumulation of DNA damage occurs early in AD pathophysiology, and that this contributed to disease progression. In two separate studies, we found that HDAC1 plays an important role in DNA damage repair and that its reduced activity is correlated with neurodegeneration. Furthermore, HDAC1 may also directly regulate the production and clearance of beta-amyloid. Thus targeting HDAC1 may be beneficial for treatment of neurodegenerative disorders.

2:30 Discrete and Novel Immunologic Roles of Individual Class I HDAC Enzymes

Wayne W. Hancock, M.D., Ph.D., Professor of Pathology and Chief of Transplant Immunology, Children's Hospital of Philadelphia and University of Pennsylvania

In the same way that one size doesn't fit all, it may not be desirable to try and efficiently block all class I HDAC enzymes. I will present data comparing the differing roles of class I enzymes in the immune system using genetic and pharmacologic approaches. While there is some redundancy and ability to compensate, HDAC1 and HDAC2 play distinct roles and their deletion has differing effects, as does targeting of HDAC3 and HDAC8. Our data point to the potential for major advances in therapeutics if, and as, the ability to target individual class I isoforms is achieved.

3:00 Session Break

Evaluating Pan v/s Isoform-Specific Inhibitors

3:45 Chairperson's Remarks

Simon Jones, Ph.D., Vice President, Biology and Preclinical Development, Acetylon Pharmaceuticals

3:50 Clinical Potential of Isoform Selective HDAC Inhibitors

Simon Jones, Ph.D., Vice President, Biology and Preclinical Development, Acetylon Pharmaceuticals, Inc.

There has been resurgence of activity in developing selective HDAC inhibitors for the clinic. The use of selective inhibitors with genetic models has substantially added to the basic biology of roles for HDACs regulating acetylation states histone and non-histone protein substrates. The potential for ricolinostat, a selective HDAC6 inhibitor, in multiple myeloma, highly selective HDAC6 inhibitors for neurological indications, and targeting HDAC1,2 in β-thalassemia and cellular differentiation in cancer will be discussed.

4:20 HDAC10 Controls Autophagy-Mediated Drug Resistance

Olaf Witt, M.D., Professor for Pediatric Oncology, Hematology and Immunology Head, CCU Pediatric Oncology German Cancer Research Center Head, Section Pediatric Brain Tumors, Department of Pediatric Oncology, Hematology and Immunology, University Children's Hospital

Pediatric neuronal cancers have been instructive in defining oncogenic functions of HDAC isoforms including HDACs 8, 5 and 9. Recently, we have identified a novel non-epigenetic function of HDAC10 in controlling autophagy-mediated drug

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Next Generation Histone Deacetylase Inhibitors Symposium*

Promising New Chemistries and Biological Strategies for Targeting HDACs

resistance. Targeting of HDAC10 inhibits autophagic flux and restores sensitivity of neuroblastoma to chemotherapy. Moreover, high level of HDAC10 expression is associated with poor clinical outcome. We will discuss molecular mechanisms of the HDAC10-autophagy-axis and potential options for isoform selective inhibition.

4:50 Coffee Break

5:10 Targeting HDACs in Cardiovascular Disease

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

Efficacy of small molecule HDAC inhibitors has been demonstrated in animal models of heart failure, where the compounds block cardiac hypertrophy and fibrosis and improve systolic and diastolic function. Since the pharmacological inhibitors used in the pre-clinical heart failure studies target 11 distinct HDAC enzymes, the identity of the HDAC isoform(s) that controls pathological responses of the heart unknown. I will present our recent data from studies of isoform-selective HDAC inhibitors and HDAC knockout mice in models of cardiac disease.

» 5:40 FEATURED PRESENTATION: CHEMICAL MODULATION OF CHROMATIN STRUCTURE AND FUNCTION

James E. Bradner, M.D., Assistant Professor, Department of Medicine, Harvard University Medical School and Staff Physician, Division of Hematologic Malignancies, Dana-Farber Cancer Institute

With an interest in understanding chromatin-dependent signal transduction to RNA polymerase in developmental and disease biology, we and others have undertaken to discover and optimize small molecule modulators of chromatin regulatory factors. These incisive chemical probes have availed new insights into chromatin structure and function, and suggest plausible translational opportunities for the targeted development of drug-like derivatives in cancer and non-malignant indications. New biotechnologies have been created which allow the rapid identification of critical regulatory regions underlying cell state and which provide the first genome-wide maps of spatial localization of drug molecules within the epigenome. Discussed in this lecture will be mechanistic and translational efforts to modulate gene regulatory pathways of lysine acetylation in cancer transcriptional signaling.

6:30 Close of Symposium

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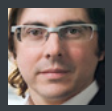
PLENARY KEYNOTE PROGRAM

Chas Bountra, Ph.D., *Professor of Translational Medicine & Head, Structural Genomics Consortium, University of Oxford*



Andrew L. Hopkins, *D.Phil., FRSC, FSB, Chair of Medicinal Informatics and SULSA Research Professor of Translational Biology, Division of Biological Chemistry and Drug Discovery, College of Life Sciences, University of Dundee*

Martin Tolar, M.D., Ph.D., *Founder, President & CEO, Alzheon, Inc.*

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 8, 2014.

- Your poster will be available to 900+ delegates
- You'll automatically be entered into our poster competition where two winners each will receive an American Express Gift Certificate
- $50 off your registration fee
- Your research will be seen by leaders from pharmaceutical, biotech, academic and government institutes

Discovery on Target Student Fellowship

Full time graduate students and PhD Candidates are encouraged to apply for the Discovery on Target Student Fellowship. Interested students must complete an online application for the 2014 Student Fellowship. Applications are due by July 25, 2014.

How Students Benefit from Presenting a Poster:

1. Showcase Your Research to 900+ 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.

Second Annual

October 8 - 9, 2014

Targeting Epigenetic Readers and Chromatin Remodelers

Drugging the "Undruggable"

Operating at the interface of translating histone marks, reader domains that recognize the histone code written in acetyl and methyl marks have now emerged as viable targets for therapeutic development. In particular, the BET bromodomain family of readers has gained significant attention for the treatment of human cancers, with several inhibitors developed and clinical-stage programs now underway. Cambridge Healthtech Institute's Second Annual Targeting Epigenetic Readers and Chromatin Remodelers meeting will unite leading academic and industry researchers for the development of chemical probes and inhibitors to further our understanding of the therapeutic opportunities associated with targeting reader domains and chromatin remodeling.

Suggested Event Package

October 7 Short Course: Targeting Protein-Protein Interactions

October 7 Short Course: Introduction to Targeted Covalent Inhibitors

October 8-9 Conference: Targeting Epigenetic Readers and Chromatin Remodelers

October 9-10 Conference: Targeting Histone Methyltransferases and Demethylases

WEDNESDAY, OCTOBER 8

7:00 am Registration and Morning Coffee

DEVELOPING NOVEL BROMODOMAIN INHIBITORS

8:05 Chairperson's Opening Remarks

Ming-Ming Zhou, Ph.D., Harold and Golden Lamport Professor and Chairman, Department of Structural & Chemical Biology; Co-Director, Experimental Therapeutics Institute, Icahn School of Medicine at Mount Sinai

» 8:15 FEATURED PRESENTATION: TARGETING GENE EXPRESSION: SELECTIVE VS. PROMISCUOUS BROMODOMAIN INHIBITION

Panagis Filippakopoulos, Ph.D., Principal Investigator, Bromodomains, Structural Genomics Consortium & Ludwig Institute for Cancer Research, Nuffield Department of Clinical Medicine, University of Oxford

I will present our efforts to identify novel inhibitors of BRDs that are site selective (in the case of BET bromodomains) as well as our efforts to destroy selectivity while retaining affinity outside the BET family (i.e., promiscuous inhibitors). I will be covering the development and characterization of these tool compounds as well as their properties targeting gene expression in diverse cellular systems, seeking to validate BRD function.

9:00 Selective Modulation of Bromodomains in Gene Activation

Ming-Ming Zhou, Ph.D., Harold and Golden Lamport Professor and Chairman, Department of Structural & Chemical Biology; Co-Director, Experimental Therapeutics Institute, Icahn School of Medicine at Mount Sinai

In this talk I will present my group's latest study of structural mechanism and function of bromodomain proteins in gene transcriptional activation using newly designed, highly selective bromodomain inhibitors. I will discuss the functional implications of their new findings of basic principles that govern the molecular interactions and regulation in gene expression, and a new strategy for developing targeted epigenetic therapy for cancer and chronic inflammation.

9:30 Development and Utilities of BET Bromodomain Inhibitors with High CNS Exposure

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

Published bromodomain inhibitors show insufficient *in vivo* CNS exposure due to a variety off issues. In collaboration with Epigenetix, Inc. we therefore developed novel small molecules, such as EP11313, with characteristics of CNS active drugs. These compounds have to date primarily been tested in various models of glioblastoma. However, they have also been useful in demonstrating a role for BET bromodomain proteins as novel epigenetic regulators of cocaine-induced behavioral plasticity.

10:00 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

10:45 Discovery of Selective BRD4 Bromodomain Inhibitors by Fragment-Based High-Throughput Docking

Dimitrios Spiliotopoulos, Ph.D., Senior Research Scientist, Biochemistry, University of Zurich

Using a fragment-based *in silico* screening approach, we identified two small molecules that selectively bind to the first bromodomain of BRD4 with low-micromolar affinity and favorable ligand efficiency (0.37 kcal/mol per non-hydrogen atom). Notably, the hit rate of the fragment-based *in silico* approach is about 10% as only 24 putative inhibitors, from an initial library of about 10 million molecules, were tested *in vitro*.

11:15 Development and Application of BET and CREBBP Bromodomain Ligands

Stuart Conway, Ph.D., Associate Professor, Chemistry, University of Oxford

I will present our work on the development of small molecule ligands for the BET bromodomain. I will describe our understanding of the SAR for BET bromodomain binding and our work to optimise the structure of our ligands both for potency and metabolic stability for use *in vivo*. I will also present our work on the development of a novel class of CREBBP ligands and describe what these compounds have taught us about the requirements for CREBBP bromodomain binding.

11:45 A Novel Chemical Probe for Family VIII Bromodomains

Dafydd Owen, Ph.D., Associate Research Fellow, Medicinal Chemistry, Biotherapeutics Worldwide R&D, Pfizer

BRG1 (SMARCA4) and BRM (SMARCA2) are the central ATPase components of the multi-component complexes. BRG1 and BRM are multi-domain proteins that contain a number of DNA and protein interaction modules. These include C-terminal bromodomains. Through collaboration with the SGC we have identified a chemical probe that interacts with just three of the Family VIII bromodomains - BRG1, BRM and PB1(5). The discovery, binding mode and phenotype derived from the use of PFI-3 will be discussed.

12:15 pm Sponsored Presentations *(Opportunities Available)*

12:45 Session Break

1:00 Luncheon Presentation: Novel Quantitative and High Throughput Biochemical Assays that Enable Discovery and Optimization of Inhibitors for Epigenetic Targets *Sponsored by* DiscoveRx

Daniel K Treiber, Vice President, R&D, DiscoveRx Corporation

There are 57 bromodomains contained in 41 different proteins; however, few small molecule bromodomain inhibitors have been reported. One primary factor limiting the discovery of new inhibitors is the absence of a comprehensive biochemical bromodomain screening platform. Here we describe the application of proven competitive binding assay technology (KINOMEscan) to the development of quantitative ligand binding assays for human bromodomains (BROMOscan). We have developed a carefully validated assay panel that covers >50 percent of the human bromodomain family, and this panel is suitable for HTS, selectivity profiling and quantitative affinity (Kd) assessment. We have used this panel to discover that several clinical kinase inhibitors are also potent bromodomain inhibitors, which suggests rationally designed polypharmacology strategies for the development of more efficacious targeted cancer therapies. A derivative technology currently in development for the ultrasensitive readout of protein methyltransferase enzyme activity shall be described as well.

MOLECULAR MECHANISMS IN CANCER

1:50 Chairperson's Opening Remarks

Dafydd Owen, Ph.D., Associate Research Fellow, Medicinal Chemistry, Biotherapeutics Worldwide R&D, Pfizer

2:00 Role of BRD4 and SWI/SNF in the Maintenance of Acute Myeloid Leukemia

Chris Vakoc, M.D., Ph.D., Assistant Professor, Cold Spring Harbor Laboratory

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

2:30 Targeting Bromodomains in NUT Midline Carcinoma

Christopher A. French, M.D., Associate Professor, Department of Pathology, Harvard Medical School; Assistant Professor, Pathology, Brigham and Women's Hospital

I will first discuss the basic clinical aspects of NUT midline carcinoma. I will then discuss three aspects of how BRD4-NUT blocks differentiation and promotes growth of affected cancer cells. Next, I will present recent findings that reveal the chromatin regions bound by BRD4-NUT, as well as NSD3, which we recently found to be a variant fusion partner of NUT in a subset of NUT midline carcinomas. Finally, I will discuss recent progress using BET bromodomain inhibitors.

3:00 Sponsored Presentations *(Opportunities Available)*

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

4:10 Treating Genetically Diverse Glioblastoma with Bromodomain Inhibitors

Jialiang Wang, Ph.D., Assistant Professor, Neurological Surgery, Vanderbilt University

Glioblastoma is a genetically heterogeneous disease. Yet, a wide range of glioblastoma tumors of diverse genotypes exhibited significant sensitivity to BET bromodomain inhibitors. I will discuss *in vitro* and *in vivo* activities of BET bromodomain inhibitors in glioblastoma primary samples. Molecular mechanisms underlie the oncogenic activities of BET proteins in glioblastoma will be discussed.

4:40 Betting on BETs for Advanced Prostate Cancer Treatment

Irfan Asangani, Ph.D., Research Investigator, Pathology, Michigan Center for Translational Pathology, University of Michigan

Maintenance of AR signaling is the most common resistance mechanism that patients with advanced prostate cancer develop after conventional hormonal treatments. Recently, selective small molecule inhibitors that target the bromodomains of BET family proteins have been shown to exhibit anti-proliferative effects in a range of malignancies. I will present our findings offering a preclinical proof of principle for the use of BET-bromodomain inhibitors that block AR signaling.

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

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

7:15 Close of Day

THURSDAY, OCTOBER 9

7:30 am Registration and Morning Coffee

EVALUATING THERAPEUTIC POTENTIAL

8:00 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

8:10 Targeting BET Bromodomains for Cancer Treatment
Bernard Haendler, Ph.D., Senior Scientist, Global Drug Discovery, Bayer Pharma AG
BRD4 belongs to the BET bromodomain family and represents an interesting target for the treatment of various pathologies, including cancer. Pharmacological *in vitro* and *in vivo* data on the activity of potent, selective BET inhibitors in tumor cell lines and in xenografts will be presented. In addition, the impact of individual point mutations in the BRD4 bromodomain on inhibitor and acetylated histone peptide binding will be discussed.

8:40 Epigenetic Control of T-Cell Biology
Jose M. Lora, Ph.D., Executive Director, Preclinical Sciences, Constellation Pharmaceuticals
In my talk I will discuss some of our research, elucidating how chromatin regulators and epigenetic factors are intimately involved in T-cell lineage commitment and function, and how their functional inhibition could lead to novel therapeutic opportunities.

9:10 Inhibition of BET Bromodomain Proteins in Solid Tumors
Anastasia Wyce, Ph.D., Investigator, R&D Oncology, GlaxoSmithKline
BET (bromodomain and extra-terminal) family proteins are epigenetic 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 cancer models, partially through down-regulation of the critical oncogene, MYC. We hypothesized that BET inhibitors will similarly regulate expression of MYC family genes (MYC, MYCN, MYCL1) in solid tumor models characterized by MYC family amplification or over-expression. In the current study, we describe the activity of GSK BET inhibitors (I-BETs) in various pre-clinical solid tumor models and discuss the role of MYC gene silencing in the observed phenotypes.

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

ASSESSING TOXICITIES

10:30 Multifocal Defects in the Hematopoietic and Lymphoid Compartments in Mice Dosed with a Broad BET Inhibitor
Dong Lee, Ph.D., Scientist, Safety Assessment, Genentech
The safety profile of BET inhibition is largely unknown. Our study shows that mice treated with JQ1, a broad BET small molecule, at efficacious concentrations develop multifocal defects in the lymphoid and immune cell compartments. In addition JQ1 at higher concentrations are not tolerated. This toxicity study establishes a baseline safety signal for JQ1 and begs the question of whether these findings are related to specific BET isoform inhibition or caused by secondary pharmacology from JQ1.

11:00 Bromodomain and ExtraTerminal (BET) Domain Inhibitors Induce a Loss of Intestinal Stem Cells and Villous Atrophy
Peter Newham, Ph.D., Global Head, Discovery Safety, R&D Innovative Medicines, AstraZeneca
The molecular and cellular mechanisms behind BET inhibitor gastrointestinal toxicity have yet to be elucidated. We have found that BET inhibitors induce a dose-limiting duodenal villous atrophy *in vivo*, accompanied by inappetance and weight loss. *Ex vivo* cultures of intestinal organoids confirm that villous atrophy occurs with multiple chemical classes of BET inhibitors and that toxicity is driven by their primary pharmacology. We find instead inhibitors induce a loss of intestinal stem cells.

11:30 Enjoy Lunch on Your Own

1:00 pm Plenary Keynote Session *(see website for details)*

2:45 Refreshment Break in the Exhibit Hall with Poster Viewing

3:45 Close of Conference

Targeting the Ubiquitin Proteasome System

Exploring the Therapeutic Potential of Ubiquitin Ligases and Deubiquitinases (DUBs)

The ubiquitin proteasome system (UPS) is an essential and highly regulated mechanism operating to tightly control intracellular protein degradation and turnover. It is therefore no surprise that emerging strategies in drug discovery moving away from single-target approaches are shifting toward targeting multicomponent cellular machineries such as the UPS to elicit therapeutic response in complex disease. Following the approval of two proteasome inhibitors, significant progress has been made in our understanding of ubiquitin biology along with the emergence of novel technologies and strategies enabling the development of small molecules targeting specific UPS components. Thus, modulating ligases within the ubiquitination cascade and "rescue" deubiquitinases (DUBs) have gained significant interest in drug discovery.

Suggested Event Package
October 7 Short Course: Targeting Protein-Protein Interactions
October 7 Short Course: Introduction to Targeted Covalent Inhibitors
October 8-9 Conference: Targeting the Ubiquitin Proteasome System
October 9-10 Conference: Maximizing Efficiency in Discovery

WEDNESDAY, OCTOBER 8

7:00am Registration and Morning Coffee

DIVERSE STRATEGIES MODULATING THE UPS & PROTEIN DEGRADATION

8:05 Chairperson's Opening Remarks
Ben Nicholson, Ph.D., Senior Director, R&D, Progenra, Inc.

» 8:15 FEATURED PRESENTATION: INDUCING 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
Induced protein degradation 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, i.e., the Ubiquitin/Proteasome System (UPS). For the past decade, we have focused on developing different strategies for inducing selective protein degradation, including the Proteolytic Targeting Chimera and Hydrophobic Tagging.

9:00 Pharmacological Activators of Tumor Suppressor PTEN
Alexander Statsyuk, Ph.D., Assistant Professor, Department of Chemistry, Northwestern University
We developed a novel fragment-based drug discovery platform, and used it to discover first in class mechanism based covalent inhibitor of Nedd4-1 ubiquitin ligase, which degrades tumor suppressor PTEN. The developed drug discovery platform is generally applicable to discover covalent drug leads for E1, E2, E3 enzymes and DUBs (~800 known enzymes). Our findings are conceptually novel and will be of significant interest to the drug discovery community.

9:30 Substrate-Assisted Inhibition of Ubiquitin-Like Protein Activation
Lawrence Dick, Ph.D., Director, Biochemistry, Oncology Drug Discovery Unit, Takeda Pharmaceuticals International Co.
We have identified small molecule inhibitors of ubiquitin-like protein (Ubl) activating enzymes (E1's) that work by a novel form of mechanism-based inhibition. These molecules serve as tools to probe the biological functions of individual Ubl conjugation pathway. To date our efforts have yielded two investigational drugs of this class that have entered into clinical trials; MLN4924, an inhibitor of the Nedd8 conjugation pathway; and MLN7243, an inhibitor of the ubiquitin conjugation pathway.

10:00 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

10:45 Targeting Ring1B-Bmi1 E3 Ubiquitin Ligase Activity
Tomasz Cierpicki, Ph.D., Assistant Professor, Pathology, University of Michigan
Small molecule inhibitors of Ring1B-Bmi1 E3 ligase activity are highly desired as potential agents targeting cancer stem cells. Targeting the Ring E3 ligases with small molecules is a challenging task due to the lack of well-defined substrate binding pocket and a complex biochemical assay required for enzymatic activity studies. To identify small molecule inhibitors of Ring1B-Bmi1 we performed fragment-based screening using NMR. I will present development of potent Ring1B-Bmi1 inhibitors.

11:15 Discovery of a Selective p97 Inhibitor that Disrupts Protein Homeostasis *in vitro* and Has Antitumor Activity *in Vivo*
Han-Jie Zhou, Ph.D., Director, Chemistry, Cleave BioSciences
Herein we reported the discovery of a selective and potent p97 inhibitor which demonstrated effects on tumor cell markers of protein homeostasis related to UPS inhibition and survival *in vitro*. After oral dosing this compound affected pharmacodynamic markers of UPS activity *in vivo* as well as antitumor activity in a xenograft model. Together these studies validate p97 as a druggable target with potential antitumor activity.

11:45 Small Molecules Targeting Integrity of the 26S Proteasome Assembly
Pawel Osmulski, Ph.D., Assistant Research Professor, Molecular Medicine, The University of Texas Health Science Center at San Antonio
Clinically recognized inhibitors used to treat aggressive blood cancers are

directly targeting catalytic sites of the core. We developed a set of small molecules disabling the proteasome with an entirely different mechanism: by targeting interactions between the catalytic core and its regulatory modules and by allosterically inhibiting the core. In a proof-of principle studies one of our compounds disables degradation of polyubiquitinylated substrates and induces apoptosis in cancer cells.

12:15 pm Sponsored Presentations *(Opportunities Available)*

12:45 Session Break

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

1:40 Session Break

TARGETING DUBs: NOVEL APPROACHES, CHEMICAL MATTER AND LEAD OPTIMIZATION

1:50 Chairperson's Opening Remarks
Lawrence Dick, Ph.D., Director, Biochemistry, Oncology Drug Discovery Unit, Takeda Pharmaceuticals International Co.

2:00 Targeting DUBs by Chemoproteomic Inhibitor Profiling in Cancer Cells
Benedikt Kessler, Ph.D., University Research Lecturer, Ubiquitin Proteolysis Group, Target Discovery Institute, Nuffield Department of Medicine, University of Oxford
We have utilized chemical proteomics and ubiquitin-based active site probes to determine the potency and selectivity of deubiquitylating enzyme (DUB) inhibitors in cell culture models. This approach is now being combined with the application of unbiased molecular probes that allowed detection of endogenous active nucleophile-dependent enzymatic activities in cell extracts by direct isotope-label based mass spectrometric quantitation to discover a broad range of small molecule cellular targets.

2:30 A Selective USP1/UAF1 Deubiquitinase Inhibitor Modulates the DNA Damage Response In Humans
Zhihao Zhuang, Ph.D., Associate Professor, Department of Chemistry & Biochemistry, University of Delaware
DUBs, as a promising therapeutic target class, have attracted increasing interest in inhibitor discovery. We conducted a quantitative high-throughput screening (qHTS) against USP1/UAF1 and a subsequent lead optimization. We obtained a reversible inhibitor that displays nanomolar inhibition and excellent selectivity towards USP1/UAF1. The USP1/UAF1 inhibitor disrupts cellular DNA damage tolerance and repair pathways, i.e. Fanconi Anemia (FA) and DNA translesion synthesis (TLS). Our study suggested a new strategy of inhibiting deubiquitinases.

3:00 Enabling and Supporting Ubiquitin System-Targeted Drug Discovery
Sponsored by UBIQUIGENT
Jason Brown, Ph.D., Managing Director, Ubiquigent Ltd
Ubiquigent's mission is to provide a full range of products and services to enable and support drug discovery programs in the ubiquitin field. The company develops and delivers HTS assays and provides extensive lead compound target selectivity profiling services to its clients. Our latest services and plans will be discussed.

3:15 Sponsored Presentation *(Opportunity Available)*

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

4:10 Identification of Selective DUB Inhibitors Targeting DDR Deficient Tumors
Niall Martin, Ph.D., COO, MISSION Therapeutics Ltd.
In cancer cells, loss of one DDR pathway leads to dependency on the remaining DDR pathways for survival. Inhibition of these remaining pathways causes synthetic lethality (SL), a powerful mechanism for selectively targeting cancer. By systematically knocking down all deubiquitylating enzymes (DUBs) in isogenic models of DDR deficiencies, we identified SL interactions in genetic backgrounds including ATM-, ATR- and BRCA2. These results have been "phenocopied" using novel inhibitors identified.

4:40 Small Molecule Inhibitors of the Deubiquitinase USP7 Interfere with Ubiquitin Binding
Ingrid E. Wertz, Ph.D., Scientist & Project Team Leader, Department of Early Discovery Biochemistry, Genentech

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

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

7:15 Close of Day

THURSDAY, OCTOBER 9

7:30 am Registration and Morning Coffee

BEYOND ONCOLOGY: DISCOVERY OF BIOACTIVE COMPOUNDS

8:00 Chairperson's Opening Remarks
Niall Martin, Ph.D., COO, MISSION Therapeutics Ltd.

8:10 Selective Inhibition of the Proteasome-Associated Deubiquitinating Enzyme USP14

Second Annual

October 8 - 9, 2014

Targeting the Ubiquitin Proteasome System

Exploring the Therapeutic Potential of Ubiquitin Ligases and Deubiquitinases (DUBs)

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

Small-molecule inhibitors of the deubiquitinating enzyme Usp14 were obtained via HTS. The compounds enhance degradation of various proteins and may have therapeutic applications for proteopathies. Proteasome substrates vary dramatically in their susceptibility to Usp14 inhibition, and surprisingly Usp14 will not act on tested substrates when only a single ubiquitin chain is present on the substrate. This principle of selectivity is to our knowledge novel for a deubiquitinating enzyme.

8:40 Small-Molecule Inhibition of JAK-STAT Signaling through the Deubiquitinase USP9X

Bridget Wagner, Ph.D., Director, Pancreatic Cell Biology, Center for the Science of Therapeutics, Broad Institute

Using phenotypic screening, we identified a small-molecule suppressor of beta-cell apoptosis. MOA studies revealed that our top compound binds USP9X and interferes with JAK-STAT signaling induced by IFN-gamma stimulation. Phenotypic screening, followed by comprehensive MOA efforts, can provide novel mechanistic insights into ostensibly well-understood cell signaling pathways. Furthermore, this study suggests USP9X as a novel target for regulating JAK2 activity in cellular inflammation.

9:10 Idolizing Ubiquitin: Novel Therapies to Treat Cardiovascular Disease

Ben Nicholson, Ph.D., Senior Director, R&D, Progenra, Inc.

Here we report that using our UbiProTM drug discovery platform we have discovered novel inhibitors of the E3 ligase IDOL that modulate cellular cholesterol homeostasis. The most promising compounds were used as starting points to develop novel drug like molecules and the efficacy of the lead compounds is being evaluated in translational models of hypercholesterolemia. Data will be presented summarizing our progress to date targeting IDOL for the treatment of hypercholesterolemia.

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

DISRUPTING PPIs OF E3 LIGASES

10:30 The Discovery of Small Molecules Targeting the VHL E3 Ubiquitin Ligase and Disrupting its Protein-Protein Interaction with HIF-alpha Subunit

Alessio Ciulli, Ph.D., Reader, Chemical & Structural Biology, College of Life Sciences, University of Dundee

We have discovered drug-like small molecules that target the ubiquitin proteosome system by disrupting, with nanomolar potencies, the key interaction between the von Hippel-Lindau protein cullin ring E3 ligase and with the Hypoxia Inducible Factor alpha subunit. Structure-based design informed by co-crystal structures and biophysical binding assays guided the medicinal chemistry optimization. Our efforts combined peptidomimetic strategies with fragment-based deconstructive analyses.

11:00 Targeting the MDM2-p53 Protein-Protein Interaction for New Cancer Therapeutics

Yujun Zhao, Ph.D., Research Investigator, Department of Internal Medicine, Division of Hemotology/Oncology, University of Michigan

Blocking the MDM2-p53 protein-protein interaction is being pursued as a new cancer therapeutic strategy. Our laboratory has designed and developed a class of highly potent and specific small-molecule inhibitors to block the MDM2-p53 PPI (MDM2 inhibitors). I will present our structure-based design and optimization of our MDM2 inhibitors and extensive preclinical studies of SAR405838 (MI-77301), which is now in phase I clinical development for the treatment of human cancers.

11:30 Enjoy Lunch on Your Own

1:00 pm Plenary Keynote Session *(see website for details)*

2:45 Refreshment Break in the Exhibit Hall with Poster Viewing

3:45 Close of Conference

Interactive Breakout Discussion Groups

This interactive session provides conference delegates and speakers an opportunity to choose a specific roundtable discussion group to join. Each group has a moderator to ensure focused discussions around key issues within the topic. This format allows participants to meet potential collaborators, share examples from their work, vet ideas with peers, and be part of a group problem-solving endeavor. The discussions provide an informal exchange of ideas and are not meant to be a corporate or specific product discussion. The Interactive Breakout Discussion Groups take place across all programs and will be held either on Wednesday, October 8 from 5:10-6:10 pm or Friday, October 10 from 8:00-9:00 am.

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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!

Big Data Analytics and Solutions

Using Big Data to Identify New Targets for Drug Discovery

According to the McKinsey Global Institute, applying big-data strategies to better inform decision making could generate up to $100 billion in value annually across the US health-care system, by optimizing innovation, improving the efficiency of research and clinical trials, and building new tools for physicians, consumers, insurers, and regulators to meet the promise of more individualized approaches. Effectively utilizing big-data opportunities can help biopharma companies better identify new potential drug candidates and develop them into effective, approved and reimbursed medicines more quickly. This potential cannot be unlocked without addressing key issues including collection of low throughput, poor quality data; the ever-growing complex and disparate datasets; scalability; bioinformatics tools not integrated; disparate analysis and visualization tools; revisiting analysis workflow; streamlining computational infrastructure; and identifying multiple drug targets (not just single drug targets) to work together as a network.

Through lectures and panel discussions, Cambridge Healthtech Institute's Big Data Analytics and Solutions Conference will bring together leading researchers and thought leaders to discuss the significant role that big data has on drug design to identify biomarkers and discover targets for potential therapies.

Suggested Event Package

October 7 Short Course: Designing Scalable Software Systems for Big Data Analytics

October 7 Short Course: Setting Up Effective RNAi Screens: From Design to Data to Validation

October 7 Short Course: A Primer to Gene Editing: Tools and Applications

October 8-9 Conference: Big Data Analytics and Solutions

October 9-10 Conference: Maximizing Efficiency in Discovery

WEDNESDAY, OCTOBER 8

7:00 am Registration and Morning Coffee

RIGHT DRUG, RIGHT TARGET: ROLE OF BIG DATA ON DRUG DESIGN TO IDENTIFY POTENTIAL THERAPIES

8:05 Chairperson's Opening Remarks

Michael Liebman, Ph.D., Managing Director, IPQ Analytics, LLC

8:15 Disease and Big (NGS) Data: Searching for Needles in Needlestacks

Joseph D. Szustakowski, Ph.D., Senior Group Head, Novartis Institutes for BioMedical Research

9:00 Big Data: We May Have the Right Drugs, but Do We Have the Right Targets?

Michael Liebman, Ph.D., Managing Director, IPQ Analytics, LLC

Drug development targets the proposed molecular mechanism associated with a disease but in much of medicine, accurate definition/diagnosis of the disease or phenotype is lacking. We focus on applying big data to understand the complexity of the disease to both improve clinical decision making/patient care and drug development, particularly in complex diseases and syndromes. Our approach uniquely starts with clinical need rather than data generation.

9:30 Rapid Drug Repositioning by Combining High-Throughput Experiments and Publicly Available Datasets

Blake Borgeson, Co-Founder and CTO, Recursion Pharmaceuticals

This talk will describe integrating various sources of data from both data-intensive high-throughput experiments and large public datasets such as the Connectivity Map project. A practical evaluation of the ways in which these sources can be integrated to support drug repositioning efforts will be discussed. Additionally, the talk will describe relevant challenges and pitfalls of combining public datasets with in-house experimental results.

10:00 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

BIG DATA APPROACHES ACROSS MULTIPLE RESEARCH INITIATIVES

10:45 Cell-Based Assays for Drug Target Discovery: Lessons from Transcriptomic Studies With Human Lymphoblastoid Cell Lines

Noam Shomron, Ph.D., Lecturer, Principal Investigator, and Head, Functional Genomics Lab, Sackler Faculty of Medicine, Tel-Aviv University

Genome-wide pharmacogenomic studies for developing targeted therapies offer the advantage of hypothesis-free search for tentative drug response biomarkers (efficacy and safety). However, they require large patient cohorts and are therefore very costly. This talk presents our experience with an alternative approach, based on genome-wide transcriptomic profiling of a panel of human lymphoblastoid cell lines (LCLs) representing unrelated healthy donors.

11:15 Using Big Data Analytics in the Cloud to Improve Vaccine Yields

Jerry Megaro, Director, Manufacturing Advanced Analytics and Innovation, Merck
Craig Sutherland, Executive Director, Technology & Data Science, Life Sciences and Health Practice, Booz Allen Hamilton

Here we present a proof-of-concept experiment where big data tools and techniques were applied to integrate and analyze 12 years worth of vaccine manufacturing data from 16 data sources to identify characteristics that influence yield. Additionally, the talk will describe how we leveraged shared data lake platform services operated within an Amazon Web Services Virtual Private Cloud (VPC) and scaled up Elastic Compute Cloud (EC2) services on-demand to support the analysis effort.

Big Data Analytics and Solutions

Using Big Data to Identify New Targets for Drug Discovery

11:45 From Big Data to Smart Data: Using Quantitative Systems Pharmacology for De-risking R&D Projects in CNS R&D

Hugo Geerts, Ph.D., CSO, Computational Neuropharmacology, In Silico Biosciences

Mechanistic Disease Modeling is a completely new data analytic approach for de-risking Drug Discovery and Development programs. The approach has been recognized by the Institute of Medicine as an innovative platform to reduce the limitations of preclinical animal models in CNS R&D, support actively rationally designed multi-target drug discovery programs, and significantly de-risk therapeutic projects for complex CNS disorders.

12:15 pm Selected Poster Presentation: An Integrative Platform for Discovery of Drugs and Small Chemicals Associated With Autism Spectrum Disorder

Adam Brown, Ph.D. Student, Biological and Biomedical Sciences, Harvard University

12:45 Session Break

1:00 Luncheon Presentation: MetaCore™: The Next Generation of Systems and Network Biology to Support Gene Variant and Expression Co-Analysis

Sponsored by THOMSON REUTERS

Chris Willis, Ph.D., Solution Scientist, Discovery and Translational Sciences, Thomson Reuters

To date, drugs have only explored targeting 10% of the coding human genome. Systems biology approaches aim to increase these numbers through understanding molecular disruptions at the pathway level in disease. This talk will discuss the challenges associated with analyzing the exponential growth in biomedical research knowledge and multi-omics data. Furthermore, this talk will demonstrate the use of Thomson Reuters MetaCore™ platform to analyze gene variant and transcriptomic data simultaneously. Lastly, the development of bioinformatic algorithms and the value of taking a combination knowledge/data driven approach to data analysis will highlight the roadmap for MetaCore™.

1:40 Session Break

1:50 Chairperson's Opening Remarks

Deepak Rajpal, Ph.D., Senior Scientific Investigator, Computational Biology, Medicines Discovery & Development, GlaxoSmithKline

2:00 Metabolic Diseases: Modulation of Microbiome

Deepak Rajpal, Ph.D., Senior Scientific Investigator, Computational Biology, Medicines Discovery & Development, GlaxoSmithKline

We present a proof-of-concept study where modulation of gut microbiome revealed novel associations with metabolic improvements in rodents. This is an important step in evaluating the gut microbiome changes with metabolic improvements.

2:30 The Water Must Flow: A Data Services Architecture for the Broad Institute

Chris Dwan, Assistant Director, Research Computing and Data Services, Broad Institute of MIT and Harvard

DATA MODELING, SIMULATING AND VISUALIZING IN NOVEL WAYS

3:00 Caleydo Entourage: Visualizing Relationships between Biological Pathways

Alexander Lex, Ph.D., Researcher, Harvard School of Engineering & Applied Sciences

This talk will introduce Entourage, a visualization technique for analyzing interrelationships between multiple related biological pathways. This talk demonstrates three case studies showing how Entourage can be used to judge potential side-effects of compounds, to find potential targets for drug-repositioning and how it can be combined with visualization of experimental data to reason about varying effects of compounds on samples. Entourage is part of Caleydo, an open-source visualization framework.

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

4:10 The Secrets in Their Landscapes: Using 'Google Exacyle' to Elucidate Activation Mechanism of GPCRs for Selective Drug Design

Diwakar Shukla, Ph.D., Simbios Distinguished Fellow, Laboratory of Vijay Pande, Chemistry Department, Stanford University and soon to be Professor, Chemical Engineering, University of Illinois at Urbana-Champaign

Mechanistic understanding of GPCR activation could be obtained via insilico approaches, although this is very challenging due to the long activation timescales. Here, we employ a novel computational paradigm that couples cloud computing and Markov state model based sampling algorithms for mapping the conformational landscape of β2-adrenergic receptor. These computations provide the atomistic picture of activation and help identify key structural intermediates for drug design.

4:40 Free Energies from a Molecular Printing Press

Kenneth M. Merz, Jr., Director, Institute for Cyber Enabled Research (iCER) and Joseph Zichis Chair in Chemistry, Department of Chemistry, Department of Biochemistry and Molecular Biology, Michigan State University

Docking calculations coupled with binding free energy estimates are a mainstay of structure-based drug design. Docking and scoring methods have steadily improved over the years, but remain challenging because of the extensive sampling that is required, the need for accurate scoring functions and challenges encountered in accurately estimating entropy effects. We developed the Moveable Type (MT) method that combines knowledge-based approaches with physics-based models to create molecular ensembles.

Inaugural

Big Data Analytics and Solutions

Using Big Data to Identify New Targets for Drug Discovery

October 8 - 9, 2014

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

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

7:15 Close of Day

THURSDAY, OCTOBER 9

7:30 am Registration and Morning Coffee

DATA MODELING, SIMULATING AND VISUALIZING IN NOVEL WAYS

8:00 Chairperson's Opening Remarks

Peter Henstock, Ph.D., Senior Principal Scientist, Research Business Technology Group, Pfizer, Inc.

8:10 CARD: A Web-Based Application for Statistical Analysis and Interactive Visualization of RNAi Screen Data

Bhaskar Dutta, Ph.D., Staff Scientist, Laboratory of Systems Biology, National Institute of Allergy and Infectious Diseases, National Institutes of Health

CARD is a web-based application for comprehensive analysis and interpretation of RNAi-screen data. It uses client-server architecture and integrates multiple types of genome-scale biological data. Different existing and novel data analysis algorithms are implemented as back-end R modules. The results generated are visualized using JavaScript libraries as interactive tables and figures. All the data and results can be saved and securely shared between researchers.

8:40 Genome Wide Association Visual Analysis (GWAVA) Enabled by a Scalable Data Pipeline

Peter Henstock, Ph.D., Senior Principal Scientist, Research Business Technology Group, Pfizer, Inc.

Ami Khandeshi, Manager, Research Business Technology Group, Pfizer Inc.

GWAVA is our corporate standard software for interactively querying and visualizing genome-wide association studies (GWAS) data loaded into the tranSMART platform. Managing multiple genes and studies, it facilitates an understanding of the relationship between SNP p-values and study endpoints by providing and managing access to different views of the data. GWAVA has recently been released as open source software available through the tranSMART Foundation.

TRANSLATING DATA INTO KNOWLEDGE FOR IMPROVED CLINICAL DECISION MAKING, PATIENT CARE AND DRUG DEVELOPMENT

Sponsored by NEXTCODE HEALTH

9:10 A Proven Platform for Diagnosis and Discovery Using Massive WGS and Phenotypic Data in Real Time

Jeffrey Gulcher, MD, PhD, Co-founder, President and CSO, NextCODE Health

NextCODE offers the world's only road-tested solutions for rapidly analyzing population-scale whole-genome and health data to detect disease-causing mutations, enabling clinical diagnosis and the optimization of existing and new treatments. Built to mine 350,000 whole genomes, our genome-ordered relational (GOR) database architecture is uniquely powered to take full advantage of the new WGS technology. Its SDL can query phenotypic datasets to define cases and controls as well as drug response.

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

10:30 The Path to Establishing a Global Data Analysis Infrastructure at AstraZeneca

Justin Johnson, Principal Translational Genomic Scientist, Oncology, AstraZeneca

It is imperative that we build tools and methods to translate NGS data into knowledge for target discovery, patient selection, and translational medicine through a flexible, scalable and secure infrastructure. The hybrid cloud / local solution and novel data warehousing strategies being built at AstraZeneca will allow for a global streamlined ability to analyze, store and interpret NGS data.

11:00 Data and Computational Requirements for Implementing the Department of Veterans Affairs Precision Oncology Program - A Partnership Between Clinical Care and Clinical Research

Louis Fiore, M.D., MPH, Executive Director, Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), Department of Veterans Affairs; Associate Professor, Boston University School of Medicine, Boston University School of Public Health

Precision Oncology is our current best chance to reduce the burden of disease attributed to cancer. Information systems that capture longitudinal medical record and genomic variant data and allow for real-time data analysis to recommend individualized patient treatments is a necessary step in the process that must be addressed by the medical informatics community. This presentation will discuss the pilot project within VA to create such an integrated system.

11:30 Enjoy Lunch on Your Own

1:00 pm Plenary Keynote Session *(see website for details)*

2:45 Refreshment Break in the Exhibit Hall with Poster Viewing

3:45 Close of Conference

Ninth Annual

GPCR-Based Drug Discovery

New Approaches, Technologies and Assays

October 8 - 9, 2014

The renewed excitement in the field of GPCR drug discovery is due to technological progress which has enabled the collection of more structural data on GPCRs and is allowing study of receptors in different conformational states. This meeting will focus on structural aspects of GPCRs and new assays and technologies whose applications may enable the discovery of more selective and therefore therapeutically attractive modulators of GPCR signaling.

Suggested Event Package

October 7 Short Course: GPCR Structured-Based Drug Discovery

October 7 Short Course: Targeting of GPCRs with Monoclonal Antibodies

October 8-9 Conference: GPCR-Based Drug Discovery

October 9-10 Conference: GPCR-Targeted Therapeutics

October 9 Dinner Course: Introduction to Allosteric Modulators and Biased Ligands of GPCRs

WEDNESDAY, OCTOBER 8

7:00 am Registration and Morning Coffee

STRUCTURAL FEATURES OF GPCRS AND IMPLICATIONS FOR DRUG DESIGN

8:05 Chairperson's Opening Remarks

Donovan Chin, Ph.D., Senior Investigator I, Novartis Institute for Biomedical Research

» 8:15 FEATURED PRESENTATION: FUNCTION AND PHARMACOLOGY OF CLASS A GPCR: NEW STRUCTURAL AND COMPUTATIONAL INSIGHTS

Vsevolod (Seva) Katritch, Ph.D., Assistant Professor, Integrative Structural and Computational Biology, The Scripps Research Institute

Class A G protein-coupled receptors represent the largest and the most evolutionary dynamic branch of the GPCR tree. This talk will describe the amazing diversity and the common features of Class A GPCR functional mechanisms emerging from recent crystallographic, spectroscopic and molecular modeling studies of the receptors. Direct applications of this atomic-level knowledge to GPCR pharmacology and drug discovery will be discussed.

9:00 Insights into Activation and Allosteric Modulation of a Muscarinic Acetylcholine Receptor

Andrew C. Kruse, Ph.D., Assistant Professor, Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School

G protein-coupled receptor (GPCR) signaling plays a central role in most aspects of human physiology, and can be regulated by a wide variety of small molecule drugs. We studied the muscarinic acetylcholine receptors as prototypical GPCRs, and solved structures of these receptors in both inactive and active conformations, as well as bound to a drug-like allosteric modulator. Taken together, these studies shed light on GPCR activation and the regulation of GPCR signaling by allosteric ligands.

9:30 The Human Glucagon Receptor Structure

Fai Siu, Ph.D., Investigator II, Center for Proteomic Chemistry, Novartis Institute for BioMedical Research

Binding of glucagon to the glucagon receptor (GCGR) triggers the release of glucose from the liver during fasting; thus GCGR is important in glucose homeostasis. I will present the crystal structure of the transmembrane domain of human GCGR at 3.4Å resolution, complemented by extensive site-specific mutagenesis, and a hybrid model of glucagon bound.

10:00 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

10:45 Structure of a Class C GPCR 7TM Domain and Its Allosteric Modulation

Huixian Wu, Ph.D., Postdoctoral Associate, The Broad Institute of MIT and Harvard

The metabotropic glutamate receptors (mGlus), which are class C GPCRs, mediate the modulatory effects of the excitatory neurotransmitter, glutamate. Allosteric modulators of mGlus are important drug candidates for many diseases such as brain disorders. In this talk, the structure of mGlu1 seven-transmembrane domain bound by a negative allosteric modulator will be presented and the structural basis of the allosteric modulation will be discussed.

11:15 Computational Design of Water Soluble Variants of GPCRs and other Membrane Proteins

Jeffery G. Saven, Ph.D., Professor, Department of Chemistry, University of Pennsylvania

Obtaining G-protein coupled receptors (GPCRs) in forms that retain native structural and functional properties remains a core problem of membrane protein science. Membrane proteins can be computationally redesigned, however, to facilitate heterologous expression in *E. coli* and characterization. We have developed and applied such methods to ion channels and to the human mu opioid receptor, the GPCR target of many pain medications.

11:45 Structural Insights into Allosteric Agonist Bound Human GPR40 Receptor

Ankita Srivastava, Ph.D., Senior Scientist, SB & Ab Core Science & Technology, Takeda California

Human GPR40 receptor (hGPR40) GPCR binds to free fatty acids and mediate the insulin secretion in a glucose dependent manner. This unique mode of action of the receptor makes it a promising therapeutic target for Type II diabetes mellitus treatment. I will discuss the crystal structure of hGPR40 bound to its allosteric agonist TAK-875. The structure not only reveals the unique binding

mode of the ligand but also provides the insight into the plausible binding of multiple ligands which has already been reported by biochemical studies.

12:15 pm Selected Poster Presentation: Design, Synthesis and Biochemical Evaluation of Novel Electrophilic and Photoaffinity Covalent Probes to Map the CB1 Receptor Allosteric Site(s)
Abhijit Kulkarni, Laboratory of Ganesh Thakur, Pharmaceutical Sciences, Northeastern University

12:30 Selected Poster Presentation: Exposing Hidden Drug Targets Within Binding Interfaces of Protein-Protein Interactions Using "Protein Painting"
Ruben Magni, Laboratory of Allesandra Luchini, Center for Applied Proteomics and Molecular Medicine, George Mason University

12:45 Session Break

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

1:40 Session Break

SIMULATIONS AND BIG DATA

1:50 Chairperson's Opening Remarks
Andrew Alt, Ph.D., Senior Research Investigator, Lead Discovery, Bristol-Myers Squibb

2:00 Exploration of Drug Disease-Related Selectivity Using Molecular Simulations of the Bioamine Receptor Family
Irina Tikhonova, Ph.D., Lecturer in Molecular Modeling, School of Pharmacy, Queen's University Belfast
Selective polypharmacology is when drugs act on multiple rather than single molecular targets involved in a disease. We focus on bioamine receptors that are targets for schizophrenia and depression. Among them, 5-HT2A, 5-HT6, D2 and D3 receptors induce cognition-enhancing effects, while H1, 5-HT2C and 5-HT2B receptors causes side effects. A computational dynamic structure-based approach will be presented to identify drugs targeting preferably the disease-active receptors.

2:30 Application of Free Energy Perturbation to GPCR Targets
Sponsored by SCHRÖDINGER.
Woody Sherman, Ph.D., Vice President, Applications Science, Shrödinger Inc
Free energy perturbation (FEP) calculations offer an attractive approach to predicting binding free energies by more accurately accounting for important aspects of binding (e.g. entropy, water networks, and receptor reorganization) that are typically neglected in molecular modeling approaches. However, the application of FEP to GPCRs has been limited due to the challenges associated with running these calculations. We have run FEP on several GPCRs to predict binding affinities for different ligand series and obtained encouraging results. Here, we discuss the FEP method, applications to GPCRs, and future work we are doing to further improve the method.

3:00 Impact and Gaps in Structural-Based GPCR Drug Discovery: Q&A Panel Discussion
Moderator: Donovan Chin, Ph.D., Senior Investigator I, Novartis Institute for Biomedical Research
- Impact on computational chemistry
- Influence in collaborative culture: interactions between biologists, structural biologists, computational chemists and medicinal chemists?
- Changing landscapes in assay techniques
- Evolving skill sets of computational chemists and modelers

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

4:10 The Secrets in Their Landscapes: Using 'Google Exacyle' to Elucidate Activation Mechanism of GPCRs for Selective Drug Design
Diwakar Shukla, Ph.D., Simbios Distinguished Fellow, Laboratory of Vijay Pande, Chemistry Department, Stanford University and soon to be Professor, Chemical Engineering, University of Illinois at Urbana-Champaign
Mechanistic understanding of GPCR activation could be obtained via *in silico* approaches, although this is very challenging due to the long activation timescales. Here, we employ a novel computational paradigm that couples cloud computing and Markov state model based sampling algorithms for mapping the conformational landscape of β2-adrenergic receptor. These computations provide the atomistic picture of activation and help identify key structural intermediates for drug design.

4:40 Free Energies from a Molecular Printing Press
Kenneth M. Merz, Jr., Director, Institute for Cyber Enabled Research (iCER) and Joseph Zichis Chair in Chemistry, Department of Chemistry, Department of Biochemistry and Molecular Biology, Michigan State University
Docking calculations coupled with binding free energy estimates are a mainstay of structure-based drug design. Docking and scoring methods have steadily improved over the years, but remain challenging because of the extensive sampling that is required, the need for accurate scoring functions and challenges encountered in accurately estimating entropy effects. We developed the Moveable Type (MT) method that combines knowledge-based approaches with physics-based models to create molecular ensembles.

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

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

7:15 Close of Day

THURSDAY, OCTOBER 9

7:30 am Registration and Morning Coffee

NEW APPROACHES FOR STUDYING GPCRS

8:00 Chairperson's Opening Remarks
Michel Bouvier, Ph.D., Professeur, Department of Biochemistry, University of Montréal

8:10 Nanobody-Enabled Fragment Screening on Active-State Constrained GPCRs
Jan Steyaert, Ph.D., Director, Structural Biology Brussels Research Center, Vrije University Brussels
Nanobodies are effective tools for stabilizing agonist-bound active states of GPCRs. Building on this technology, we have developed a nanobody-enabled fragment screening approach to explore new chemical space for the development of drugs targeting GPCRs. Our approach has the advantage over other methods in that we can screen fragments that exclusively bind to particular functional conformations of the receptor, allowing us to triage our fragments according to efficacy profile and potency from a single biophysical assay.

8:40 BRET to Study Receptor Pharmacology
Kevin Pfleger, Ph.D., Harry Perkins Institute of Medical Research, Australia
Exciting advances have been made recently with respect to the development of bioluminescence resonance energy transfer (BRET) for studying GPCRs. This includes the validation of the latest BRET reagents and new BRET-based approaches to study all facets of GPCR pharmacology, from ligand binding and G protein-coupling to arrestin recruitment and intracellular trafficking, particularly in terms of heteromeric complexes.

9:10 The Use of Backscattering Interferometry to Investigate Positive Allosteric Modulators of the M4 Receptor
Sponsored by MOLECULAR SENSING
Jonathan Ellery, Ph.D., Principal Scientist, Takeda Cambridge Ltd
Evidence suggests that the activation of the muscarinic acetycholine receptors (mAChRs) in the central nervous system (CNS) may have therapeutic benefit in the treatment of a number of CNS disorders. The use of non-selective agonists is limited due to un-desirable peripheral side effects. One approach to overcome this issue is to identify compounds that selectively positively modulate the M4 mAChR subtype via an allosteric binding site. Here we describe the use of backscattering interferometry, a label free assay technology, to investigate the nature of modulator binding and its co-operative effects upon the binding of the natural ligand acetylcholine to the M4 mAChR.

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

10:30 Designing Ligands that Specifically Target Nuclear GPCRs
Terry Hébert, Ph.D., Professor, Department of Pharmacology and Therapeutics,McGill University
An increasing number of GPCRs have been demonstrated to be targeted to the endomembrane locations as have their associated signalling cascades. What if half the drugs we deliver reach the wrong intracellular target? What if the target is an intracellular GPCR rather than the better-characterized cell surface version? Caging ligands may be an excellent means of further stratifying the phenotypic effects of known pharmacophores.

11:00 Targeting Dopamine Receptors with Biased Agonists
John A. Allen, Ph.D., Principal Scientist, Neuroscience, Pfizer

11:30 Enjoy Lunch on Your Own

1:00 pm Plenary Keynote Session *(see website for details)*

2:45 Refreshment Break in the Exhibit Hall with Poster Viewing

3:45 Close of Conference

RNAi for Functional Genomics Screening - Part 1

Utilizing RNA Interference Screens to Explore Drug Targets and Pathways

Cambridge Healthtech Institute's eleventh annual conference on RNAi for Functional Genomics Screening will cover the latest in the use of RNA interference (RNAi) screens for identifying and validating new drug targets and exploring unknown cellular pathways. It will cover everything from assay design to data analysis for the use of *in vitro* and *in vivo* siRNA (small interfering RNA) and shRNA (short hairpin RNA) screens, in a way that will evoke thought-provoking discussions and inspire collaborations.

Suggested Event Package

October 7 Short Course: Setting Up Effective RNAi Screens
October 7 Short Course: A Primer to Gene Editing
October 8-9 Conference: RNAi for Functional Genomics Screening
October 9-10 Conference: Genome Editing for Functional Genomics Screens
October 9 Dinner Course: Setting Up Effective Functional Screens Using 3D Cell Cultures

WEDNESDAY, OCTOBER 8

7:00 am Registration and Morning Coffee

EMERGING APPLICATIONS FOR IN VIVO RNAi SCREENING

8:05 Chairperson's Opening Remarks

» 8:15 FEATURED PRESENTATION: FUNCTIONAL RNAi SCREENS FOR CANCER IN MICE

Elaine Fuchs, Ph.D., Rebecca C. Lancefield Professor and Investigator, Howard Hughes Medical Institute, Laboratory of Mammalian Cell Biology and Development, The Rockefeller University

Using mouse as a model, Fuchs' team has made major contributions towards understanding how tissues repair injuries and how abnormalities in stem cell behavior can lead to cancers. Recently, her team developed technology to conduct genome-wide RNAi screens in mice for oncogenic regulators of growth. She'll discuss the methodology, findings and implications for sifting through the functional significance of hundreds of gene mutations found in human epithelial cancers.

9:00 *In vivo* Synthetic Lethality Screens to Identify Genetic Dependencies in Patient-Derived Tumor Models

Timothy Heffernan, Ph.D., Senior Associate Director, Target Discovery and Deputy Head, Center for Co-Clinical Trials, Institute for Applied Cancer Science, University of Texas, MD Anderson Cancer Center

Large scale sequencing has uncovered a staggering level of complexity of cancer genomes and made clear that translation of genomic knowledge into effective therapeutics will require systematic approaches to inform on context-specific genetic dependencies. We describe an *in vivo* synthetic lethality platform that leverages deep coverage shRNA libraries to interrogate genetic dependencies in patient-derived tumor models. We report how this platform has informed novel targets and strategies to overcome drug resistance.

9:30 Applying Pooled RNAi Screens in CD8 T Cells During Viral Infections in Mice

Matthew Pipkin, Ph.D., Assistant Professor, Department of Cancer Biology, Florida Campus, The Scripps Research Institute

Naïve CD8 T cells differentiate into cytotoxic T lymphocytes (CTL) that lyse infected or malignant host cells. Most CD8 T cell-intrinsic factors that regulate this process are unknown. I will present an approach to conduct pooled RNAi screens in antigen-specific CD8 T cells using shRNAmirs in the context of viral infections in mice, as well as identification and validation of some novel players that underlie generation of protective CTL, and mechanistic insight into their function(s).

10:00 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

EXPLORING RNAi AND cDNA SCREENS FOR NOVEL USES

10:45 *In vivo* Target Validation with Viral Vectors: Translating *in vitro* Hits to *in vivo* Functions

Ki Jeong Lee, Ph.D., Principal Scientist, Genome Analysis Unit, Amgen, Inc.

We investigated the *in vivo* biological roles of cDNAs that were identified through *in vitro* functional genomic screens or based on expression patterns related to disease states. Recombinant adeno-associated virus (rAAV) was utilized for *in vivo* gene expression, partly because of its ability to confer long-term gene expression with a single injection. This strategy was also used to further validate hits from *in vitro* screens and to identify novel drug targets based on *in vivo* phenotypes.

11:15 Cell-based Screening to Empower Human Genetics: Moving From Gene to Genetic Variant

Heiko Runz, M.D., Director, Human Genetics, Merck Research Laboratories

Sequencing technologies identify a number of potentially disease-relevant variants in the human genome, but our abilities to accurately evaluate which of these variants are of the highest relevance to human health and disease are lagging behind. I will demonstrate how systematic strategies to profile the biological effects of genetic variants by RNAi and cDNA-overexpression in cells can help us to prioritize genetic factors that control blood cholesterol levels and the risk for early-onset risk for early-onset myocardial infarction.

RNAi for Functional Genomics Screening - Part 1

Utilizing RNA Interference Screens to Explore Drug Targets and Pathways

11:45 RNAi Screens for Identification of Rare Genetic Disease Treatments

Chris Gibson, Ph.D., CEO, Recursion Pharmaceuticals

Orphan diseases are increasingly targets of interest for both large and small pharmaceutical companies. A large proportion of orphan diseases are due to loss-of function genetic mutations. As such, RNAi presents an opportunity and a challenge in terms of efficiently modeling a large number of these diseases. A variety of strategies for modeling genetic diseases using RNAi in human cells will be discussed, including highlights of the many challenges associated with working in this space.

12:15 pm Identification of Novel Anti-Obesity Genes in Primary Human Adipocytes using RNAi Screening

Sponsored by charles river

David Fischer, Ph.D., Senior Director, Biological Sciences, BioFocus, a Charles River Company

We sought to identify novel genes implicated in adipose fat reduction by affecting triglyceride hydrolysis and/or increasing the metabolic capacity of the adipocytes. These gene products directly or components in the signaling pathway(s) of these gene products can be used as drug targets for the development of novel targeted anti-obesity therapies.

12:30 Sponsored Presentation *(Opportunity Available)*

12:45 Session Break

1:00 Luncheon Presentation - The State of CRISPR Technology

Sponsored by SIGMA-ALDRICH

Shawn Shafer, Ph.D., Functional Genomics Market Segment Manager, Sigma-Aldrich Emerging Technologies

Since it's elucidation a mere two years ago, applications for the CRISPR pathway have expanded broadly and rapidly. In this talk, we will review the current state of the technology and look at how CRISPR is being applied to the fields of genome editing, screening, and gene regulation, among other topics.

1:40 Session Break

EVALUATING NEW MODELS AND DATA ANALYSIS TOOLS

1:50 Chairperson's Opening Remarks

Geoffrey A. Bartholomeusz, Ph.D., Assistant Professor and Director, siRNA Core Facility, Department of Experimental Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center

2:00 Relevance of 3D Cell Culture Models and siRNA Screens for Target Identification and Drug Development

Geoffrey A. Bartholomeusz, Ph.D., Assistant Professor and Director, siRNA Core Facility, Department of Experimental Therapeutics, Division of Cancer Medicine, The University of Texas, MD Anderson Cancer Center

3D cell culture models are varied and complex and unlike 2D monolayer cell cultures, replicate certain biological outcomes observed in a tumor microenvironment. The reliability of data generated from 3D cell culture-based studies is dependent on the development of appropriate model. The development of 3D models used in high-throughput screening to address relevant questions in cancer biology will be discussed.

2:30 RNAi Off-Target Effects - Can They Be Used to Our Advantage?

Christian von Mering, Ph.D., Chair, Computational Biology, Institute of Molecular Life Sciences, University of Zurich and Swiss Institute of Bioinformatics

A comparative analysis of several genome-wide RNAi screens has been performed. This enabled the relative quantification of on-target and off-target effects, considering real-life phenotypes in a high-throughput setting. In all cases, the average phenotypic consequence of a given RNAi oligo is dominated by the off-target mechanism, with on-target signals low or completely absent. However, custom-designed oligos focusing exclusively on the off-target mechanism may become promising perturbation reagents, targeting entire pathways instead of single genes.

3:00 Loss-of-Function Genetic Screens to Find Genes Regulating Cell Responses and Identify Potential Drug Targets

Sponsored by CELLECTA

Paul Diehl, Ph.D., Director, Commercial Development, Cellecta, Inc.

RNAi-based loss-of-function genetic screens using pooled shRNA libraries have proven to be an efficient way to identify genes responsible for a range of cell responses. However, generating robust results with this technique requires viral-based shRNA libraries with constrained hairpin representation and sequence-optimized barcodes. This presentation will discuss enhancements in genetic screens that enable tracking of distinct clonal cell populations in pooled screens, dropout viability screening in xenograft tumor models, and complementary CRISPR-based approaches to genetic screens.

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

4:10 Integrating High-Throughput Imaging and Genomics to Identify Drug Combinations in Cancer

Arvind Rao, Ph.D., Assistant Professor, Department of Bioinformatics and Computational Biology, The University of Texas, MD Anderson Cancer Center

High-throughput screening is routinely used to identify the role of RNAi in modulating cellular phenotype as well as to study the effects of therapeutics on diseased cell morphology. A high-throughput kinome siRNA screen was carried out to study their effects on tumor architecture in 3D tumor spheroids. We present a workflow to identify and interpret gene function in such large scale 3D RNAi experiments by analyzing such image-derived data in the context of associated molecular data.

RNAi for Functional Genomics Screening - Part 1

Utilizing RNA Interference Screens to Explore Drug Targets and Pathways

4:40 CARD: A Platform for Comprehensive and Integrative Analysis of RNAi Screen Data

Bhaskar Dutta, Ph.D., Staff Scientist, Laboratory of Systems Biology, National Institute of Allergy and Infectious Diseases, National Institutes of Health

Although RNAi screen is widely used, there is no user-friendly application for comprehensive analysis and interpretation of the data. We have developed a web-based application that integrates different existing and novel algorithms associated with screen data analysis, e.g., different normalizations, transformations, common seed analysis, expression filter, RNAiCut, pathway enrichment, network analysis, etc.

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

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

7:15 Close of Day

THURSDAY, OCTOBER 9

7:30 am Registration and Morning Coffee

DISSECTING FUNCTIONAL SCREENS: MAKING THE RIGHT CHOICES

8:00 Chairperson's Opening Remarks

Scott Martin, Ph.D., Team Leader, RNAi Screening, NIH Chemical Genomics Center, National Center for Advancing Translational Sciences, National Institutes for Health

8:10 From Superstar to Washed-Up Delinquent: Is it Time to Abandon RNAi Screening?

Scott Martin, Ph.D., Team Leader, RNAi Screening, NIH Chemical Genomics Center, National Center for Advancing Translational Sciences, National Institutes for Health

"Hits" from RNAi screens have evolved from being treated as mostly true positives to a laundry list of false positives. However, much is understood about the pitfalls of RNAi screening, and when applied with these in mind, the technology delivers. This talk will highlight some fruitful assays, illustrate how understanding the pitfalls improves outcome, and discuss leveraging other technologies to further refine results.

8:40 Multiple Genome-Wide JAK/STAT Cell-Based Screens Reveal a Core, Conserved Functional Pathway

Stephen Brown, Ph.D., Manager, RNAi Facility Screening, Department of Biomedical Science, University of Sheffield

The Sheffield RNAi Screening Facility is the UK's National Drosophila cell-based functional genomics centre and has recently screened human siRNA libraries. This presentation will talk about the technical challenges of assay development and improvements we have implemented to our approaches. Specifically, I will focus on the JAK/STAT pathway and what impact our screening practices have had on three genome-wide JAK/STAT screens.

9:10 RNAi is Dead, Long Live RNAi: Reinventing the RNAi Screening Workflow

Samuel Hasson, Ph.D., Principal Investigator, Neuroscience, Pfizer, Inc.

As some contemplate the impending demise of RNAi with the rapid maturation of genome editing technologies, now is the time to rethink RNAi-based functional genomics. New systematic methodologies that embrace the rampant off-target effects can strengthen the utility and effectiveness of RNAi screening. By enhancing the screening workflow with seed-profiling, reagent multiplicity, c911 controls, and a genome editing-powered RNAi "breakout", the platform can evolve in a changing landscape.

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

10:30 siRNA Screening for Drug Target Identification: Synthetic Lethal Genes and Optimal Drug Combinations

Carla Grandori, M.D., Ph.D., Research Associate Member, Human Biology Division, Fred Hutchinson Cancer Research Center

To overcome the challenge of identifying cancer drug targets, in particular for undruggable oncogenes, we have employed a unique platform of high-throughput siRNA screening that combines use of isogenic cell systems, cancer cell lines and primary cancer cultures with an integrated genomic approach for hit selection. Results to validate novel targets across different cancer types will be presented suggesting that despite tissue specific programs and concurrent genetic changes, certain MYC-synthetic lethal interactions are shared among tissues.

11:00 A High-Content Screen of an Arrayed cDNA Library for Modulators of Adipogenic Differentiation

Patrick Collins, Ph.D., Senior Scientist, Genome Analysis Unit, Amgen, Inc.

We screened an arrayed cDNA library in a mouse mesenchymal stem cell line to identify proteins with an effect on adipogenesis. Images of stained cells were analyzed and dozens of features extracted. A variety of multiparametric analyses identified clones for further study by imaging and highly multiplexed gene expression analysis. The screen revealed modulators of adipogenesis, as well as a variety of phenotypes providing broader insight into mesenchymal stem cell biology.

11:30 Enjoy Lunch on Your Own

1:00 pm Plenary Keynote Session *(see website for details)*

2:45 Refreshment Break in the Exhibit Hall with Poster Viewing

3:45 Close of Conference

Inaugural

Protein-Protein Interactions as Drug Targets

Beyond Enzyme Catalytic Sites for Therapeutic Intervention

October 8 - 9, 2014

Inhibiting protein-protein interactions (PPIs) is gaining ground in the drug discovery industry as a way to find new drug candidates either against previously intractable targets such as protein regulatory complexes or 'tried and true' targets such as kinases but where new options are needed. PPI approaches are in contrast to traditional drug discovery that focuses on indentifying direct inhibitors of an enzyme's catalytic site. This meeting will provide examples of PPIs that are being targeted in the drug discovery industry, applications of new approaches for finding PPI inhibitors and some of the resulting drug development challenges.

Suggested Event Package
October 7 Short Course: Targeting Protein-Protein Interactions
October 7 Short Course: Introduction to Targeted Covalent Inhibitors
October 8-9 Conference: Protein-Protein Interactions as Drug Targets
October 9-10 Conference: Cancer Metabolism
October 9 Dinner Course: Setting Up Effective Functional Screens Using 3D Cell Cultures

WEDNESDAY, OCTOBER 8

7:00 am Registration and Morning Coffee

CASE STUDIES ON PPI TARGETS

8:05 Chairperson's Opening Remarks
Robert H. Scannevin, Ph.D., Director, Neurology Research, Biogen Idec

» 8:15 FEATURED PRESENTATION: SELECTIVE BCL-2 FAMILY INHIBITORS: POTENTIAL THERAPEUTICS AND POWERFUL RESEARCH TOOLS
Andrew J. Souers, Ph.D., Project Director, Oncology Discovery, Abbvie
Many cancer cells maintain survival through over-expression of anti-apoptotic BCL-2 family proteins, making them compelling targets for the development of cancer therapeutics. However, disrupting protein-protein interactions, such as the BCL-2 or BCL xL interactions with pro-apoptotic BH3 proteins, has been a major challenge for the field. The BCL-2/BCL-xL inhibitor ABT-263 (navitoclax) has shown promising activity in the clinic but its efficacy has been limited by thrombocytopenia caused by BCL-xL inhibition. This clinical result led to the design of ABT-199/GDC-0199, a BCL-2-selective inhibitor that maintains efficacy in hematologic malignancies while sparing platelets. The challenging path to ABT-199/GDC-0199 will be presented, as will clinical data that represents validation of the hypothesis behind selectively targeting BCL-2 . While ABT-199/GDC-0199 has helped establish the importance of targeting BCL-2 in hematologic malignancies, expression of BCL-xL has been linked with drug resistance and disease progression in multiple solid tumors. Efforts towards the development of novel BCL-xL-selective inhibitors will also be discussed.

9:00 Dimethyl Fumarate and Activation of the Nrf2 Pathway via Keap1 Modification
Robert H. Scannevin, Ph.D., Director, Neurology Research, Biogen Idec
Delayed release dimethyl fumarate (DMF) is an approved oral therapy for multiple sclerosis. One of the primary DMF mechanisms of action is activation of the Nrf2 pathway by covalent modification of Keap1 and subsequent liberation of Nrf2 from constitutive degradation. Our current works focuses on understanding how differential modification of Keap1 influences interaction with Nrf2 and downstream gene transcription.

9:30 ERK- DNMT3A Interaction Epigenetically Regulates Gene Expression
Deepak Kumar, Ph.D., Senior. Scientist, TIP Immunology, EMD Serono
DNA methylation is one of the critical events that epigenetically regulate gene expression during various physiological and pathological conditions. We have found that FGF signaling via ERK1/2 not only phosphorylates *de novo* DNA methyltransferase, DNMT3A, but also blocks its recruitment and function in mesenchymal stem cells. Further understanding of ERK-DNMT3A interaction may provide us with a novel target to regulate gene expression.

10:00 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

PEPTIDES FOR PPIs

10:45 Pinning Hot Spot Sites at the Proteasome-PIN (Protein interaction Network) Interface
Prasanna Venkatraman, Ph.D., Professor, Structural and Functional Biology, Tata Memorial Centre/India
The concept that protein-interfaces are characterized by hot spot sites that contribute to the bulk of binding energy and the fact that oncoproteins and tumor suppressors act as major hubs in the network, has revolutionized the area of drug discovery. In this talk, I will substantiate that hot spot sites and short linear sequence motifs at the protein interfaces of proteasomal chaperones are potential, pan cancer drug targets.

11:15 Get Exposed: Cell-Permeable Peptide Modulators Targeting Wnt Signaling in Cancer Stemness with Anti-Tumoral Activities upon Systemic Delivery
Jörg Vollmer, Ph.D., Managing Director, Nexigen GmbH
The identification of inhibitors of protein-protein interactions is not trivial but allows the extension of the druggable target space. Novel and improved PPI screening systems such as Nexigen's peptide screening combine a wide applicability among target protein classes, increased sensitivity, better reliability and high hit rates. Cell-permeable peptides identifiedby Nexigen's screening engine allow intracellular targeting of the Wnt pathway resulting in anti-tumoral activities.

Protein-Protein Interactions as Drug Targets

Beyond Enzyme Catalytic Sites for Therapeutic Intervention

11:45 An Allosteric Switch for Pro-HGF/Met Signaling Using Zymogen Activator Peptides

Robert A. Lazarus, Ph.D., Principal Scientist, Early Discovery Biochemistry, Genentech, Inc.

Hepatocyte growth factor (HGF) binds Met, leading to cell proliferation, migration, and survival. By incorporating structural and mechanistic insights from trypsin-like serine proteases into a novel phage display selection, we establish a path for reversible allosteric activators of zymogen-like pro-HGF that selectively bind the trypsin-like activation pocket to stimulate Met signaling for tissue repair. This strategy is extendable to zymogen serine protease and protease-like targets.

12:15 pm Selected Poster Presentation: Evidence of Conformational Selection Driving the Formation of Ligand Binding Sites in Protein-Protein Interfaces

Kathryn Porter, Laboratories of Dima Kozakov and Sandor Vajda, Structural Bioinformatics, Biomedical Engineering Department, Boston University

12:30 Selected Poster Presentation: Interfering with the OX40-OX40L Costimulatory Protein-Protein Interaction: Identification of Small-Molecule Partial Agonists

Yun (Eric) Song, Laboratory of Peter Buchwald, Diabetes Research Institute and Department of Molecular and Cellular Pharmacology, university of Miami

12:45 Session Break

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

1:40 Session Break

TARGETING PPIS: STRUCTURAL, FRAGMENT AND OTHER APPROACHES

1:50 Chairperson's Opening Remarks

Robert H. Scannevin, Ph.D., Director, Neurology Research, Biogen Idec

2:00 Protein-Protein Interactions: An Easy Drug Target

Daria Mochly-Rosen, Ph.D., Professor, Chemical and Systems Biology, Stanford

Since 1991, we used a rational approach to identify peptide inhibitors of protein-protein interactions (PPI) as drugs in a variety of animal models of human diseases and in clinical trials. Over 40 peptides with select biological activities were designed and characterized for different signaling proteins. Two examples of the rational approach, the preclinical work and one clinical study with these PPI inhibitors will be discussed.

2:30 Fragment and Structural-Based Approaches for PPIs of Apoptotic Pathways

Pamela Williams, Ph.D., Director, Structural Biology, Astex

Fragment based drug discovery (FBDD) has been successfully used to identify hits for PPI targets, providing alternatives to more traditional methods like high-throughput screening or peptidomimetics. I will describe the use of FBDD to identify dual antagonists of XIAP and cIAP1, members of the inhibitor of apoptosis protein (IAP) family, key regulators of anti-apoptotic and pro-survival signalling pathways.

Sponsored by

3:00 Co-Presentation: DNA-Encoded Chemistry: A New Approach to PPI and Other Difficult Targets

Anthony D. Keefe, Ph.D., Senior Director, Lead Discovery, X-Chem Pharmaceuticals

Matthew A. Clark, Ph.D., Senior Vice President, Research, X-Chem Pharmaceuticals

X-Chem Inc. operates a proprietary drug-discovery technology using its library of 100 Billion on-DNA small-molecules. Members of this library that inhibit therapeutic targets may be identified by affinity-mediated selection for target-binding followed by sequencing of the associated oligonucleotide tags, re-synthesis off-DNA and confirmation by biochemical assay. An overview of the technology will be presented along with examples of successful programs for difficult targets such as protein-protein interaction inhibitors, ubiquitin ligase, antibacterial and epigenetic targets.

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

4:10 Allosteric JAK Inhibition for Autoimmune Diseases

Atli Thorarensen, Ph.D., Associate Research Fellow, Immunoscience Research Chemistry, Pfizer

Selective target inhibition is a fundamental goal of drug discovery in order to deliver efficacy while sparing potential adverse side effects from off-targets. This talk will outline the strategy and results from phenotypic screening strategies using primary cells and in cell binding experiments that identified active, non-ATP competitive modulators for JAK.

4:40 Small Solutions for Big Problems: NMR as a Hit Generation Tool for PPIs

Edward R. Zartler, Ph.D., President & CSO, Quantum Tessera Consulting

Protein-Protein Interactions (PPIs) have great therapeutic promise, but are difficult targets to ligand. PPIs don't have defined binding sites, instead having plastic binding interfaces. Fragment-based Hit Generation using NMR offers a robust avenue into this very difficult target class.

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

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

7:15 Close of Day

THURSDAY, OCTOBER 9

7:30 am Registration and Morning Coffee

EMERGING PPI TARGETS

8:00 Chairperson's Opening Remarks
Daria Mochly-Rosen, Ph.D., Professor, Chemical and Systems Biology, Stanford

8:10 Targeting Protein-Protein Interactions: Novel Treatment for Neglected Tropical Diseases
Nir Qvit, Ph.D., Post-Doctoral Fellow, Chemical and System Biology, Stanford University
Based on rational approach we have developed novel peptide inhibitors of protein-protein interactions between LACK, scaffold Leishmania protein,and its binding proteins. The peptides inhibited promastigotes growth (IC50~10μM) and reduced *in vivo* parasitemia by 60%. Without any knowledge on partner proteins, we were able to design inhibitors of LACK's function and affect the parasite's viability. Our method is likely applicable to design other anti-parasitic drugs.

8:40 The Papillomavirus E1-E2 Interaction: a Surprisingly Druggable Target
Peter W. White, former Director, Infectious Disease at Boehringer Ingelheim
Inhibitors of protein-protein interactions could be one of the few options for treating conditions with no more obviously druggable targets. We identified inhibitors of the papillomavirus E1-E2 PPI by high-throughput screening, and a range of *in vitro* experiments were used to characterize them. Our experience may provide guidance for evaluating specific PPIs as drug targets and then for successfully identifying leads with potential for optimization.

9:10 Identifying Weak Protein-Protein Interactions
Richard R. Burgess, Ph.D., Professor Emeritus of Oncology, McArdle Laboratory for Cancer Research, University of Wisconsin-Madison
Important biological complexes are often dependent on weak protein-protein interactions with components that bind specifically but with low affinities or participate in transient interactions. Such weak PPIs, with T1/2's of seconds, are often difficult or impossible to detect. This presentation discusses an innovative biochemical-based technology that relies on magnetic affinity beads and microfluidics to detect previously unseen weak PPI's that may become important drug targets.

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

TARGETING UBIQUITIN LIGASES WITH PPI APPROACHES

10:30 The Discovery of Small Molecules Targeting the VHL E3 Ubiquitin Ligase and Disrupting Its Protein-Protein Interaction with HIF-alpha Subunit
Alessio Ciulli, Ph.D., Reader in Chemical & Structural Biology, Division of Biological Chemistry and Drug Discovery, College of Life Sciences, University of Dundee
We have discovered drug-like small molecules that target the ubiquitin proteosome system by disrupting, with nanomolar potencies, the key interaction between the von Hippel-Lindau protein (VHL) cullin ring E3 ligase and with the Hypoxia Inducible Factor alpha subunit (HIF-α). Structure-based design informed by co-crystal structures and biophysical binding characterisation guided the medicinal chemistry optimization of our compounds. Our efforts combined peptidomimetic strategies with fragment-based deconstructive analyses.

11:00 Targeting the MDM2-p53 Protein-Protein Interaction for New Cancer Therapeutics
Yujun Zhao, Ph.D., Research Investigator, Department of Internal Medicine, Division of Hemotology/Oncology, University of Michigan
Blocking the MDM2-p53 protein-protein interaction is being pursued as a new cancer therapeutic strategy. Our laboratory has designed and developed a class of highly potent and specific small-molecule inhibitors to block the MDM2-p53 PPI (MDM2 inhibitors). I will present our structure-based design and optimization of our MDM2 inhibitors and extensive preclinical studies of SAR405838 (MI-77301), which is now in phase I clinical development for the treatment of human cancers.

11:30 Enjoy Lunch on Your Own

1:00 pm Plenary Keynote Session *(see website for details)*

2:45 Refreshment Break in the Exhibit Hall with Poster Viewing

3:45 Close of Conference

Second Annual

October 8 - 9, 2014

Antibodies Against Membrane Protein Targets - Part 1

Membrane Protein Targets and Targeting

The two-part Antibodies Against Membrane Protein Targets provides a forum in which discovery biologists and protein engineers can come together to discuss next generation strategies and technologies that will allow antibody-and alternate scaffold-based therapeutics directed against these target families to advance into the clinic and beyond. The first meeting in the set, Membrane Protein Targets and Targeting, will discuss the fundamental challenges associated with targeting specific membrane protein families, and provide updates of the application of nanobodies and other small protein scaffolds to optimize binding.

Suggested Event Package

October 7 Short Course: Targeting of GPCRs with Monoclonal Antibodies

October 8-9 Conference: Antibodies Against Membrane Protein Targets – Part 1

October 9-10 Conference: Antibodies Against Membrane Protein Targets – Part 2

WEDNESDAY, OCTOBER 8

7:00 am Registration and Morning Coffee

8:05 Chairperson's Opening Remarks

Benjamin Doranz, Ph.D., President & CSO, Integral Molecular Inc.

» 8:15 FEATURED PRESENTATION: EVOLVING STABLE GPCRS FOR DRUG SCREENING AND STRUCTURAL ANALYSIS

Andreas Plückthun, Ph.D., Professor of Biochemistry, University of Zürich, Switzerland

GPCRs are validated drug targets for small molecules and antibodies alike, yet their low expression levels and poor biophysical properties have limited progress. We have developed several technologies to evolve functional receptors with greatly improved stability in detergents, based on a polymer encapsulation of a whole *E. coli* library (termed CHESS). This has allowed us to crystallize functional GPCRs from protein produced in *E. coli* and use such receptors for advanced drug screening.

GPCR ANTIBODY TARGETS

9:00 Discovery and Optimization of Novel Anti-G-Protein Coupled Receptor Monoclonal Antibodies

Trevor Wilkinson, Ph.D., Associate Director, Protein Sciences, Antibody Discovery and Protein Engineering, MedImmune, United Kingdom

G-protein coupled receptors represent a challenging target class for the isolation and optimization of therapeutic biologics. We have used a combination of immunization and phage display to isolate antibodies that potently block the activity of the formyl peptide receptor (FPR). Using combinatorial mutagenesis approaches, significant improvements to both affinity and species cross-reactivity of the lead molecules are demonstrated resulting in antibodies that show significant potency in cellular disease assays.

9:30 Using Patient Derived Tumor Models to Predict Response and Impact on Cancer Stem Cells by Targeting NOTCH and WNT Signaling Pathways

Christopher Murriel, Ph.D., Senior Scientist, Cancer Biology, OncoMed Pharmaceuticals

We previously demonstrated that targeting NOTCH, using an anti-DLL4 antibody, and WNT, using FZD receptor (OMP-18R5) or WNT ligand binding antagonists (OMP-FZD8-Fc) in patient-derived xenograft models (PDX), inhibited tumor growth and decreased CSC frequency. Additionally, anti-DLL4 and anti-WNT therapy decreased the expression of many genes associated with NOTCH, WNT, EMT, multidrug resistance, and DNA repair, with increased expression of differentiation markers. Therefore, our findings provide a rationale to target cancer stem cells through interference with NOTCH and WNT signaling pathways.

10:00 Grand Opening Coffee Break in the Exhibit Hall with Poster Viewing

10:45 Targeting of Clinically-Important GPCRs with Fully Human Antibodies

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

We are developing antagonistic fully human antibodies derived from our proprietary G- MAB® library targeting GPCR chemokine receptors, including CCR2, CXCR3 and CXCR5. These antibodies possess excellent *in vitro* characteristics regarding cell binding and inhibition of calcium flux and chemotaxis. The antibodies have been evaluated in pilot *in vivo* models and IND-enabling activities have been initiated for development as future anti-cancer and/or anti-inflammatory therapeutics.

11:15 Generation and Characterization of Antibodies against the Small Extra Cellular Loops of Glucagon Receptor

Bas van der Woning, Ph.D., Senior Scientist, arGEN-X, Belgium

Glucagon receptor (GCGR) is a type B GPCR, characterized by a large N-terminal domain that covers the small extracellular loops (ECLs). Glucagon activates GCGR by binding to the N-terminal domain and a pocket formed by the ECLs. By DNA immunization of outbred llamas we generated monoclonal antibodies (mAbs) binding to the N-terminal domain or to the ECLs of GCGR. Using these antibodies we will able to study the involvement of the ECLs in glucagon mediated GCGR activation.

11:45 Discovery of GPCR Antibody Therapeutics: Modulation of Cannabinoid Receptor 1 (CB1) Signaling

Antibodies Against Membrane Protein Targets - Part 1

Membrane Protein Targets and Targeting

Erik Karrer, Ph.D., CSO, RuiYi, Inc.

Clinical and experimental evidence supports involvement of Cannabinoid Receptor 1 (CB1) signaling in metabolic and fibrotic diseases. RuiYi's iCAPS technology (intramembranous conformation antigen presenting system) was used to generate antibodies to CB1 that recognize native structural epitopes. Antibodies with a range of functional activities were identified, including antagonist (inverse agonist), agonist and neutral effects on CB1 receptor signaling. Detailed *in vitro* characterization of an inverse agonist antibody will be presented.

12:15 pm Developing Functional Monoclonal Antibodies for Beta-3 Adrenergic Receptor

Sponsored by MULTISPAN

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

Although GPCRs represent 40% of medicinal small molecule therapeutics, there are no successful monoclonal antibody therapeutics. Using cell based functional assays to characterize antibody properties may help develop successful therapeutics. In this presentation, we detail the development of Beta-3 adrenergic receptor mAbs characterized using Multispan's GPCR cell based assay platforms. Our preliminary data show that several mAb clones specifically bound to the receptor while increasing the receptor function by acting as agonists.

12:45 Session Break

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

1:40 Session Break

1:50 Chairperson's Opening Remarks

Chris Mathes, Ph.D., Chief Commercial Officer, ChanTest Corporation

» 2:00 FEATURED PRESENTATION: FAB ASSISTED SINGLE PARTICLE CRYO-EM STUDIES OF INTEGRAL MEMBRANE PROTEINS

Yifan Cheng, Ph.D., Associate Professor, Department of Biochemistry and Biophysics, University of California San Francisco

We developed a novel approach of using Fab to assist single particle cryo-EM studies of small integral membrane proteins. Using this approach, we determined a 3D reconstruction of a bacterial ABC exporter at ~8A resolution.

ION CHANNEL TARGETS

2:30 Development of Pore-Blocking Antibodies Targeting Ion Channels

Sam Xu, Ph.D., Senior Lecturer, Center for Cardiovascular and Metabolic Research, Hull York Medical School, United Kingdom

Antibody targeting ion channel pore is a very useful tool for studying individual ion channel functionality. We have developed TRP cationic channel and sodium channel pore-blocking antibodies with a strategy named E3-targeting. This concept has been successfully extended to other ion channel families. The talk will give an overview of recent development in the field including pore-blocking antibody design, generation, functional characterization, application and therapeutic potential.

3:00 Development of an Electrophysiological Screening Tool to Identify Sub-Type Selective Nicotinic Receptor Compounds

Sponsored by ChanTest THE ION CHANNEL EXPERT

Glenn Kirsch, Ph.D., Senior Director, Pharmacology and Program Management

Our objective was to develop a screening tool for rapid identification of compounds with sub type-selective nicotinic receptor modulation properties. We developed cell lines and automated patch clamp assays for screening and profiling in IonWorks Barracuda. We will present progress in development, optimization and assay validation of cell lines that stably express human neuronal nicotinic receptors, including α3β4, α7, α4β2, and α3β4α5 subtypes.

3:15 Novel Strategies for Developing Functional Transporter and Ion Channel Assays

Sponsored by XRpro

Nathan Zahler, Ph.D., Senior Scientist, XRPro Corporation

A high-throughput method for ion transporter and ion channel investigations based on X-ray fluorescence (XRF). This broadly applicable technique measures ion uptake and efflux using populations of cells without requirement for fluorophores or radiolabels. Results are insensitive to chemical form, permitting use of complex cell media including serum and high DMSO concentrations. This complimentary capability is efficient and is compatible with current HTS workflows.

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

4:10 Discovery of MAbs against Difficult GPCRs, Ion Channels, and Transporters

Sponsored by integral molecular

Joseph Rucker, Ph.D., Vice President, Research & Development, Integral Molecular

To enable the isolation, characterization, and engineering of MAbs against challenging membrane protein targets, Integral Molecular has developed the MPS Discovery Engine™ platform, encompassing Lipoparticles for concentrating native membrane proteins and Shotgun Mutagenesis for membrane protein engineering and epitope mapping. Using the MPS platform, we have generated inhibitory MAbs against the ion channel P2X3 for treating neuropathic and inflammatory pain, and have ongoing discovery programs against additional GPCR, ion channel, and transporter targets.

4:40 Generation of Monoclonal Antibodies to Understand the Structure and Function of TRPV2 Ion Channel
Matthew Cohen, Graduate Student, Case Western Reserve University
TRPV2 is a Ca2+-permeable cation channel implicated in numerous physiological processes including neuronal cell development. In order to define the cellular function of TRPV2 in neurons, we generated monoclonal antibodies using full-length recombinant TRPV2 as an antigen. These antibodies are suitable for detection of endogenous TRPV2 by western blot, immunoprecipitation and immunocytochemistry. Employing full-length TRP channels as antigens may allow for production of antibodies against other TRP channels of uncertain function in the future.

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

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

7:15 Close of Day

THURSDAY, OCTOBER 9

7:30 am Registration and Morning Coffee

OTHER MEMBRANE PROTEIN TARGETS

8:00 Chairperson's Opening Remarks
Mark Tornetta, Ph.D., Scientist, Molecular Discovery Technologies, Janssen Pharmaceuticals

8:10 New Tools for Modification of Antibodies and Antibody Fragments
Hidde Ploegh, Ph.D., Member, Whitehead Institute, Professor of Biology, Massachusetts Institute of Technology
The application of sortase-catalyzed transacylation reactions to full sized antibodies and antibody fragments is a convenient and versatile tool to prepare derivatives over a wide spectrum of modifications. Applications of this methodology will be discussed.

8:40 Aquaporins as Potential Drug Targets for Antibody Therapeutics
Alan S. Verkman, M.D., Ph.D., Professor of Medicine and Physiology, University of California, San Francisco
The aquaporins are membrane water channels expressed widely in epithelia, endothelia and other cell types. Animal data suggest that modulation of aquaporin function or expression could have therapeutic potential in edema, cancer, obesity, brain injury, glaucoma and other conditions. Autoantibodies against AQP4 cause the autoimmune demyelinating disease neuromyelitis optica, for which a monoclonal non-pathogenic anti-AQP4 antibody (aquaporumab) is in development.

9:10 Targeting Siglec-15 for Therapeutic Inhibition of Osteoclastic Bone Resorption Results in the Maintenance of Bone Formation
Mario Filion, Ph.D., CSO, Alethia Biotherapeutics
Siglec-15 has recently emerged as an osteoclast-specific receptor that could potentially be targeted therapeutically for treatment of bone loss. Antibodies targeting this receptor impair osteoclast differentiation and activity while maintaining bone formation by osteoblasts. The combination of antiresorptive activity with the maintenance of bone formation offers a new treatment paradigm in areas of unmet medical needs such as severe bone loss that occurs in multiple myeloma and invasive carcinomas.

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

10:30 Solute Carriers as Targets for Biotherapeutics
Mathias Rask-Andersen, Ph.D., Post Doctoral Researcher, Department of Neuroscience, Functional Pharmacology, Uppsala University, Sweden
Solute carriers (SLCs) comprise a large family of membrane transporters. Despite being the largest family of membrane transport proteins, SLCs have been relatively under-utilized as therapeutic drug targets by approved drugs. To gain a better overview of the drug-targeted portion of the human proteome and the directions of current drug development, we developed a comprehensive dataset of established and clinical trial drug-target interactions.

11:00 Targeting Receptors with Cell Penetrating Pepducins: From the Bench to Bedside
Athan Kuliopulos, M.D., Ph.D., CEO, Oasis Pharmaceuticals; Professor of Medicine and Biochemistry, Tufts Medical Center

11:30 Enjoy Lunch on Your Own

1:00 pm Plenary Keynote Session *(see website for details)*

2:45 Refreshment Break in the Exhibit Hall with Poster Viewing

3:45 Close of Conference

Third Annual

October 9 - 10, 2014

Targeting Histone Methyltransferases and Demethylases

Regulating the Histone Methylome through Small Molecule Inhibition

Epigenetic drug development has quickly gained widespread interest due to the apparent therapeutic efficacy now being demonstrated in preclinical and clinical studies.. Drugging the histone methylome remains at the center of discovery with new findings of mutations and deregulation of genes coding for Histone Methyltransferase and Demethylase enzymes. Cambridge Healthtech Institute will once again convene leaders in epigenetic drug development to provide updates on preclinical and clinical programs, introduce novel targets and chemical matter, and discuss strategies for targeting and validating histone methyltransferases and demethylases.

Suggested Event Package

October 7 Short Course: Biologically-Relevant Chemical Diversity

October 7 Short Course: Introduction to Targeted Covalent Inhibitors

October 8-9 Conference: Targeting Epigenetic Readers and Chromatin Remodelers

October 9-10 Conference: Targeting Histone Methyltransferases and Demethylases

THURSDAY, OCTOBER 9

11:30 am Registration

1:00 pm Plenary Keynote Session *(see website for details)*

2:45 Refreshment Break in the Exhibit Hall with Poster Viewing

3:45 Chairperson's Opening Remarks

Jonathan D. Licht, M.D., Johanna Dobe Professor & Chief, Division of Hematology/Oncology, Feinberg School of Medicine, Northwestern University

3:55 Disorders of Histone Methylation in Hematological Malignancy

Jonathan D. Licht, M.D., Johanna Dobe Professor & Chief, Division of Hematology/Oncology, Feinberg School of Medicine, Northwestern University

I will discuss the recurrent mutations in epigenetic enemies affecting methylation between histone 3 lysine 4 (H3K4me- activation) and H3K27me (repression). Among the proteins that will be discussed are EZH2, which is mutated in a substantial fraction of germinal center derived lymphomas; UTX, a histone demethylase for H3K27 that is deleted in multiple myeloma and other tumors; and WHSC1/MMSET, a gene over expressed in multiple myeloma as well as many solid tumors and mutated in a subset of ALL.

4:25 Epigenetic Reprogramming by Tumor Derived EZH2 Gain-of-Function Mutations Promotes Aggressive 3D Cell Morphologies and Enhances Melanoma Tumor Growth

Robert Rollins, Ph.D., Principal Scientist, Oncology, Pfizer

To elucidate the role of EZH2 gain-of-function (GOF) mutations in the solid tumor, we ectopically expressed EZH2 GOF mutations in multiple cell models. These mutations dramatically altered 3D cell morphology/motility and regulated related intracellular pathways. In addition, melanoma cells expressing ectopic mutations form larger tumors than control mice in mouse xenograft studies. These results suggest EZH2 GOF mutations may alter the interaction of cancer cells with their microenvironment.

4:55 Kinetics and Assay Condition-Dependence of Activity Enhancement by the NSD2 E1099K and T1150A Mutations

Sponsored by REACTION BIOLOGY CORP.

Konrad T. Howitz, Ph.D., Director, Epigenetics, Reaction Biology Corporation

Over expression of the histone H3K36 methyltransferase NSD2 (MMSET/WHSC1), for example due to the t(4;14) translocation in multiple myelomas, can help drive oncogenesis. This effect may be phenocopied, particularly in certain leukemias and lymphomas, by what are presumed to be hyperactivating NSD2 mutations. We have investigated the effects of two such mutations, E1099K and T1150A, using full-length, insect cell-expressed, wild-type and mutant enzymes to perform *in vitro* kinetic studies with nucleosomal substrates.

5:25 Coffee Break in the Foyer

5:40 Critical Roles of Histone Methyltransferases and Demethylases in Human Carcinogenesis

Ryuji Hamamoto, Ph.D., Associate Professor, Hematology & Oncology, The University of Chicago

Recent development of basic cancer research indicated that deregulation of histone methylation plays a critical role in human carcinogenesis. We have comprehensively conducted expression profile and functional analyses of histone methyltransferases and demethylases, and identified several ideal candidates for anti-cancer therapy. Furthermore, we have also been developing anti-cancer drugs targeting these enzymes. I will introduce the current progress of our research.

6:10 JARID1/KDM5 Demethylases as Cancer Targets

Qin Yan, Ph.D., Assistant Professor, Pathology, School of Medicine, Yale University

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

6:40 Close of Day

Targeting Histone Methyltransferases and Demethylases

Regulating the Histone Methylome through Small Molecule Inhibition

FRIDAY, OCTOBER 10

7:30 am Registration

THERAPEUTIC OPPORTUNITIES TARGETING THE HISTONE METHYLOME

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

9:00 Chairperson's Remarks
Peter Staller, Ph.D., Director, Oncology Research, EpiTherapeutics ApS

» 9:10 FEATURED PRESENTATION: EZH2 AS A TARGET FOR GENETICALLY DEFINED CANCERS
Roy M. Pollock, Ph.D., Senior Director, Biological Sciences, Epizyme
Epizyme has discovered potent and selective small molecule inhibitors of EZH2 as targeted therapeutics for subsets of human cancers bearing defined genetic lesions. These include non-Hodgkin's lymphomas with EZH2 gain-of-function mutations and other tumor types with loss of INI1 function. The properties of these inhibitors, including their ability to selectively kill tumor cells bearing specific genetic alterations in cell culture and animal models will be discussed as well as an update on the early clinical experience with EPZ-6438 (E7438) – an EZH2 inhibitor that recently entered Phase I clinical testing.

9:40 EZH2 Inhibitors and Their Application in Cancer
Bill Bradley, Ph.D., Scientist, Constellation Pharmaceuticals
Constellation has identified potent, selective small molecule inhibitors of the histone H3 lysine 27 (H3K27)-specific EZH2. These compounds cause selective cell killing of Non-Hodgkin Lymphoma cell lines and regression in subcutaneous NHL models *in vivo*. The impact on tumor growth is correlated with global reduction of H3K27me3 levels and the induction of EZH2 target gene expression. We have identified Multiple Myeloma and drug combinations that expand the application of EZH2 inhibitiors.

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

10:55 Development of Histone Demethylase Inhibitors for Oncological and Neurodegenerative Disease
Tamara Maes, Ph.D., Co-Founder, Vice President & CSO, Oryzon Genomics
Oryzon's LSD1 inhibitors were shown to selectively abrogate the clonogenic potential of AML cells with MLL translocations, sparing the repopulating potential of normal hematopoietic stem cells. ORY-1001 is a potent, selective LSD1 inhibitor, with excellent pharmacological characteristics. ORY-2001 is a dual LSD1/MAO-B inhibitor and protects mice from MPTP insult, demonstrating its brainMAOBi capacity, and restores the memory loss of SAMP-8 mice, a non-transgenic model for Alzheimer's.

11:25 Inhibition of LSD1 as a Therapeutic Strategy for the Treatment of AML and SCLC
Ryan Kruger, Ph.D., Director, Discovery Biology, GlaxoSmithKline
Pre-clinical data demonstrate that pharmacological inhibition of LSD1 causes differentiation of AML cells *in vitro* and *in vivo*. In SCLC cell line and primary sample xenograft studies LSD1 inhibition resulted in potent tumor growth inhibition. The current study describes the anti-tumor effects of GSK2879552, a novel, potent, selective, irreversible LSD1 inhibitor currently in clinical development.

11:55 Therapeutic Inhibitors of the KDM5 Histone Demethylases
Peter Staller, Ph.D., Director, Oncology Research, EpiTherapeutics ApS
The histone demethylases KDM5A and KDM5B target methylation of histone H3 at lysine 4 and contribute to cancer cell proliferation and to the induction of drug tolerance. EpiTherapeutics has developed specific and potent inhibitors of KDM5. The pharmacological properties of selected compounds and their *in vivo* activity as well as potential therapeutic applications will be discussed.

12:25 pm Label-Free Biochemical Assays for Epigenetics Targets *Sponsored by* SAMDI
Michael D. Scholle, Co-Founder, Director, Technology and Operations, SAMDI Tech, Inc
SAMDI is a unique label-free assay platform for quantitative measurement of biochemical activity of epigenetics targets: including methyltranferases, demethylases, deacetylases and many others. This pioneering technology uses high-throughput mass spectrometry in 1536 format for rapid assay development, high-throughput screening, and peptide substrate discovery efforts.

12:40 Sponsored Presentation *(Opportunities Available)*

12:55 Session Break

1:05 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Lunch on Your Own**

1:45 Session Break

DISCOVERY AND DEVELOPMENT OF NOVEL BIOACTIVE CHEMICAL MATTER

1:55 Chairperson's Remarks
Qin Yan, Ph.D., Assistant Professor, Pathology, School of Medicine, Yale University

2:00 Targeting the MLL1-WDR5 Protein-Protein Interaction as a Novel Therapeutic Strategy for Acute Leukemia Harboring MLL1 Fusion Protein
Shaomeng Wang, Ph.D., Director, Center for Discovery of New Medicines; Warner-Lambert/Parke-Davis Professor, Medicine, Pharmacology and

Targeting Histone Methyltransferases and Demethylases

Regulating the Histone Methylome through Small Molecule Inhibition

Medicinal Chemistry, University of Michigan Comprehensive Cancer Center

I will present our structure-based design of highly potent and specific small-molecule inhibitors of the MLL1-WDR5 protein-protein interaction as a new therapeutic strategy for the treatment of acute leukemia harboring MLL1 fusion protein. Their mode of action and therapeutic potential will be discussed.

2:30 Targeting Arginine Methyltransferases

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

Protein arginine methyltransferases (PRMTs) is an emerging class of therapeutic targets. We previously reported the first allosteric inhibitor of PRMT3 with an IC50 value of 2.5 μM, and a significantly more potent next generation inhibitor with an IC50 value of 230 nM. Here we will report on further optimization of this series of inhibitors (<100 nM), discuss their target engagement in cells, and possible allosteric inhibition of other PRMTs.

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing

3:30 A Dual Approach to Develop Inhibitors of Protein Methyltransferases

Minkui Luo, Ph.D., Assistant Member & Assistant Professor, Molecular Pharmacology and Chemistry, Memorial Sloan-Kettering Cancer Center

It is of great challenge to develop PMT inhibitors aiming at potency and specificity. We combined rational design and HTS to develop PMT inhibitors within the scope of our interest in chemical probes and cancer therapy. We designed sinefungin analogues against a collection of human PMTs and identified structurally-distinct sinefungin scaffolds that can selectively bind a subset of PMTs such as SETD2, CARM1 and SET7/9. We have also identified novel scaffolds to inhibit SET8.

4:00 Small Molecule Epigenetic Modulators for the Treatment of Cardiovascular Disorders

Patrick M Woster, Ph.D., Endowed Chair, Drug Discovery; Professor, Pharmaceutical and Biomedical Sciences, College of Pharmacy, Medical University of South Carolina

We have identified a new series of small molecules that act as potent and selective LSD1 inhibitors. Because of their relatively low toxicity, we have explored the use of these molecules in diseases other than cancer, where cytotoxicity is not a desirable endpoint. In this presentation, we will describe the optimization of this new series of LSD1 inhibitors, and present evidence that LSD1 inhibitor-mediated correction of aberrant gene silencing can have therapeutic potential.

4:30 Strategies for Developing Histone Demethylase Inhibitors

Akane Kawamura, Ph.D., Senior Investigator, Department of Chemistry, University of Oxford

Histone demethylases are involved in the epigenetic regulation of gene transcription via controlling the methylation status on histone tails. Chemical probes against these enzymes are needed to understand their complex biology in development and disease. Approximately 20 JmjC-domain containing KDMs have been identified, which forms a cluster within the Fe(II) and 2OG-dependent oxygenase superfamily of proteins. This talk will focus on our recent efforts and different strategies employed for JmjC-KDM inhibitor development.

5:00 Close of Conference

Screening Drug Transporter Proteins

Using New Assays and Cellular Models for Functional Predictions

Cambridge Healthtech Institute's Inaugural conference on Screening Drug Transporter Proteins will cover the latest in the use of 2D and 3D *in vitro* systems and *in vivo* models for studying the function, expression and localization of important classes of drug transporters. What transporters to study and when? How physiologically relevant are these systems and how reliable are the predictions made from the data? How can you design assays that are clinically significant and how will the regulatory agencies receive this data? Experts in the field share their experiences leveraging the utility of diverse assays and endpoints, and help address some of the key bottlenecks.

Suggested Event Package
October 7 Short Course: GPCR Structure-Based Drug Discovery
October 8-9 Conference: GPCR-Based Drug Discovery
October 9-10 Conference: Screening Drug Transporter Proteins
October 9 Dinner Course: Integration of BDDCS and Extended Clearance Principles for Understanding Disposition and ADME Liabilities

THURSDAY, OCTOBER 9

11:30 am Registration

1:00 pm Plenary Keynote Session *(see website for details)*

2:45 Refreshment Break in the Exhibit Hall with Poster Viewing

UTILIZING RELEVANT *IN VITRO* ASSAYS AND MODELS

3:45 Chairperson's Opening Remarks
Yvonne Will, Ph.D., Associate Research Fellow, Compound Safety Prediction, Pfizer Global Research & Development

3:55 Novel Applications of the Sandwich-Cultured Hepatocyte Model for Transporter Investigations
Kim Brouwer, Pharm.D., Ph.D., W.R. Kenan, Jr., Distinguished Professor and Chair, Division of Pharmacotherapy and Experimental Therapeutics, Eshelman School of Pharmacy, The University of North Carolina at Chapel Hill
Sandwich-cultured hepatocytes (SCH) are a versatile *in vitro* model to assess hepatic drug transport (uptake, basolateral efflux, biliary clearance). Recently, the utility of SCH to quantify intracellular drug/metabolite concentrations, drug interactions in hepatic transport, and the drug metabolism-transport interplay has been demonstrated. Novel applications of SCH as a screening tool to assess phospholipidosis potential and bile-acid mediated drug-induced liver will be discussed.

4:40 Informing the Potential of Drug-induced Liver Injury (DILI): Predictive Models for Bile Acid Synthesis and Disposition
Yurong Lai, Ph.D., Senior Principal Scientist, Pharmaceutical Candidate Optimization, Bristol-Myers Squibb Company
DILI is a major concern for the pharmaceutical industry. Drug-induced disruption of BSEP function leads to accumulation of bile acids (BAs) in hepatocytes, and subsequently regulates bile acid transport and biosynthesis through feed-forward and feedback regulatory mechanism. Disruption of these complex processes could lead to BA accumulation and liver injury. The presentation will describe the *in vitro* efforts on bile acid profiling to inform the potential for liver injury.

5:25 Coffee Break in the Foyer

5:40 Developing Cell-Based Assays to Accurately Predict Liver Injury Due to Mitochondrial Toxicity and BSEP Inhibition
Yvonne Will, Ph.D., Associate Research Fellow, Compound Safety Prediction, Pfizer Global Research & Development
For many years we have studied drug induced mitochondrial toxicity in a variety of drug classes. Of those drugs that cause clinical drug-induced liver injury (DILI), we noticed that some of the drugs also inhibited the bile salt efflux pump. We conducted a study and found that indeed dual inhibition correlated with severe human DILI, whereas inhibition of only one or the other had less of a correlate.

6:25 Q&A with Session Speakers

6:40 Close of Day

FRIDAY, OCTOBER 10

7:30 am Registration

TRANSLATING TRANSPORTER DATA INTO IMPROVED UNDERSTANDING

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

9:00 Chairperson's Remarks
Toshihisa Ishikawa, Ph.D., President, NGO Personalized Medicine & Healthcare, Yokohama, Japan

9:10 The Use of Genomic and Systems Biology Approaches to Identify Genetic Determinants of Susceptibility to Chemical-Induced Hepatotoxicity

Inaugural

Screening Drug Transporter Proteins

Using New Assays and Cellular Models for Functional Predictions

October 9 - 10, 2014

Jose Manautou, Ph.D., Professor of Toxicology, Department of Pharmaceutical Sciences, School of Pharmacy, University of Connecticut

Treatment of rodents with low hepatotoxic doses of acetaminophen (APAP) results in resistance to subsequent, more toxic doses of APAP, termed APAP autoprotection. We are interested in studying the genetic determinants of this heightened tolerance to APAP hepatotoxicity. I will highlight the results of studies analyzing differentially expressed hepatic transporters in the APAP autoprotection model, with emphasis on Mrp4 (ABCC4). The regulatory mechanisms governing such changes and our characterization of the structure and regulation of the Mrp4 gene core promoter will be presented.

9:40 *In vitro* and *in silico* Investigations of BCRP Polymorphism on Statin Transport

Mingxiang Liao, Ph.D., Senior Scientist I, DMPK, Takeda Pharmaceutical Intl. Company

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

10:55 Lost in Translation? – A Focus on Renal Transporter Mediated Drug-Drug Interactions

Kari Morrissey, Ph.D., Associate Scientist, Department of Clinical Pharmacology, Genentech, Inc.

Typically, one compares the *in vivo* $C_{max,u}$ of a potential inhibitor to its *in vitro* IC_{50} to predict the likelihood for a transporter DDI to occur. However, other factors such as the inhibitor's half-life and activity against other transporters should also be considered. This presentation will highlight *in vitro* and clinical studies with promiscuous and selective inhibitors of renal transporters, with a focus on the clinical impact of renal transporter-mediated DDIs.

11:25 Towards an Increased Understanding of the Complex Drug–Drug Interactions Involving OATP Transporters: Recent Experiences and Key Learnings

Xiaoyan Chu, Ph.D., Department of Pharmacokinetics, Pharmacodynamics & Drug Metabolism (PPDM), Merck & Co.

Inhibition of OATP1B1-mediated hepatic uptake may cause clinically significant drug-drug interactions (DDIs). To assess risk for such DDIs, *in vitro* approaches, decision trees, and clinical studies have been recommended by the US FDA and EMA (European Medicines Agency). Case studies will be presented which highlight potential complications associated with statin related DDIs. *In vitro* and *in vivo* approaches to better understand such DDIs will also be discussed.

11:55 *In vivo* Models to Bridge the Translational Gaps for Pharmacokinetics Influenced by Hepatic OATPs

Maciej Zamek-Gliszczynski, Ph.D., Director, Drug Metabolism and Pharmacokinetics, GlaxoSmithKline

The fraction of total hepatic uptake mediated by OATP1B1 is key to understanding clinical DDIs and pharmacogenetic variability. Studies with OATP-substrate drugs support the utility of oatp1a/1b-knockout mice in determining whether hepatic OATPs affect drug pharmacokinetics and hepatic distribution. If so, OATP1B1-humanized knockout-mice can be used to accurately predict the fractional contribution of OATP1B1 to hepatic uptake in humans after correcting for protein expression differences be expression differences between humanized mouse and human liver.

12:25 pm Sponsored Presentation *(Opportunity Available)*

12:55 Session Break

1:05 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Lunch on Your Own**

1:45 Session Break

IN VITRO TO *IN VIVO* EXTRAPOLATION

1:55 Chairperson's Remarks

Joseph Polli, Ph.D., Worldwide Director, DMPK, GlaxoSmithKline

» 2:00 FEATURED PRESENTATION: DRUG TRANSPORTERS, DRUG INTERACTIONS AND AGENCY REVIEW EXPERIENCES

Joseph Polli, Ph.D., Worldwide Director, DMPK, GlaxoSmithKline

With the publication of the International Transporter Consortium Whitepapers and the Drug Interaction Guidances from EMA and FDA in 2013, there has been a surge of research and regulatory activity in the area of drug transporters over the past 12 months. The objective of this presentation is to share a perspective on when transporter related work should be undertaken during drug discovery/development and how this fits with current regulatory guidances.

2:45 Questions from Attendees

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing

3:30 Modulation of OATP1B1/1B3 Uptake Alter Systemic and Hepatic Exposure of Drug Substrates, Right! Think Again

Ayman El-Kattan, Ph.D., Associate Research Fellow, Department of Pharmacokinetics, Dynamics, and Metabolism, Pfizer, Inc.

Systemic and hepatic exposure of OATP1B1 and 1B3 substrates is governed by different mechanisms. The systemic exposure of these substrates is governed by active uptake as highlighted by the extended clearance concept. However, liver exposure is driven by metabolism/bilairy elimination. This presentation will highlight these principles and substantiate it with *in silico*/*in vitro*/clinical drug-drug interactions and pharmacogenomics findings.

4:00 Evaluation of the Interaction of Poorly Permeable Metabolites with Hepatic Uptake and Efflux Transporters

Mitchell E. Taub, Ph.D., Senior Research Fellow, Drug Metabolism & Pharmacokinetics, Boehringer Ingelheim Pharmaceuticals, Inc.

To comply with current regulatory guidelines, the potential interaction of major metabolites of investigational drugs with uptake and efflux transporters should be evaluated. However, metabolites are typically more hydrophilic than the parent drug, and due to their lower membrane permeability, may be challenging to study using commonly employed bidirectional transport assays. Two case studies involving late-stage development compounds will be presented.

4:30 Mechanistic Modeling of Drug-Induced Liver Injury that Involves Bile Acid Transport Inhibition: A Case Study with Troglitazone

Kyunghee Yang, Ph.D., Postdoctoral Fellow, The Hamner Institutes for Health Sciences

Drug-mediated functional disturbances in hepatic bile acid transporters leads to intracellular bile acid accumulation and subsequent hepatic injury. DILIsym® is a mechanistic model of DILI that integrates data from different experimental systems and species, and biological knowledge, to predict human DILI. In this presentation, troglitazone will be employed as a model hepatotoxic compound to demonstrate how DILIsym® can be used to predict hepatotoxic potential of compounds that involve bile acid transport inhibition.

5:00 Close of Conference

Inaugural

October 9 - 10, 2014

Maximizing Efficiency in Discovery

Right Drug - Right Target: Strategies for Preclinical Efficiency to Improve Outcomes & Reduce Attrition

Despite the continued success in unlocking the druggable genome, the ability to efficiently translate novel science to meet patients in need has declined, due to mounting reports of compounds displaying lack of efficacy or toxicity in early phases of clinical trials. With attrition rates climbing, developers are being challenged to respond by becoming more efficient during preclinical activities by identifying "right" targets and mechanisms of action; selecting "right" compounds without mechanism-based, compound-based or off-target toxicities, and utilizing disease-relevant models to validate and identify translatable biomarkers to enable POC earlier in development.

Suggested Event Package

October 7 Short Course: Biologically-Relevant Chemical Diversity

October 7 Short Course: Advances in Metagenomic Drug Discovery for New Anti-Infective Agents

October 8-9 Conference: Big Data Analytics and Solutions

October 9-10 Conference: Maximizing Efficiency in Discovery

THURSDAY, OCTOBER 9

11:30 am Registration

1:00 pm Plenary Keynote Session *(see website for details)*

2:45 Refreshment Break in the Exhibit Hall with Poster Viewing

3:45 Chairperson's Opening Remarks

Meir Glick, Ph.D., Head, In Silico Lead Discovery, Novartis Institutes for BioMedical Research, Inc.

HIGH-THROUGHPUT CHEMICAL DIVERSITY

» **3:55 FEATURED PRESENTATION: Industrializing Drug Discovery – Make More Compounds and Better Compounds and Make Them Faster**

Russell C. Petter, Ph.D., Vice President, Chemistry, Celgene

I will discuss placing high-throughput medicinal chemistry (HTMC) on the critical path, such that chemistry is actually driving programs into clinical POC.

ADVANCES IN PHENOTYPIC DISCOVERY

4:25 Toward Enabling Physiologically Relevant Assays: Taking Advantage of 3D/Complex Cell Systems for Drug Discovery

Christophe Antczak, Ph.D., Laboratory Head, CPC Integrated Lead Discovery, Novartis Institutes for BioMedical Research

In vitro organoid models are emerging that maintain aspects of *in vivo* tissue organization and function. Those complex cell systems may better mimic physiological conditions; in turn, more predictive assays may emerge by screening those complex cell systems. However, challenges exist in the path toward enabling high-throughput screening with such models, such as simplifying long and complex workflows, facilitating the handling of cells in suspension, and designing minimally invasive readouts.

4:55 Success is Key in Innovation Efficiency

Sponsored by evotec

Craig Johnstone, Ph.D., Senior Vice President, Drug Discovery and Innovation Efficiency, Evotec

Creating success while others fail for lack of speed, quality or willingness to take risk is the task at hand in drug discovery. All projects encounter multiple technical problems, and so success must stem from solving or circumnavigating those problems in an effective manner. Finding the way forward in these circumstances requires experience, intellect, invention, seamless cooperation, slick execution and a passion for success.

5:25 Coffee Break in the Foyer

5:40 Regenerative Medicine Drug Discovery: Increasing Effectiveness in Drug Discovery Using Physiologically Relevant Human Cells and Biologically Annotated Compound Libraries

Alleyn Plowright, Ph.D., Senior Principal Scientist, Medicinal Chemistry, AstraZeneca

Physiologically relevant human cells, including primary cells from patients and human induced pluripotent stem cells, in compound phenotypic screening and toxicology testing, has the potential to transform drug. Challenges lay ahead including target deconvolution and the potential need to optimize chemistry against multiple targets. This presentation will describe advances in this area, including application in the field of identifying novel therapeutics for regeneration of cardiac tissue.

6:10 Tackling Metastasis through a Phenotypic Assay: Discovery of Compounds that Reduce the Perinucleolar Compartment

Samarjit Patnaik, Ph.D., Reseach Scientist, Probe Development Center, NCATS, NIH

Using a high content imaging assay we have discovered a chemical series that is able to reduce PNC prevalence in multiple cells lines without significant impact on cell viability. The lead compound shows *in vitro* anti-oncogenic properties including inhibition of migration and invasion. When tested in a pancreatic mestastasis model, derived from pancreatic cancer stem-like cells, daily treatment significantly reduced metastasis to the lung and liver with no signs of toxicity.

6:40 Close of Day

Maximizing Efficiency in Discovery

Right Drug - Right Target: Strategies for Preclinical Efficiency to Improve Outcomes & Reduce Attrition

FRIDAY, OCTOBER 10

7:30 am Registration

ENSURING TARGET ENGAGEMENT

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

9:00 Chairperson's Remarks
Alleyn Plowright, Ph.D., Senior Principal Scientist, Medicinal Chemistry, AstraZeneca

9:10 Improving Translation in Drug Discovery by Monitoring Target Engagement Using CETSA
Michael Dabrowski, Ph.D., Associate, Pär Nordlund Group,Research Division of Biophysics, Karolinska Institute; CEO, Pelago Biosciences AB
We have developed a novel generic method for evaluating drug binding to target proteins in cells, tissues and organs. (CETSA™) is based on ligand-induced thermal stabilization of target proteins. It is possible to quantify drug-target interactions completely label free. We have validated the translational utility of the method to monitor drug binding and mode of action of the native target in physiological relevant conditions in *in vitro* cell cultures and *in vivo* samples from mice and man.

9:40 Positron Emission Tomography (PET): Enabling Earlier, More Confident Decisions in Drug Discovery and Development
Eric Hostetler, Ph.D., Lead, PET Tracer Group, Merck Research Laboratories
Pharmaceutical industry productivity has been decreasing at a steady rate, spending more to discover fewer drugs. Given the probability of success, Phase II as the default clinical decision-making stage is not sustainable. Attrition can be shifted to earlier stages of drug development by better use of biomarkers. We will discuss PET tracer discovery and how PET can be integrated into Phase I to ensure target engagement, focus dose range, and maximize benefit to risk for clinical drug candidates.

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

DEVELOPMENT OF HIGH-QUALITY CANDIDATES: IMPROVED DMPK CRITERIA, NOVEL DATA ANALYTICS AND EXPLOITING POLYPHARMACOLOGY

10:55 A Proposed DMPK Screening Paradigm for Efficient Discovery of Reversible and Irreversible Drugs
Mehran F. Moghaddam, Ph.D., Head, Drug Metabolism and Pharmacokinetics, Celgene
Discovery of high-quality drug development candidates in an efficient, timely, and cost effective manner remains a challenge for the biopharmaceutical industry. Discovery groups are now forced to seek compound advancement criteria that allow faster discovery, with the most probability of clinical success, while speedily removing low quality compounds. In this presentation, our proposed screening paradigms for discovery of non-covalent and covalent drugs and their nuances will be discussed.

11:25 *In silico* Lead Finding through Holistic Understanding of Screening Data from Multiple Approaches
Meir Glick, Ph.D., Head, In Silico Lead Discovery, Novartis Institutes for BioMedical Research, Inc.
The changing drug discovery environment presents a richer, more complicated and novel data landscape. How can state of the art data analytics increase the probability of a lead compound to be disease relevant? We will discuss how *in silico* approaches actively shape the lead discovery process: informing on relevant assays, compounds subset design to probe the biology, visualization of complex biological data, models elucidating target / MOA hypothesis and design of chemical matter.

11:55 Novel Inter-Omics Approaches for Big Data Analysis and Drug Discovery
Shuxing Zhang, Ph.D., Head, Integrated Molecular Discovery Laboratory; Director, Molecular Modeling/Structural Biology Core; Assistant Professor, Department of Experimental Therapeutics, University of Texas MD Anderson Cancer Center
The large scale data available to date can help us understand cancer biology and accelerate development of novel agents for targeted therapies. We recently embarked on the implementation of novel inter-omics approaches by integrating concepts and technologies in cheminformatics, bioinformatics, and systems biology. These tools have significantly sped up our analysis of the big chemogenomics data and guided our translational cancer research. In particular, we have built an integrated platform to

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SHAMROCK STRUCTURES

12:25 pm Accelerate Your Drug Discovery R&D with Protein Crystallography, Medicinal Chemistry and Cell Biology Research Services from Shamrock Structures
Michael T. Flavin, Ph.D., CEO, Shamrock Structures, LLC
Shamrock Structures can enable your team to more rapidly discover potent and selective new drug lead compounds. Our scientists can help characterize your protein target with X-ray crystallography, synthesize small molecule analogs and fragments for target binding and screen your compounds against oncology targets to determine potency and selectivity.

12:55 Session Break

1:05 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Lunch on Your Own**

1:45 Session Break

CASE STUDIES IN EPIGENETICS: EXPANDING CHEMICAL SPACE INTO PPI AND ALLOSTERY

1:55 Chairperson's Remarks

Eugene Chekler, Ph.D., Senior Principal Scientist, Medicinal Chemistry, Pfizer

2:00 Targeting the MLL1-WDR5 Protein-Protein Interaction as a Novel Therapeutic Strategy for Acute Leukemia Harboring MLL1 Fusion Protein

Shaomeng Wang, Ph.D., Director, Center for Discovery of New Medicines; Warner-Lambert/Parke-Davis Professor, Medicine, Pharmacology and Medicinal Chemistry, University of Michigan Comprehensive Cancer Center

I will present our structure-based design of highly potent and specific small-molecule inhibitors of the MLL1-WDR5 protein-protein interaction as a new therapeutic strategy for the treatment of acute leukemia harboring MLL1 fusion protein. Their mode of action and therapeutic potential will be discussed.

2:30 Targeting Arginine Methyltransferases

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

Protein arginine methyltransferases (PRMTs) is an emerging class of therapeutic targets. We previously reported the first allosteric inhibitor of PRMT3 with an IC50 value of 2.5 μM, and a significantly more potent next generation inhibitor with an IC50 value of 230 nM. Here we will report on further optimization of this series of inhibitors (<100 nM), discuss their target engagement in cells, and possible allosteric inhibition of other PRMTs.

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing

MODERN DRUG DISCOVERY: A RIGOROUS APPROACH TO TARGET VALIDATION

3:30 Target Validation Using Chemical Probes in Medicinal Chemistry

Eugene Chekler, Ph.D., Senior Principal Scientist, Medicinal Chemistry, Pfizer

Development of CREB Binding Protein (CREBBP) selective chemical probe to elucidate biology associated with this bromodomain epigenetic target is presented. The selectivity of the chemical probe against other bromodomain family members was investigated using biochemical and biophysical assays. To address the selectivity issue with BRD4, X-ray crystal structures of the probe candidates bound to CREBBP and BRD4 were used to guide the design.

4:00 Development of Highly Potent and Selective Reversible Covalent BTK Inhibitors

Erik Verner, Ph.D., Director, Chemistry, Principia Biopharma

4:30 Evaluation of Cancer Dependence and Druggability of PRP4 Kinase Using Cellular, Biochemical and Proteomic Approaches

Qiang Gao, Ph.D., Senior Investigator, Oncology, Sanofi

In this presentation, the requirement of enzymatic activity of PRP4 in regulating cancer cell growth is reported. An array of novel proteomics approaches for its substrates identification is proposed and transferable to exploring the kinase substrates for other kinases. These results provide new and important information for further exploration of PRP4 kinase function in cancer.

5:00 Close of Conference

Second Annual

GPCR-Targeted Therapeutics

Preclinical and Pharmacological Challenges

October 9 - 10, 2014

G protein-coupled receptors (GPCRs) are attractive targets for pharmacological modulation due to their role in many medically-relevant biological processes. This meeting will present tools and new knowledge that is aiding the discovery of compounds with more precise control of receptor signaling. Case studies of lead compounds progressing (or not) in the drug discovery pipeline will also be included.

Suggested Event Package

October 7 Short Course: GPCR Structured-Based Drug Discovery
October 7 Short Course: Targeting of GPCRs with Monoclonal Antibodies
October 8-9 Conference: GPCR-Based Drug Discovery
October 9-10 Conference: GPCR-Targeted Therapeutics
October 9 Dinner Course: Introduction to Allosteric Modulators and Biased Ligands of GPCR

THURSDAY, OCTOBER 9

11:30 am Registration

1:00 pm Plenary Keynote Session *(see website for details)*

2:45 Refreshment Break in the Exhibit Hall with Poster Viewing

Inflammation, Metabolism and GPCRs

3:45 Chairperson's Opening Remarks

Jeffrey Brown, Ph.D., Senior Research Investigator II, Department of Experimental Biology and Genomics, Bristol-Myers Squibb

3:55 Discovery of Potent and Selective Inhibitors of CRTH2

Kevin W. Hunt, Ph.D., Senior Research Investigator, Medicinal Chemistry, Array Biopharma

ARRY-502 is a potent, selective inhibitor of CRTh2, a key GPCR emerging as an effective drug target for allergic asthma. As current asthma therapies do not fully target this pathway, CRTh2 antagonists represent an exciting new approach to enhanced disease control. The preclinical and clinical data to be presented suggest broad applicability of ARRY-502 in the asthma population, as well as in other Th-2 driven diseases.

4:25 Targeting Chemokine Receptors for Inflammation

Dan Dairaghi, Ph.D., Senior Director, Molecular Pharmacology and Biomarkers, ChemoCentryx

The chemokine system, including chemokines and chemo-attractants, directs inflammatory responses, serving to precisely coordinate immune system cell movement. As drivers of the inflammatory response, chemokines and their receptors present opportunities for the development of new therapies. Each of ChemoCentryx's novel small molecule drug candidates is designed to target a specific chemokine receptor, thereby blocking the inflammatory response driven by that particular chemokine while leavin

Sponsored by Intana Bioscience GmbH

4:55 An Innovative Biochemical Assay Measures Affinities and Rate Constants of CXCR4-Ligand Binding: New Perspectives for GPCRs as Drug Targets

Manal Chatila, Ph.D., Manager, Strategic Alliance & Business Development, Intana Bioscience

GPCR assay development relies on cellular assays due to solubilization and purification difficulties. Using our fluorescence correlation spectroscopy approach we can bypass these pitfalls and measure Kds and rate constants of GPCR-Ligand interactions and thus allows a comprehensive interaction analysis. Here, we show the establishment of a mix-and-read assay for GFP-labeled CXCR4 as a proof of concept, amenable to extension to other GPCRs

5:25 Coffee Break in the Foyer

5:40 Oral FSH? Discovery of Oral FSHR (Follicle Stimulating Hormone Receptor) Allosteric Modulators

Henry Yu, Ph.D., Head, Medicinal Chemistry, TocopheRx, Inc.

Follicle-stimulating hormone (FSH), acting on its receptor (FSHR), plays a pivotal role in the stimulation of follicular development and maturation. Multiple injections of FSH are used in clinics for ovulation induction and for in-vitro fertilization. An orally bioavailable FSH mimetics would increase patient convenience and compliance. Our effort leading to orally active positive allosteric modulators (PAM) targeting FSHR will be described. We will present SAR, selectivity, DMPK, and efficacy

6:10 Targeting GPCRs for Cardiometabolic Diseases

Brian J. Murphy, Ph.D., Senior Principal Scientist, Fibrosis Drug Discovery, Bristol-Myers Squibb

This presentation spans SAR optimization to our clinical candidate and proof of principle efforts in humans of MCHR1 antagonists for the treatment of obesity. We found that compounds with slow-off rates/long residence times were required for efficacy. This prompted us to develop a FLIPR-based assay to triage off-rates in a medium throughput mode which greatly facilitated compound selection for more detailed kinetic work and *in vivo* testing.

6:40 Close of Day

7:00 Dinner Short Course: Introduction to Allosteric Modulators and Biased Ligands of GPCRs (SC12)*

Michel Bouvier, Ph.D., Professeur, Department of Biochemistry, University of Montréal
Stephan Schann, Ph.D., Head, Research, Domain Therapeutics SA

**Separate registration is required*

GPCR-Targeted Therapeutics

Preclinical and Pharmacological Challenges

FRIDAY, OCTOBER 10

7:30 am Registration

ALLOSTERIC MODULATORS

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

9:00 Chairperson's Remarks

Dario Doller, Ph.D., Director, Discovery Chemistry & DMPK, Lundbeck Research USA

9:10 Complexities in Allosteric Modulation of the mu-Opioid Receptor

John Traynor, Ph.D., Professor of Pharmacology, University of Michigan Medical School

The orthosteric binding site of the opioid mu-receptor (MOPr) is the major target for all clinically used opioid analgesics. We have recently discovered the first positive allosteric modulator (PAM) of MOPr. Identification of MOPr-PAMs provides a new approach to the development of novel analgesic agents. I will discuss the complex probe-dependent nature of the MOPr-PAM activity and the potential mechanism of allosteric modulation.

9:40 Identification of a Novel D1 Dopamine Receptor PAM Binding Site

Jeffrey Brown, Ph.D., Senior Research Investigator II, Department of Experimental Biology and Genomics, Bristol-Myers Squibb

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

FEATURED SESSION: ALLOSTERIC AND BIASED LIGANDS

» 10:55 STRUCTURAL BASIS FOR ALLOSTERIC MODULATION OF GPCRS

Ron Dror, Ph.D., Associate Professor, Computer Science, Stanford University

Using atomic-level simulations, we determined the binding sites and binding modes of multiple allosteric modulators of a muscarinic GPCR. Simulations also revealed mechanisms that contribute to positive and negative allosteric modulation of classical ligand binding. These findings, which we validated experimentally, provide an initial structural basis for the rational design of allosteric GPCR modulators.

» 11:25 IMPACT OF DIVERSE MODES OF EFFICACY ON *IN VIVO* ACTIONS OF ALLOSTERIC MODULATORS OF GPCRS

P. Jeffrey Conn, Ph.D., Professor of Pharmacology, Director, Vanderbilt Center for Neuroscience Drug Discovery

Allosteric modulators of the metabotropic glutamate (mGlu) receptors provide excellent examples of the multiple modes of efficacy that can be achieved with allosteric modulators of GPCRs. The diversity of mGlu allosteric modulators now available are providing fundamental new insights into the impact of stimulus bias, actions on homodimer versus heterodimer forms of the receptors, and unique modes of efficacy of structurally related allosteric modulators.

» 11:55 UNBIASED APPROACHES TO STUDY LIGAND-BIASED SIGNALING AND GPCR FUNCTIONAL SELECTIVITY

Michel Bouvier, Ph.D., Professeur, Department of Biochemistry, University of Montréal

It is now well established that a given GPCR can engage multiple G protein-dependent and independent signaling pathways. This pluri-dimensionality of efficacy gave rise to the concepts of functional selectivity and ligand-biased signaling that open great opportunities for drug discovery but also present important technical challenges. We will discuss the development of BRET-based biosensors as well as label-free approaches that can be used as unbiased means to map the signaling repertoire of G

12:25 pm Novel Melanin-Concentrating Hormone Receptor-1 (MCH1) Antagonists: From Concept to Clinic

Sponsored by AMRI

Pete Guzzo, Ph.D., Director, Drug Discovery, AMRI

Clinical development of drugs for CNS disorders can be a challenging and risky endeavor. In this presentation we look at the steps required to move a preclinical candidate compound into clinical development. We use the case study of ALB-127158(a), an MCH1 receptor antagonist for the treatment of obesity via a central mechanism.

12:40 GPCR Allosteric Compound Selectivity through Large Scale Profiling

Sponsored by eurofins | Discovery Services

Kimberly Italiano, Scientist, Cell-Based Assay Team Lead, Eurofins Discovery Services

One expected advantage of allosteric compounds is a higher degree of selectivity relative to orthosteric compounds. To empirically explore this hypothesis, we profiled twenty-seven different compounds reported to be GPCR allosteric modulators against a panel of over 156 GPCRs using cell based assays to detect agonist, positive allosteric modulation and inhibitory activities.

12:55 Session Break

GPCR-Targeted Therapeutics

Preclinical and Pharmacological Challenges

1:05 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Lunch on Your Own**

1:45 Session Break

GPCR-TARGETED COMPOUNDS FOR COMBATING CNS-RELATED CONDITIONS

1:55 Chairperson's Remarks

John Traynor, Ph.D., Professor of Pharmacology, University of Michigan Medical School

2:00 Structures of the Nociceptin/Orphanin FQ Receptor (NOP/ORL1): Black Sheep of the Opioid Receptor Family

Aaron Thompson, Ph.D., Staff Scientist, Molecular and Cell Biology Department, Scripps Research Institute

Despite high sequence similarity with classical opioid G protein-coupled receptor subtypes, the nociceptin/orphanin FQ (N/OFQ) peptide receptor (NOP/ORL1) displays markedly distinct pharmacology. Crystal structures reveal substantial conformational differences in the orthosteric pocket regions between NOP and the "classical" opioid receptors resulting in the distinct ligand preference. NOP's emerging pharmacore provides a new structural template for the design of novel, selective ligands.

2:30 Targeting a Family B GPCR: CGRP Receptor Antagonists for Migraine

Ian Bell, Ph.D., Principal Scientist, Discovery Chemistry, Merck Research Laboratories

Calcitonin gene-related peptide receptor antagonists (CGRP-RAs) have demonstrated clinical efficacy for acute treatment of migraine. In general, these agents have shown similar clinical responses to triptans with a reduced incidence of adverse events. Interestingly, the precise mechanism of action of CGRP-RAs, in particular whether they act centrally or peripherally, continues to be a matter of debate. Our program to develop novel, orally bioavailable CGRP-RAs and our efforts to elucidate their

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing

3:30 Targeting mGluR4 for Parkinson's Disease

François Conquet, Ph.D., C.E.O., Prexton Therapeutics

One of the major objectives of research into new treatments for Parkinson's disease (PD) is to find alternatives to the stimulation of the dopaminergic system through L-DOPA and dopamine agonists, as long-term use of these established treatments are responsible for severe side effects. Prexton is developing positive allosteric modulators of the metabotropic glutamate receptor mGluR4 for the treatment of motor symptoms of PD.

4:00 Chemical Biology of mGlu4 Receptor Activation: Dogmas, Challenges, Strategies and Opportunities

Dario Doller, Ph.D., Director, Discovery Chemistry & DMPK, Lundbeck Research USA

L-glutamate exerts its physiological functions acting through transmembrane ion channels and G protein-coupled receptors (GPCRs). Progress using allosteric modulators to evaluate the therapeutic potential of mGlu4 receptor activation continues. Our aim is to present a number of reflections on recent developments and unique challenges that point out the singularities in the Chemical Biology of mGlu4 positive allosteric modulators.

4:30 The Signaling of Adhesion GPCR GPR56 in Neural Development and Diseases

Xianhua Piao, M.D., Ph.D., Assistant Professor of Pediatrics, Children's Hospital Boston, Harvard Medical School

Being a family of noncanonical seven transmembrane spanning (7TM) receptors, adhesion GPCRs have an exceptionally long extracellular N-terminal region and juxtamembrane GPCR autoproteolysis-inducing (GAIN) domain. Most adhesion GPCRs undergo GAIN domain-mediated autoproteolytic process at the GPCR proteolysis site (GPS) to generate an N- and a C-terminal fragment. GPR56, a member of adhesion GPCRs family, plays an important role in neural development and diseases. Identification and Characterization of GPR56 endogenous ligand(s) pave the way for future drug discovery.

5:00 Close of Conference

11th Annual

October 9 - 10, 2014

Genome Editing for Functional Genomics Screens - Part 2

Exploring CRISPRs and New Cellular Models For Next-Generation Screens

Cambridge Healthtech Institute's conference on Genome Editing for Functional Genomics Screens will bring together experts to try and figure out how and where genome editing can be best applied in functional screening. What are the different tools and reagents that can be used, and based on those choices what are the downstream challenges encountered with assay design and data analysis? What are the strengths and limitations of CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) -based screens, when compared to siRNA and shRNA screens? Can some of the lessons learned from the early days of RNAi screening, help with setting up these newer screens?

Suggested Event Package

October 7 Short Course: Setting Up Effective RNAi Screens
October 7 Short Course: A Primer to Gene Editing
October 8-9 Conference: RNAi for Functional Genomics Screening
October 9-10 Conference: Genome Editing for Functional Genomics Screens
October 9 Dinner Course: Setting Up Effective Functional Screens Using 3D Cell Cultures

THURSDAY, OCTOBER 9

11:30 am Registration

1:00 pm Plenary Keynote Session *(see website for details)*

2:45 Refreshment Break in the Exhibit Hall with Poster Viewing

NON-CODING RNA SCREENS: AN UNKNOWN FRONTIER

3:45 Chairperson's Opening Remarks

Christophe Echeverri, Ph.D., CEO & CSO, Cenix BioScience USA, Inc.

3:55 Using ncRNAs to Identify Cancer Cell Vulnerabilities

Alexander Pertsemlidis, Ph.D., Associate Professor, Greehey Children's Cancer Research Institute, University of Texas Health Science Center at San Antonio

In an unbiased and comprehensive approach, we have combined a high-throughput screening platform with a library of inhibitors of short and long non-coding RNAs. We use this platform to identify ncRNAs that reduce cell viability and specifically sensitize cells to microtubule-targeting agents. Regulatory targets of candidate ncRNAs are identified and the response of cancer cells to perturbations in ncRNA levels are assessed through a combination of *in vitro*, *in silico* and *in vivo* approaches.

4:25 First Screens Using a LncRNA siRNA Library: Shedding Some Light on the Dark Matter of the Transcriptome

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

Recently, commercial RNAi libraries have become available to target long non-coding RNAs. Using screening results of one of these libraries in several assays that we have previously interrogated using a conventional library, we can begin to compare frequencies of detection for coding versus non-coding siRNA libraries. We will discuss the implications of these results for the functional activity of lncRNAs and the cost/benefit of screening for functional members of this class of genes.

4:55 Sensor-Based shRNA-mir Reagents for More Effective RNAi Screens

Sponsored by transOMIC technologies

Gwen D. Fewell, Ph.D., Co-Founder & Chief Commercial Officer, transOMIC

New shERWOOD algorithm, based on a high throughput sensor assay, provides potent shRNA designs for single copy gene-knockdown. When combined with an improved microRNA scaffold, this algorithm provides consistently effective shRNAs, making hit analysis in multiplexed RNAi screens more straightforward. Here we present the advantages of employing next generation shRNA libraries, designed using these strategies, in gene knockdown assays including multiplexed RNAi screens.

5:25 Coffee Break in the Foyer

5:40 TECHNOLOGY PANEL: Tools for Next-Generation Functional Genomics Screens

Moderator: Christophe Echeverri, Ph.D., CEO & CSO, Cenix BioScience USA, Inc.

Panelists:

Paul Diehl, Ph.D., Director, Business Development, Cellecta, Inc.

Gwen D. Fewell, Ph.D., Chief Commercial Officer, TransOMIC Technologies, Inc.

Alex Amiet, Senior Product Manager, Dharmacon, part of GE Healthcare

Nitin Puri, Ph.D., Associate Director, Product Management, Gene Silencing & Gene Editing, Life Technologies, Brand of Thermo Fisher

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

(Opportunities Available for Sponsoring Panelists)

Topics to be covered:

-For what types of applications will emerging CRISPR-Cas9 capabilities replace RNAi, as opposed to complementing it?

-What efforts are being made to update RNAi reagents to help users tackle off-target effects?

-To what degree are vendors making efforts to address the risk of off-target effects with CRISPR-Cas9 reagents?

-Are there plans to build and offer genome-scale CRISPR-Cas9 libraries only for pooled, selection-based screening or also for arrayed screening?

6:40 Close of Day

FRIDAY, OCTOBER 10

7:30 am Registration

shRNA AND CRISPR SCREENS: COMPETING OR COMPLEMENTING?

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

9:00 Chairperson's Remarks
Ralph J. Garippa, Ph.D., Director, RNAi Core Facility, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center

9:10 Creating a State-of-the-Art Pipeline for RNAi and Gene Editing in an Academic Setting
Ralph J. Garippa, Ph.D., Director, RNAi Core Facility, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center
As a multi-faceted core lab, we have instituted a broad genomics platform to address biological questions using the tools of RNAi interference and gene editing via the CRISPR-Cas9 system. Screening is offered in both pooled and arrayed formats, with subsequent readouts via HCS, HTS, FACS or NGS deconvolution. Here we present a series of case studies highlighting the flexible utility of this platform, and innovative methodologies to improve and enhance interpretation of RNAi screening results.

9:40 Exploring the Secretory Pathway Using ER-Trafficking Toxins, High-Complexity shRNA Libraries, and Genetic Interaction Maps
Michael Bassik, Ph.D., Assistant Professor, Department of Genetics, Stanford University
We have developed high-complexity shRNA libraries (25 shRNAs/gene) that greatly reduce false negatives/false positives for RNAi screens, and have adapted these libraries to knock down gene pairs to perform systematic genetic interaction maps in mammalian cells. We are using this strategy for functional genomics efforts and identification of novel drug targets, and are continuing to develop our screening platform using the CRISPR/Cas9 system.

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

UTILIZING CRISPR/Cas9 FOR FUNCTIONAL SCREENING

» 10:55 FEATURED PRESENTATION: ANALYSES OF SIGNALING NETWORKS IN DROSOPHILA
Norbert Perrimon, Ph.D., Professor, Department of Genetics, Harvard Medical School and Investigator, Howard Hughes Medical Institute
I will describe how our laboratory is applying the tools of CRISPR genome engineering to analyze the structure and spatio-temporal regulation of signaling pathways both in tissue culture cells and *in vivo*.

» 11:25 FEATURED PRESENTATION: DEVELOPMENTS IN MAMMALIAN FUNCTIONAL GENOMICS TOOLS AND APPLICATIONS
David Root, Ph.D., Director, RNAi Platform and Project Leader, The RNAi Consortium, The Broad Institute of MIT and Harvard

11:55 EXPERT PANEL: How to Best Utilize Gene Editing for Functional Genomics Screens
Moderator: Christophe Echeverri, Ph.D., CEO & CSO, Cenix BioScience USA, Inc.
Panelist:
Norbert Perrimon, Ph.D., Professor, Genetics, Harvard Medical School and Investigator, Howard Hughes Medical Institute
David Root, Ph.D., Director, RNAi Platform and Project Leader, The RNAi Consortium, The Broad Institute of MIT and Harvard
David Bumcrot, Ph.D., Senior Director, Molecular and Cell Biology, Editas Medicine

12:25 pm Driving Integrated Solutions for Functional Genomics – CRISPRs, TALENs and RNAi
Sponsored by life technologies
Nitin Puri, Ph.D., Associate Director, Product Management, Gene Silencing & Gene Editing, Life Technologies, Brand of Thermo Fisher
CRISPR technology has revolutionized functional genomics and how the field is approaching discovery to validation of novel drug targets. In this highlight, we will share efforts for a holistic approach in adoption of this technology along with TALENs and RNAi.

12:40 Rewriting the Genome: Gene Construction and Genome Modification with gBlocks® Gene Fragments
Sponsored by IDT
Adam Clore, Ph.D., Manager, Synthetic Biology Design, Integrated DNA Technologies
The development of the CRISPR/CAS9 system in conjunction with rapid and inexpensive DNA synthesis and Fragment construction has created opportunities in genome design and manipulation on an unprecedented scale. This talk will describe proven methods to create gene deletions, insertions, and modulation of gene regulation using gBlocks® Gene Fragments with CRISPR/CAS9 systems.

Genome Editing for Functional Genomics Screens - Part 2

Exploring CRISPRs and New Cellular Models For Next-Generation Screens

12:55 Session Break

1:05 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Lunch on Your Own**

1:45 Session Break

EXPLORING THE DIVERSITY OF GENE EDITING

1:55 Chairperson's Remarks

2:00 Genome-Scale CRISPR Knock-Out Screen in Human Cancer and Stem Cells

Neville Sanjana, Ph.D., Simons Postdoctoral Fellow, Laboratory of Dr. Feng Zhang, Broad Institute and the Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology

The simplicity of programming the CRISPR/ Cas9 to modify specific genomic loci suggests a new way to interrogate gene function on a genome-wide scale. We show that lentiviral delivery of a genome-scale CRISPR-Cas9 knockout (GeCKO) library targeting 18,080 human genes enables both negative and positive selection. When compared to shRNA knock-down, CRISPR reagents are more consistent in their ability to knock-out (not knock-down) genes, resulting in a greater number of validated hits.

2:30 Functional Genomics, Genomics and Clinical Need: The Successful Output of Large Genetic Screens for Novel Treatment Combinations

Roderick Beijersbergen, Ph.D., Group Leader, Division of Molecular Carcinogenesis, The Netherlands Cancer Institute

Several screening technologies exist that allow for large scale perturbation of gene expression in mammalian cells including siRNA, shRNA, gene traps and CRISPR based gene editing. In particular, pooled screening approaches have been applied widely to identify genes that are lethal under specific circumstances, e.g. in combination with a drug treatment or only in the context of disease specific genetic alterations. We will discuss the challenges associated with these efforts, their performance and their power in the identification of novel treatment combinations.

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing

3:30 Functional Human Genetics through Genome Editing in Human Embryonic Stem Cells

Danwei Huangfu, Ph.D., Assistant Professor, Developmental Biology, Memorial Sloan-Kettering Cancer Center

Through applying TALENs and CRISPRs to human embryonic stem cells (hESCs), we have generated knockout hESCs for 8 of the 10 neonatal diabetes-associate transcription factors identified to date. Mutations in these genes may also contribute to juvenile and adult onset diabetes. Through directed differentiation of these mutant hESCs, our studies are beginning to shed light on both conserved and human-specific mechanisms of pancreatic development and neonatal diabetes.

4:00 A Computational Algorithm to Predict shRNA Potency

Simon Knott, Ph.D., Postdoctoral Fellow, Howard Hughes Medical Institute, Cold Spring Harbor Laboratory

To date, no established method has emerged to identify effective shRNAs. Using a multiplexed assay we have generated over ~250,000 shRNA efficacy data points. Using these data, we developed shERWOOD, an algorithm capable of predicting, for any shRNA, the likelihood that it will elicit potent target knockdown. Combined with additional shRNA design strategies, shERWOOD allows the ab initio identification of potent shRNAs that target, the majority of each gene's multiple transcripts.

4:30 Phenotypic Screening: Opportunities and Challenges

Jing Li, Ph.D., Director, Genomics and Phenotypic Screening, Merck Research Laboratories

In the first-in-class drug category, phenotypic screens have yielded more approved drugs than target-centric approach during 1999-2008. The lack of chemistry support and the immaturity of technologiess for protein target identification have contributed to the low success rate for phenotypic screens. Recent advances in affinity capture, quantitative mass spectrometry, and chemoinformatics greatly improve the identification of underlying protein targets. With the lessons learnt, the possibility of successfully applying phenotypic screens in drug discovery can improve significantly.

5:00 Close of Conference

Cancer Metabolism

Emerging Targets for Combating Cancer

Inhibition of glycolytic energy production is providing the framework for the discovery of new anti-cancer compounds. This meeting will cover the progress of therapeutic agents against these newer cancer targets, discuss the latest findings that are influencing their development and highlight newer metabolism-related cancer targets.

Suggested Event Package
October 7 Short Course: Targeting Protein-Protein Interactions
October 7 Short Course: Introduction to Targeted Covalent Inhibitors
October 8-9 Conference: Protein-Protein Interactions as Drug Targets
October 9-10 Conference: Cancer Metabolism
October 9 Dinner Course: Integration of BDDCS and Extended Clearance Principles for Understanding Disposition and ADME Liabilities

THURSDAY, OCTOBER 9

11:30 am Registration

1:00 pm Plenary Keynote Session *(see website for details)*

2:45 Refreshment Break in the Exhibit Hall with Poster Viewing

ONCO-METABOLIC CANDIDATES IN DEVELOPMENT

3:45 Chairperson's Opening Remarks
Marcia Haigis, Ph.D., Associate Professor, Department of Cell Biology, Harvard Medical School

» 3:55 FEATURED PRESENTATION: DRUGGING MUTANT IDH AT THE CROSSROADS OF CANCER AND 2HG ACIDURIA
Lenny Dang, Ph.D., Senior Director, Biochemistry, Agios Pharmaceuticals, Inc.
We previously demonstrated recurrent IDH mutations found in low-grade glioma, AML and cholangiocarcinoma produce the oncometabolite 2-hydroxyglutarate (2HG) leading to impaired histone methylation and a block in differentiation. Interestingly, D-2HG is also pathogenic for the rare and devastating D-2HG aciduria. We have developed selective potent inhibitors against mutant IDH1 & IDH2 for the treatment of 2HG-driven diseases. These drug candidates have just entered clinical trials.

4:25 Inhibition of Glucose Uptake by PFK-158, a Novel Anti-Cancer Agent
Gilles Tapolsky, Ph.D., CSO, Advanced Cancer Therapeutics

4:55 Challenges and Insights for Monitoring and Measuring Cancer Metabolomics
Sponsored by HMT Human Metabolome Technologies America, Inc.
Alexander M. Buko, Ph.D., Vice President, Business and Product Development, Human Metabolome Technologies America
Cancer is a disease that is frequently defined by an altered cellular metabolism, therefore, metabolomics can play a major role in early detection and diagnosis and in the evaluation of medical interventions and therapies. HMT performs quantitative metabolite profiling in combination with statistical informatics and pathway analysis to perform metabolite measurements and biomarker discovery. We will discuss HMT applications in Pre-clinical and Clinical studies.

5:25 Coffee Break in the Foyer

5:40 CPI-613's Two-Pronged Attack on Glucose Metabolism and Tumor Growth
Paul Bingham, Ph.D., Associate Professor, Department of Biochemistry and Cell Biology, Stony Brook University and Vice President Research, Cornerstone Pharmaceuticals
Attacking altered mitochondrial metabolism is a potent approach to cancer chemotherapy. Lipoate plays a central role in regulating tumor-specific mitochondrial energy flows. We have pioneered the use of lipoate analogs to target tumor metabolism with power and selectivity. I will discuss new progress in understanding both the fundamental mechanism of action and the clinical performance of these first-in-class agents.

6:10 Discovery and Development of CB-839, a Glutaminase Inhibitor that Targets Tumor-Specific Metabolism
Francesco Parlati, Ph.D., Director, Department of Biology, Calithera Biosciences

6:40 Close of Day

FRIDAY, OCTOBER 10

7:30 am Registration

CELLULAR METABOLISM AND CANCER TARGETS

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

9:00 Chairperson's Remarks
Francesco Parlati, Ph.D., Director, Department of Biology, Calithera Biosciences

9:10 New Insights in Tumor Metabolism: Lessons Learned from Sirtuins
Marcia Haigis, Ph.D., Associate Professor, Department of Cell Biology, Harvard Medical School
Tumor cells redirect metabolism of fuels in order to meet their demands for energy, stress responses and generation of anabolic metabolites needed for rapid proliferation. Understanding how mitochondria contribute to tumorigenesis

and emerging therapeutic resistance is a major focus in cancer biology. Mitochondrial sirtuins are NAD-dependent enzymes that post-translationally modify enzymes involved in metabolism and stress responses. Here we will discuss how mitochondrial acetylation impacts cell survival and growth. A better understanding of sirtuin-mediated regulation may identify novel ways to therapeutically target diseases associated with aging, such as cancer.

9:40 Metabolic Regulation of Stem-like Cancer Cells through AKT Activation and Therapeutic Implications

Peng Huang, M.D., Ph.D., Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center

This presentation will focus on the regulation of stem-like cancer cells (side population, or SP cells) by glucose, a key metabolic substrate in generation of cellular energy and metabolic intermediates for cell proliferation. The potential mechanisms involved in this metabolic regulation of SP cells will be discussed. A potential therapeutic strategy to target this process and kill cancer stem cells will also be presented.

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

10:55 Identifying Metabolic Dependencies in Pancreatic Cancer

Alec Kimmelman, M.D., Ph.D., Assistant Professor, Dana Farber Cancer Institute, Harvard Medical School

Our work has shown that pancreatic cancers have an altered cellular metabolism. We have demonstrated that in many cases, oncogenic Kras plays a key role in regulating the metabolism of this tumor type. Importantly, several of these metabolic pathways are critical for tumor growth and therefore represent potential therapeutic targets. These and other aspects of pancreatic cancer metabolism will be discussed.

11:25 Cell Cycle Regulators Link Metabolism and Proliferation in Cancer Cells

Lluis Fajas, Ph.D., Professor and Director, Physiology, University of Lausanne

Analysis of genetically engineered mice deficient for cell cycle regulators, including E2F1, cdk4, or, pRB showed that the major phenotypes are metabolic perturbations. We proved that these key cell cycle regulators contribute to lipid synthesis, glucose production, insulin secretion, and oxidative metabolism and how deregulation of those pathways can lead to metabolic perturbations. These examples illustrate the growing notion that cell cycle regulatory proteins can also modulate metabolic processes.

11:55 mTOR/S6K Pathway-Dependent Metabolic Reprogramming in Cancer Cells Mediates Resistance to Glycolytic Inhibitors

Raju Pusapati, Ph.D., Postdoctoral Research Fellow, Discovery Oncology (Jeff Settleman Lab), Genentech, Inc.

Although the targeting of "glycolytic addiction" offers tremendous potential in cancer therapy, it has not been successful in the clinic thus far. Our work attempts at understanding the underlying mechanisms by which cancer cells escape glycolytic dependency. Employing a combination of metabolomic and biochemical approaches we tease out the metabolic and signaling pathways that underlie cancer cell resistance to glycolytic drugs.

12:25 pm Metabolic Reprogramming of Myc- dependencies by a Histone Demethylase Inhibitor

Udo Oppermann, Ph.D., Professor and Principal Investigator, Structural Genomics Consortium, Oxford University

The reversible N-epsilon methylation of lysyl residues in chromatin proteins plays an important role in gene regulation and chromatin stability. Here we show that a recently developed histone demethylase inhibitor induces specific pro-apoptotic signatures and stress responses in Myc-dependent malignancies which is caused by a metabolic reprogramming of cancer cells.

12:55 Session Break

1:05 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Lunch on Your Own**

1:45 Session Break

METABOLISM, METASTASIS, MITOCHONDRIA, MORE TARGETS

1:55 Chairperson's Remarks

Raju Pusapati, Ph.D., Post-Doctoral Research Fellow, Discovery Oncology (Jeff Settleman Lab), Genentech, Inc.

2:00 Mitochondrial Complex 1 Dysfunction and Cancer

Ivana Kurelac, Ph.D., Postdoctoral Fellow, Genetics Unit, University of Bologna

Respiratory complex I (CI) has shown to be essential for the induction of Warburg effect and adaptation to hypoxia of cancer cells, allowing them to sustain tumor growth. The mechanistic link between CI and Warburg effect will be discussed, together with how different CI defects may lead to opposite effects on tumor growth, introducing thus a novel cancer gene definition of oncojanus.

2:30 Targeting Energy Metabolism for Brain Cancer

Purna Mukherjee, Ph.D., Research Assistant Professor, Department of Biology, Boston College

Emerging evidence indicates that cancer is primarily a metabolic disease arising from defects in cell mitochondria. In contrast to normal neurons and glia, which transition to ketone bodies for respiratory energy when glucose levels are reduced, malignant brain tumors are mostly dependent on non-oxidative substrate level phosphorylation. We propose a different approach to brain cancer management that exploits the metabolic flexibility of normal cells at the expense of the genetically defective a

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing

3:30 Physiological and Oncogenic Regulation of Nucleotide Biosynthesis

Issam Ben-Sahra, Ph.D., Senior Fellow, Laboratory of Brendan Manning, Oncology, Harvard Medical School

The mechanistic target of rapamycin (mTOR), as part of mTORC1, is a protein kinase that senses growth signals to regulate anabolic growth and proliferation. We found that activation of mTORC1 leads to the acute stimulation of metabolic flux through the *de novo*pyrimidine synthesis pathway. I will discuss a new mechanism of regulation of nucleotide synthesis by mTORC1 signaling in response to growth and oncogenic signals.

4:00 Serine Catabolism and Mitochondrial Redox Control

Jiangbin Ye, Ph.D., Research Scholar, Thompson Lab, Memorial Sloan-Kettering Cancer Center

The *de novo* synthesis of the non-essential amino acid serine is often upregulated in cancer. We demonstrate that mitochondrial serine hydroxymethyltransferase (SHMT2) is induced when Myc-transformed cells are subjected to hypoxia. In mitochondria, SHMT2 can initiate the catabolism of serine, resulting in net production of NADPH, which is critical for maintaining redox balance and cell survival under hypoxia.

4:30 New Inhibitors for Lactate Dehydrogenase A

Marie Evangelista, Ph.D., Scientist, Discovery Oncology, Genentech Inc.

GNE-140 is a novel small molecule inhibitor targeting LDHA, an enzyme which catalyzes the conversion of pyruvate to lactate in the last step of glycolysis. Pharmacogenomic profiling of ~400 tumor cell lines with GNE-140 identified subsets (~15%) of glycolytically-dependent cell lines. Despite the metabolic plasticity of cells, the timing of acquired resistance to GNE-140 was comparable with other targeted agents. Under long-term treatment with GNE-140, glycolytic cells acquired resistance by increased oxidative phosporylation (OX-PHOS) in a mechanism dependent on the AMPK stress response pathway; targeting either AMPK, downstream kinases, or OX-PHOS using tool compounds synergized with and prevented acquired resistance to GNE-140. Our data suggests that targeting aerobic glycolysis may benefit a subset of patients and that combinations with agents that block AMPK signaling or the mitochondria will be effective at delaying tumor relapse.

5:00 Close of Conference

Second Annual

October 9 - 10, 2014

Antibodies Against Membrane Protein Targets - Part 2

Generation, Preparation and Selection of Membrane Protein Targets

The two-part Antibodies Against Membrane Protein Targets provides a forum in which discovery biologists and protein engineers can come together to discuss next generation strategies and technologies that will allow antibody-and alternate scaffold-based therapeutics directed against these target families to advance into the clinic and beyond. The second conference, Generation, Preparation and Selection of Membrane Protein Targets, explores approaches to generating antigens of sufficient quality and purity to enable structural and modeling studies of target engagement and the associated screening and selection strategies used to isolate high-quality binders.

Suggested Event Package

October 7 Short Course: Targeting of GPCRs with Monoclonal Antibodies

October 8-9 Conference: Antibodies Against Membrane Protein Targets – Part 1

October 9-10 Conference: Antibodies Against Membrane Protein Targets – Part 2

THURSDAY, OCTOBER 9

11:30 am Registration

1:00 pm Plenary Keynote Session *(see website for details)*

2:45 Refreshment Break in the Exhibit Hall with Poster Viewing

GENERATION OF FUNCTIONAL MEMBRANE PROTEINS

3:45 Chairperson's Opening Remarks

Christopher Koth, Ph.D., Senior Scientist, Structural Biology, Genentech

3:55 Why VLPs for Generating Biologics to Cell Surface Proteins?

Mark Tornetta, Ph.D., Scientist, Molecular Discovery Technologies, Janssen Pharmaceuticals

Viral lipoparticles (VLP) present a great means to display cell surface targets. VLPs are either viruses or non-replicating viral particles. They contain the host cell's membrane by way of budding, there in which the ability to capture the target protein in its natural conformation. This presentation will discuss VLPs as a format of 'target display' within the process of generating biological molecules to cell surface proteins.

4:25 High-Throughput Platforms for Expression of Bacterial and Eukaryotic Membrane Proteins

Renato Bruni, Ph.D., Head, Eukaryotic Membrane Protein Expression, New York Structural Biology Center

We describe here recent developments of two HTP platforms for the cloning and expression of integral membrane proteins. In the first one, prokaryotic membrane proteins are expressed in E.coli using a variety of expression vectors, growth conditions and purification methods. The second platform was developed for eukaryotic membrane proteins using mammalian cells for screening by fluorescence-detection size-exclusion chromatography and insect cells for expression and purification.

4:55 Creating Focused Mutant Libraries for Protein Engineering

Sponsored by CHEMICAL COMPUTING GROUP

Michael Drummond, Ph.D., Applications Scientist, Chemical Computing Group

In protein engineering, efficient search and evaluation of excessively large sequence design space is challenging and requires multiple experimental rounds. Here we have developed a computational approach which predicts mutation probabilities for given residue sites in specified sequences. In assessing the probabilities at given residue sites, the sequence search space can be efficiently sampled to design and produce focused mutant libraries.

5:25 Coffee Break in the Foyer

5:40 Development of Engineered Crystallization Chaperones to Promote Membrane Protein Crystallization

Raquel Lieberman, Ph.D., Associate Professor, School of Chemistry & Biochemistry, Georgia Institute of Technology

We are developing for cost-effective non-covalent crystallization chaperones for membrane protein (MP) crystallization. The method is generalizable through insertion of a short epitope into a surface-exposed loop of a MP by site directed mutagenesis. Complexation and crystallization trials of representative chaperone-MP complexes are currently underway. In the long term, we hope these approaches will aid the community in solving structures of MPs of interest.

6:10 Optimization of Channels and Receptors for High-Throughput Screening and Antibody Development

Susmith Mukund, Senior Research Associate, Genentech

Membrane proteins are therapeutic targets for many diseases but are generally very difficult to express and purify. Considerable optimization is often required for downstream applications such as assay development, functional antibody screening and structural studies. This talk will provide a practical perspective on how to generate suitable purified membrane protein reagents in a drug development environment. Consensus 'first-pass' techniques for ion channel and receptor targets will be discussed, where functional antibodies or small molecule drugs are the desired outcome.

6:40 Close of Day

FRIDAY, OCTOBER 10

7:30 am Registration

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

PREPARATION OF MEMBRANE PROTEINS FOR ANTIBODY PRODUCTION

9:00 Chairperson's Remarks

9:10 Using Purified Membrane Proteins for Antibody Development: When and How
Christopher Koth, Ph.D., Senior Scientist, Structural Biology, Genentech

9:40 Stabilizing Membrane Protein and Membrane Protein Complex on Analytical Surface
Rick Chu, Ph.D., Lead Research Investigator, Genzyme
Traditionally, membrane protein binding assays rely on utilizing radioactive labeled ligands. In order to simplify membrane protein kinetics binding assay, purified membrane proteins, such as G-protein-coupled receptors (GPCRs), are captured on analytical surfaces and further stabilized by limited chemical crosslinking. This limited chemical crosslinking enables high quality label-free kinetics assays of membrane proteins via the same methods that are conventionally used for soluble proteins.

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

10:55 Challenges of Membrane Proteins Antigen Production for Antibody Generation
Ramkrishna (Ramu) Sadhukhan, Ph.D,. Senior Group Leader, Global Biologics, AbbVie

ASSAYS FOR DEVELOPING MABS AGAINST MEMBRANE PROTEIN TARGETS

11:25 Therapeutic Monoclonal Antibodies Targeting APJ Receptor
Krzysztof Palczewski, Ph.D., John H. Hord Professor and Chair, Department of Pharmacology, School of Medicine, Case Western Reserve University
The apelin receptor (APJ) is a G protein-coupled receptor (GPCR) widely expressed in various tissues, and it is associated with cardiovascular diseases and metabolic syndrome. A short peptide apelin is the only known APJ ligand, is rapidly degraded, and stable APJ agonists and antagonists with therapeutic potential are urgently needed. Monoclonal antibodies provide an attractive alternative strategy for targeting APJ therapeutically because they have significantly stability and high specificity. A strategy and molecular assays will be discussed toward developing therapeutically active mAb.

11:55 Characterization of a Nanobody Library Against Cannabinoid Receptor CB2
Alexei Yeliseev, Ph.D., Staff Scientist, Protein Biochemistry, LMBB, NIH
Cannabinoid receptor CB2 has become a prominent target for pharmaceutical drug development. We expressed and purified a full-length functional CB2, and optimized its stabilization in detergent micelles and lipid bilayers in a form of proteoliposomes and nanodiscs. A library of functional fold-specific camelid antibody fragments (nanobodies) was created, and their interaction with the receptor characterized by ELISA, G protein-activation assay, as well as by surface plasmon resonance and biolayer interferometry.

12:25 pm High-Throughput Microfluidic Platform for Functional Antibody Screening from Single Cells
Sponsored by AbCellera
Carl L. Hansen, Ph.D., President & CEO, AbCellera Biologics Inc.
AbCellera has developed a microfluidic-based platform for the high-throughput selection of monoclonal antibodies from single cells. This technology enables direct screening and characterization of antibody-secreting cells from any species using binding and functional cellular assays at a throughput of 400,000 cells per run.

12:55 Session Break

1:05 Luncheon Presentation - Discovery of Rare Antibody Specificities to Difficult Targets Using High Content Screening of Avian Repertoires
Sponsored by Crystal Bioscience
Bill Harriman, Ph.D., CSO, Crystal Bioscience
Chickens are known to generate antibodies to epitopes on therapeutic targets that are highly conserved amongst mammals. These antibodies often demonstrate reactivity across multiple species, and are preferred when rodent or primate models of disease are anticipated. Using alternative immunization strategies we can enhance the prevalence of such clones, and by evaluating antibody profiles through a multi-parameter GEM screen of primary B cells, we can efficiently recover antibodies with desired biological activity and/or multispecies cross-reactivity.

1:45 Session Break

ANTIBODY GENERATION, SELECTION AND SCREENING

1:55 Chairperson's Remarks
Ralph Minter, Ph.D., Fellow, Technology, Antibody Discovery and Protein Engineering MedImmune, United Kingdom

Antibodies Against Membrane Protein Targets - Part 2

Generation, Preparation and Selection of Membrane Protein Targets

2:00 Innovative Methods for the Generation of Nanobodies against Membrane Proteins

Jan Steyaert, Ph.D., Department Head, Structural Biology, Vrije University Brussels, Belgium

By rigidifying flexible regions and obscuring aggregative surfaces, nanobody complexes warrant conformationally uniform samples that are key to protein structure determination by X-ray crystallography. The elucidation of the first GPCR structure in its active state using a conformationally selective Nanobody demonstrates the power of the Nanobody platform to generate diffracting quality crystals of the most challenging targets including membrane proteins, and their complexes.

2:30 Fluorescent Approaches for Screening and Characterizing Ligand and Antibody Binding to Membrane Proteins and Surface-Displayed Proteins in Yeast

Mark E. Dumont, Ph.D., Professor, Biochemistry & Biophysics, University of Rochester Medical Center

The genetic manipulability of yeast, coupled with genetic screening via flow cytometry, provides a powerful way of isolating rare variants with desired phenotypes from randomized libraries. We have used this approach to identify mutations of the endogenous yeast G protein coupled receptor Ste2p that specifically affect ligand binding, oligomeric state, and protein stability. We are also screening HIV envelope glycoprotein expressed at the yeast cell surface for variants exhibiting optimized antibody binding for vaccine development.

3:30 Activity-Based Screening of Antibodies to Cell Surface Targets

Ralph Minter, Ph.D., Fellow, Technology, Antibody Discovery and Protein Engineering MedImmune, United Kingdom

Target-led drug discovery is associated with a high attrition rate and also a high level of competition on each target. Our approach is to perform target-agnostic enrichment of antibodies on cells of interest and then to screen these antibodies for activity, prior to determining the target antigen. By following this phenotypic screening approach we have isolated many antibodies to novel disease-relevant targets, some of which will be described in more detail.

4:00 Single Domain Antibodies Against GPCRs and Ion Channels

Mick Foley, Ph.D., CSO, Biochemistry, AdAlta, Australia

The i-body is a human scaffold derived from information gained from the structure of the shark single domain antibody. The presence of a long CDR3 enables better access to GPCRs and ion channels than monoclonal antibodies. We have obtained high affinity single domain antibodies specific for the chemokine receptor CXCR4 that modulate β-arrestin signaling and block HIV infection. Binders to another GPCR LPA-1 and the ion channel TrpV4 have also been identified.

4:30 Close of Conference

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

Exhibit

Exhibitors will enjoy facilitated networking opportunities with qualified delegates, making it the perfect platform to launch a new product, collect feedback, and generate new leads. Exhibit space sells out quickly, so reserve yours today!

Additional branding and promotional opportunities are available, including:

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

For additional sponsorship & exhibit information, please contact:

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

Click Here to Register Online!
DiscoveryOnTarget.com

HOTEL & TRAVEL INFORMATION

Conference Venue and Host Hotel
Westin Boston Waterfront
425 Summer St.
Boston, MA 02210
T:617-532-4600
westinbostonwaterfront.com

Room Rate: $269 s/d
Reservation Cutoff: September 8, 2014

Click here or call the hotel directly to reserve your sleeping accommodations. You will need to identify yourself as a Cambridge Healthtech Institute conference attendee to receive the discounted room rate with the host hotel. Reservations made after the cut-off date or after the group room block has been filled (whichever comes first) will be accepted at the descretion of the hotel. Rooms are limited, so please book early.

We understand that you have many choices when making your travel arrangements, and may ultimately decide to stay at another hotel. Please understand that reserving your room in the CHI room block allows you to take full advantage of the conference sessions, events and networking opportunities, and ensures that our staff will be available to help should you have any issues with your accommodations.

Flight Discounts:
Special discounts have been established with American Airlines for this conference.

- Call American Airlines 800-433-1790 and use Conference code 23H4BR.
- Go to aa.com/group and enter Conference code 23H4BR in promotion discount box.
- Contact our designated travel agent, Rona Meizler, at 617-559-3735 or rona.meizler@protravelinc.com

Car Rental Discounts:
Special discount rentals have been established with Hertz for this conference.

- Please call HERTZ, 800-654-3131 use our Hertz Convention Number (CV): 04KL0005- Click here and use our Hertz Convention Number (CV): 04KL0005

Public Transportation information is available here.
Driving Directions are available here.

Top Reasons to Stay at the Westin Boston Waterfront Hotel

- Take advantage of the deeply discounted $269 group rate!
- No Commute, since meeting takes place at hotel
- Lots of new restaurants within walking distances. Waterfront is the up and coming area of Boston!
- Complimentary wireless internet access in guest rooms

Click Here to Register Online!
DiscoveryOnTarget.com

CONFERENCE PRICING

STANDARD PACKAGE (Includes access to 2 conferences, excludes short courses)	**Commercial**	**Academic, Government, Hospital-affiliated**
Special Registration Discount until October 3, 2014	$2409	$1199
Registrations after October 3, 2014, and on-site	$2709	$1299
SINGLE CONFERENCE PRICING (Includes access to 1 conferences, excludes short courses)		
Special Registration Discount until October 3, 2014	$1599	$875
Registrations after October 3, 2014, and on-site	$1799	$975
ALL ACCESS (Includes access to 2 Short Courses or 1 Symposium and 2 conferences)		
Special Registration Discount until October 3, 2014	$3099	$1799
Registrations after October 3, 2014, and on-site	$3199	$1899

October 8-9	October 9-10
1A: Targeting Epigenetic Readers and Chromatin Remodelers	1B: Targeting Histone Methyltransferases and Demethylases
2A: Targeting the Ubiquitin Proteasome System	2B: Screening Drug Transporter Proteins
3A: Big Data Analytics and Solutions	3B: Maximizing Efficiency in Discovery
4A: GPCR-Based Drug Discovery	4B: GPCR-Targeted Therapeutics
5A: RNAi for Functional Genomics Screening – Part 1	5B: Genome Editing for Functional Genomics Screens – Part 2
6A: Protein-Protein Interactions as Drug Targets	6B: Cancer Metabolism
7A: Antibodies Against Membrane Protein Targets – Part 1	7B: Antibodies Against Membrane Protein Targets – Part 2

SYMPOSIUM PRICING

Next-Generation Histone Deacetylase Inhibitors	$999	$699

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	$1199	$899

Tuesday, October 7	
8:00 am - 11:00 am	~~SC1: Designing Scalable Software Systems for Big Data Analytics~~
12:00 pm - 3:00 pm	SC2: Approaches for Biologically-Relevant Chemical Diversity
	SC3: Setting Up Effective RNAi Screens: From Design to Data to Validation
	SC4: Targeting Protein-Protein Interactions
	SC5: GPCR Structure-Based Drug Discovery
3:45 pm - 6:45 pm	~~SC6: Advances in Metagenomic Drug Discovery for New Anti-Infective Agents~~
	SC7: Targeting of GPCRs with Monoclonal Antibodies
	SC8: A Primer to Gene Editing: Tools and Applications
	SC9: Introduction to Targeted Covalent Inhibitors

Thursday, October 9 | 7:00 pm - 10:00 pm (Dinner provided)
SC10: Setting Up Effective Functional Screens Using 3D Cell Cultures
~~SC11: Integration of BDDCS and Extended Clearance Principles for Understanding Disposition and ADME Liabilities~~
SC12: Introduction to Allosteric Modulators and Biased Ligands of GPCRs
~~SC13: Introduction to Drug Metabolism~~

How to Register:
DiscoveryOnTarget.com
reg@healthtech.com
P: 781.972.5400 or
Toll-free in the U.S.
888.999.6288

Please use keycode DOT F when registering

CONFERENCE DISCOUNTS

Poster Submission - Discount ($50 Off): Poster abstracts are due by August 8, 2014. 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.

Group Discounts: Discounts are available for multiple attendees from the same organization. For more information on group rates contact David Cunningham at +1-781-972-5472

If you are unable to attend but would like to purchase the Discovery On Target CD for $750 (plus shipping), please visit DiscoveryOnTarget.com. Massachusetts delivery will include sales tax.