

FINAL AGENDA

The *Leading Event* on
NOVEL DRUG TARGETS

NINTH INTERNATIONAL

Discovery on TARGET

**Register by
September 30
and SAVE up to
\$200!**

November 2-4, 2011
Park Plaza Hotel & Towers
Boston, MA

SCIENTIFIC CONFERENCE PROGRAMS

November 2-3

Fifth Annual

Targeting Histone Deacetylases

Sixth Annual

GPCR-Based Drug Discovery

Fifth Annual

The Kinase Inhibitor Pipeline

Inaugural

Cancer Cell Metabolism

November 3-4

Ninth Annual

RNAi for Functional Screens

Inaugural

Allosteric Modulators

Second Annual

Targeting the PI3K Pathways

Fourth Annual

Diabetes Drug Discovery

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EVENT FEATURES

- **Co-Located: November 1st Ion Channel Symposium**
- **130+ Scientific and Technical Presentations**
- **500+ Participants**
- **Breakout Discussion Groups**
- **30+ Exhibiting Companies**
- **9 Interactive Short Courses**
- **Dedicated Poster Viewing**

Discovery on Target 2011 known as the leading event showcasing novel "hot" targets for the pharmaceutical industry will be held November 2-4 in Boston, Massachusetts at the historic Park Plaza Hotel & Towers. This is a must attend event to keep up with current and upcoming developments in target discovery and to collaborate and connect with experienced scientists and high level decision makers.

Networking opportunities will be available through interactive sessions including roundtable breakouts, workshops and panel discussions.

Conference-at-a-Glance		
Wednesday, November 2	Thursday, November 3	Friday, November 4
● Program 1 Targeting HDAC	● Program 5 RNAi for Functional Screens	
● Program 2 GPCR-Based Drug Discovery	● Program 6 Allosteric Modulators	
● Program 3 The Kinase Inhibitor Pipeline	● Program 7 PI3K Pathways	
● Program 4 Cancer Cell Metabolism	● Program 8 Diabetes Drug Discovery	

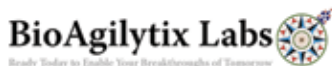
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Conference Program Schedule

TUESDAY, NOVEMBER 1

7:00 am–3:00 pm	Registration for Short Courses + Symposium
8:00 pm–6:30 pm	Short Courses (see page 3)
8:00 pm–6:30 pm	Symposium (see page 3)

WEDNESDAY, NOVEMBER 2

7:00 am–8:30 am	Registration and Morning Coffee
8:30 am–10:10 am	Concurrent Programs 1-4 ● ● ● ●
10:10 am–10:40 am	Networking Coffee Break in the Exhibit Hall
10:40 am–12:40 pm	Concurrent Programs 1-4 ● ● ● ●
12:40 pm–2:20 pm	Luncheon Presentations or Lunch on Your Own
2:20 pm–3:25 pm	Concurrent Programs 1-4 ● ● ● ●
3:25 pm–4:05 pm	Networking Refreshment Break in the Exhibit Hall
4:05 pm–5:05 pm	Concurrent Programs 1-4 ● ● ● ●
5:05 pm–6:10 pm	Breakout Discussion Sessions
6:15 pm–7:15 pm	Welcoming Reception in the Exhibit Hall

THURSDAY, NOVEMBER 3

7:30 am–8:15 am	Registration and Morning Coffee
8:15 am–9:50 am	Concurrent Programs 1-4 ● ● ● ●
9:50 am–10:40 am	Networking Coffee Break in the Exhibit Hall
10:40 am–12:10 pm	Concurrent Programs 1-4 ● ● ● ●
12:10 pm	Close of Nov 2-3 programs ● ● ● ●
12:30-1:30pm	Luncheon Presentations or Lunch on Your Own
1:30 pm–3:10 pm	Concurrent Programs 5-8 ● ● ● ●
3:10 pm–3:45 pm	Networking Refreshment Break in the Exhibit Hall
3:45 pm–5:45 pm	Concurrent Programs 5-8 ● ● ● ●
6:00 pm–9:00 pm	Dinner Short Courses (see page 3)

FRIDAY, NOVEMBER 4

7:30 am–8:30 am	Continental Breakfast Breakout Discussion Sessions
8:35 am–10:10 am	Concurrent Programs 5-8 ● ● ● ●
10:10 am–10:55 am	Networking Coffee Break in the Exhibit Hall
10:55 am–12:40 pm	Concurrent Programs 5-8 ● ● ● ●
12:40 pm–1:55 pm	Luncheon Presentations or Lunch on Your Own
1:55 pm–3:00pm	Concurrent Programs 5-8 ● ● ● ●
3:00 pm–3:40 pm	Networking Ice Cream Refreshment Break in Exhibit Hall (Last Chance for Viewing)
3:40 pm–5:10 pm	Concurrent Programs 5-8 ● ● ● ●
5:10 pm	Close of Discovery on Target

TUESDAY, NOVEMBER 1



ION CHANNEL SYMPOSIUM: Tools and Targets

(SC1) 8:00 - 11:00 am The Challenge of Targeting Ion Channels for Therapeutic Benefit

Topics to be Discussed:

- Safety
- Emerging Targets
- Lead Generation

Gregory J. Kaczorowski, Ph.D., President, CEO, Kanalis Consulting; Adjunct Professor, Physiology and Pharmacology, New Jersey Medical School

Maria Garcia, Ph.D., Vice President, Kanalis Consulting, LLC

(SC2) 12:00 - 3:00 pm Ion Channel Assays for Safety Screening

- Overview of current and emerging assays and methodologies
- Use of automation and high-throughput techniques
- Comparison of platforms and applications
- Factors affecting sensitivity and specificity

(SC 3) 3:30 – 6:30 pm Automatic Patch Clamp for Ion Channel Screening

Chris Mathes, Ph.D., Vice President & General Manager, North America, Sophion Bioscience, Inc.

(SC4) 12:00 - 4:00 pm Biomarkers for Tracking the Efficacy and Safety of HDACi

- Use of PCR to Measure Breaks in Genomic DNA to Evaluate Drug Efficiency and to Predict the Benefits of Combination Therapy
France Carrier, Ph.D., Associate Professor, Radiation Oncology, Marlene and Stewart Greenebaum Cancer Center, University of Maryland
- The Candidate and Proteomics Approaches for Identifying HDACi Biomarkers
Yingming Zhao, Ph.D., Associate Professor, The Ben May Department for Cancer Research, University of Chicago
- Identification, Validation and Utility of mRNA and miRNA Biomarkers in the Clinical Development of HDAC Inhibitors
Sriram Balasubramanian, Ph.D., Senior Director, Translational Research, Pharmacyclics Inc.
- Clinical Biomarkers for Monitoring HDAC Inhibitor Treatment in Friedreich's Ataxia
Heather Plasterer, Ph.D., Senior Research Scientist, Repligen Corporation
- Utilization of HDACi Biomarkers in the Clinic
Pamela Munster, M.D., Professor, Department of Medicine, University of California San Francisco

(SC5) 12:00 - 3:00 pm The Art and Science of Kinases

This course is designed for chemists and biologists new to kinase research or with some experience in the field and looking to learn more. This course will cover topics that are critical to know for any kinase research program, including protein structure, assays, kinome selectivity, technologies, inhibitors and late-stage challenges.

Kent Stewart, Ph.D., Research Fellow, Structural Biology, Abbott
Maricel Torrent, Ph.D., Senior Scientist, Abbott

(SC6) 3:30 – 6:30 pm Label Free Assays for GPCRs and Safety and Metabolic Profiling

This course is designed for scientists who would like to learn more about incorporating label-free technologies in their pre-clinical assays for

advancing GPCR targeted compounds and/or compounds that need to be assessed for specific toxicities.

- Types of label-free platforms and their pros and cons
- Label-free, cell based assays for GPCRs
- Tyrosine kinase-based label free assays for selectivity considerations
- Metabolic profiling applications (measuring pH and oxygen consumption changes)

Lisa K. Minor, Ph.D., President, In Vitro Strategies, LLC.

Hong Xin, Ph.D., Senior Scientist, Lead Generation, J&JPRD

THURSDAY, NOVEMBER 3

(SC7) 9:00 am-12:00 pm Best Practices for Setting Up Effective RNAi Screens

The course is designed to provide in-depth information on how to go about setting up RNAi screening experiments, how to design assays for getting optimal results. The challenges working with different types of molecules i.e. siRNAs, shRNAs and the delivery systems 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.

Hakim Djaballah, Ph.D., Director, HTS Core Facility, Memorial Sloan Kettering Cancer Center

Marc Ferrer, Ph.D., Team Leader, NIH Chemical Genomics Center, National Human Genome Research Institute, NIH

Eugen Buehler, Ph.D., Senior Research Associate, Informatics IT, Merck & Co., Inc.

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

(SC8) 6:00-9:00 pm Dinner Course: Pharmacology and Drug Discovery in the Allosteric World

The advancing technology of high-throughput screening is changing the type of molecules found. With protein function more physiologically relevant, the quality of the molecules that pharmacologists and medicinal chemists must deal with is changing. This course will familiarize researchers with the tools needed to exploit this potentially fruitful area of new drug discovery through discussion of allosteric molecules, detection of allosterism, and quantifying allosterism for chemical lead optimization. The course is designed to answer these questions:

- What is protein allostery?
- What makes allosteric molecules unique and how can this contribute to unique therapeutic properties?
- How can we detect allosterism?
- How to quantify allosterism for chemical lead optimization?

Terry P. Kenakin, Ph.D., Principal Research Investigator Molecular Discovery, Assay Development, GlaxoSmithKline R & D

Annette Gilchrist, Ph.D., Assistant Professor, Pharmaceutical Sciences, Midwestern University

(SC9) 6:00-9:00 pm Dinner Course: Targeting Pancreatic Islets for Type 2 Diabetes

In recent years, ways to regenerate the beta islet cells of the pancreas, the producers of insulin, have been of great interest to scientists searching for new ways to treat diabetes. This course will review the basics of the role of the pancreas in diabetes and cover the current progress being made and challenges to overcome for developing therapies directed at regenerating pancreatic beta cells.

Rohit Kulkarni, M.D., Assistant Professor, Medicine, Joslin Diabetes Center, Harvard Medical School

Fumihiko Urano, M.D., Ph.D., Associate Professor, University of Massachusetts Medical School

*Separate Registration Required.



Fifth Annual

Targeting Histone Deacetylases

Understanding and Screening for HDAC Inhibition in Diverse Therapeutic Indications

November 2 - 3
Program 1

WEDNESDAY, NOVEMBER 2

7:00 am Conference Registration and Morning Coffee

ADDRESSING SELECTIVITY

8:30 Chairperson's Opening Remarks

8:40 Highly Selective Inhibitors of HDAC6 for the Treatment of Chronic Inflammatory Diseases

Matthew Jarpe, Ph.D., Director of Biological Screening, Biology, Acetylon Pharmaceuticals

Non-selective HDAC inhibitors typically target the Class I HDACs as well as HDAC6. Selective HDAC6 versus selective Class I inhibitors can allow us to differentiate the role of the HDACs in inflammation. Acetylon's potent, oral, highly selective HDAC6 inhibitors decrease the secretion of pro-inflammatory cytokines from stimulated human macrophages *in vitro* and demonstrate a significant therapeutic response in animal inflammatory disease models. We expect these compounds will be effective at treating inflammatory diseases while demonstrating a superior safety profile suitable for chronic inflammation due to the absence of Class I HDAC inhibition and its broad epigenetic dysregulation of gene expression.

9:10 Selective Inhibitors of Class IIa HDACs and Their Role in Cell Biology and Inflammation

Michael Nolan, Ph.D., Principal Scientist, Biology, Tempero Pharmaceuticals

We have identified small molecule inhibitors of the Class IIa HDACs that do not inhibit Class I enzymes and used these compounds to evaluate changes in gene expression and T cell biology both *in vitro* and in mouse models. These first-in-class compounds provide insight to the distinct roles of Class IIa HDACs in cell biology and inflammation.

9:40 Selective Targeting of HDACs in Pediatric Oncology

Olaf Witt, M.D., CCU Pediatric Oncology, German Cancer Research Center

Pediatric cancers differ in many aspects from adult tumors with respect to histology, developmental origin and molecular genetics. Whereas in adult cancers HDACs 1,2,3 are in the focus of current research and drug development, our work in pediatric cancers of neuronal origin has uncovered unexpected expression and function of so far not well studied HDAC family members. Our results point to selective targeting of individual HDACs in a tumor type specific manner.

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

10:40 Development of Tetrahydroisoquinoline-Based Hydroxamic Acid Derivatives: Potent HDACi with Marked *in vitro* and *in vivo* Anti-Tumor Activities

Wenfang Xu, Ph.D., Professor, Medicinal Chemistry, School of Pharmacy, Shandong University

A novel class of tetrahydroisoquinoline bearing hydroxamic acid derivatives as 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. Most importantly, relative to SAHA, several derivatives exhibited even

more potent *in vivo* anticancer activities in a human breast carcinoma xenograft model, a human colon tumor xenograft model and a mice hepatoma-22 pulmonary metastasis model.

11:10 Epigenetics Target Profiling – The Tailor-Made Solution for Cellular Epigenetic Selectivity Analysis

Jutta Fritz, Ph.D., Vice President, Business Development, Evotec Munich

To transfer superior preclinical profiles to the clinic, a cellular assay that facilitates meaningful native selectivity profiling of HDAC inhibitors has been developed. Epigenetics Target Profiling delivers detailed information about an inhibitor's target profile in a physiological context and in the presence of relevant co-factors. It thus allows prediction of off-target liabilities and compound toxicity and helps to reveal HDAC isoforms essential to optimize drug efficacy, thereby providing a rational approach to designing HDACi.

11:40 HDACs in Memory and Cognition: Development of Isoform Selective Inhibitors with Improved CNS Drug Properties

Edward Holson Ph.D., Director, Medicinal Chemistry, Stanley Center for Psychiatric Research, The Broad Institute of MIT and Harvard

Deficits in cognition and memory are associated with many disease states including Alzheimer's disease, Rubinstein Taybi Syndrome and Schizophrenia. Altered acetylation states and the effects on specific gene expression and protein regulation underlie components of CNS disorders. Hypoacetylation states are found in neurological contexts and HDACs offer an attractive target to remedy these altered acetylation states. We describe our efforts to optimize HDAC inhibitors with greater isoform selectivity, improved CNS drug properties and efficacy in mouse models of learning and memory.

12:10 pm Panel Discussion: How Can We Improve Cell and Tissue Selectivity for HDAC Inhibition?

Panelists: All speakers from this session.

12:40 Luncheon Presentation (Sponsorship Opportunity Available) or Lunch on Your Own

UNDERSTANDING CELLULAR FUNCTION

2:20 Chairperson's Remarks

2:25 HDAC Inhibition and Knockdown Increase Pluripotency of Human Stem Cells

Paul Sammak, Ph.D., Research Associate Professor, Cell Biology and Physiology, University of Pittsburgh

The HDAC inhibitor trichostatin A (TSA) and siRNA knock down (KD) of HDAC1, 2 and 3 were used to evaluate the role of HDACs for expression of developmental markers and for chromatin organization. TSA and HDAC1, 2 and 3 KD reduced chromatin condensation, histone and DNA methylation. TSA reduced differentiation markers and increased pluripotency markers. HDAC1 and 2 KD increased expression of the conjugate HDAC, while HDAC3 KD did not. Only HDAC3 increased Oct4 expression, a key regulator of pluripotency, suggesting that HDAC3 is a unique target for regulating dedifferentiation and reprogramming.

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2:55 Identification of HDAC Substrates and Biomarkers of HDAC Inhibitors Using Proteomics Approach

Yingming Zhao, Ph.D., Associate Professor, The Ben May Department for Cancer Research, University of Chicago

Most substrates for each lysine acetyltransferases and HDACs remain unknown. In addition, LysAc substrates that are responsible for HDAC inhibitors' anti-tumor sensitivity have not been carefully examined. This knowledge gap needs to be filled to improve our understanding of LysAc in cancer and other diseases. Our group carried out the first two proteomics screenings of lysine acetylation in both mammalian cells and bacterial cells. In this presentation, we will report our current studies on extending this proteomics approach to identifying substrates for LysAc regulatory enzymes and biomarkers.

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

4:05 Anti-Inflammatory Effects of HDAC Inhibitors in Autoimmunity and Transplantation

Wayne Hancock, Professor, Pathology and Laboratory Medicine, University of Pennsylvania; Chief, Division of Transplant Immunology, Children's Hospital of Philadelphia

Proof-of-principle studies of the importance of specific HDACs in animal models of autoimmunity and transplantation have provided a rationale to seek isoform-specific and subclass-specific HDAC inhibitors. Several such inhibitors have now been developed and are being evaluated in animal models and using human cells *in vitro*. Isoform- and subclass-specific HDACi offer considerable potential as anti-inflammatory agents for inflammatory and immunologically-mediated human diseases.

4:35 Metabolism as a Therapeutic Target of HDAC Inhibitors

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

While epigenetics has always been considered the primary therapeutic target of HDAC inhibitors, growing evidence has linked HDAC and protein acetylation to cellular metabolism. The impact of HDAC inhibitors on physiological and tumor metabolism will no doubt become a central issue in their future clinical application. I will discuss the underlying biology of HDAC and metabolic regulation and the potential therapeutic opportunity of targeting metabolic pathways by HDAC inhibitors.

5:05 Interactive Breakout Discussion Groups

6:15 – 7:15 Welcoming Reception in the Exhibit Hall with Poster Viewing

THURSDAY, NOVEMBER 3

7:30 am Breakfast Presentation (Sponsorship Opportunity Available) or Morning Coffee

DIVERSIFYING THERAPEUTIC TARGETS

8:15 Chairperson's Opening Remarks

Timothy A. McKinsey, Ph.D., University of Colorado Denver

8:20 Therapeutic Potential for HDAC Inhibitors in the Heart

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

Small molecule HDAC inhibitors block adverse cardiac remodeling in animal models, suggesting unforeseen potential for this class of compounds for the treatment of heart failure. However, since broad-spectrum, 'pan' HDAC inhibition is associated with toxicities such as thrombocytopenia, many remain skeptical of the prospects of

translating these findings to the clinic. I will highlight roles of HDACs in the heart and the therapeutic potential of isoform-selective HDAC inhibitors for the treatment of heart failure.

8:50 Development of HDACi for the Therapy of Neurodegenerative Diseases: The Friedreich's Ataxia Example

Vincent Jacques, Ph.D., Senior Director, Preclinical Development, RepliGen Corp.

Friedreich's ataxia is an autosomal recessive disease associated with an intronic GAA triplet repeat expansion in the frataxin gene leading to heterochromatin formation and reduced levels of frataxin. Intervention with HDACi's has been shown to increase acetylation at the promoter region of the frataxin gene and thus restore frataxin levels. Data will be presented that highlight the development of a clinical candidate through medicinal chemistry aimed at optimizing efficacy (selectivity, tissue distribution, pharmacokinetics) while minimizing toxicity.

9:20 HDACi and GVHD

Pavan Reddy, M.D., Associate Division Chief (Basic Research), Division of Hematology-Oncology, Department of Medicine, University of Michigan Comprehensive Cancer Center

We demonstrate that HDACi regulate experimental acute graft-versus-host disease (GVHD) in multiple murine models through STAT3 acetylation dependent induction of indoleamine 2, 3 dioxygenase (IDO) in host antigen presenting cells (APCs). Based on these preclinical data we have recently initiated a proof-of-concept Phase I/II clinical to determine whether addition of HDACi, to standard immune-prophylaxis will reduce the rates of acute GVHD. The pre-clinical and mechanistic data along with the preliminary data on GVHD will be presented.

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

10:40 Panel Discussion: HDACi and Their Progress in the Clinic

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

Panelists:

An Update on the Clinical Phase II Program of Resminostat in HL, HCC and CRC

Stefan W. Henning, Ph.D., M.Sc., Senior Project Manager, Development, 4SC AG

Results from Phase 2 Studies with Entinostat Combinations in Advanced Breast and Lung Cancer

Peter Ordentlich, Ph.D., Executive Director, Translational Science and Founder, Syndax Pharmaceuticals

Romidepsin in Relapsed Peripheral T Cell Lymphoma

Kenneth Foon M.D., Vice President, Disease State Lead, Medical Affairs, Celgene Corp

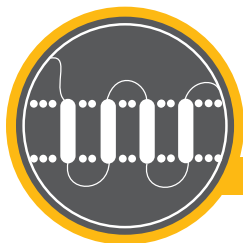
Clinical Update on the Macrophage-Targeted HDAC Inhibitor CHR-2845 (Tefinostat)

Alan H. Drummond, Ph.D., CSO, Chroma Therapeutics Ltd.

Update on the Clinical Study of PCI-24781 in Combination with Doxorubicin in Soft-tissue Sarcoma

Sriram Balasubramanian, Ph.D., Senior Director, Translational Research, Pharmacoclytics

12:10 pm Close of Conference



Sixth Annual

GPCR-Based Drug Discovery

New Tools and Therapeutic Areas for a Tried and True Target Class

November 2 - 3
Program 2

WEDNESDAY, NOVEMBER 2

7:00 am Conference Registration and Morning Coffee

LIGAND-BIASED SIGNALING

8:30 Chairperson's Opening Remarks

Annette Gilchrist, Ph.D., Assistant Professor, Department of Pharmaceutical Sciences, Midwestern University

» 8:40 KEYNOTE PRESENTATION:



Harnessing the Functional Selectivity of GPCRs for Drug Discovery

Michel Bouvier, Ph.D., Professor, Department of Biochemistry, University of Montreal

G protein-coupled receptors can engage multiple signaling cascades that may or may not involve G protein activation. This functional selectivity of GPCRs is controlled by the ligand that binds the receptor. Such ligand-biased signaling can be exploited for the development of new drugs with increased selectivity profiles and less undesirable effects. I present approaches we used involving both BRET-based biosensors and label-free methods that hold promise for large scale drug discovery applications.

9:40 GPCR Biased Ligands: Translating Theory to Improved Therapies

Jonathan Violin, Ph.D., Head of Biology, Trevina

Biased GPCR ligands selectively engage or elude distinct receptor signaling mechanisms, and may provide a strategy for designing safer and more efficacious GPCR-targeted drugs. Two examples illustrate how biased ligands can elicit novel pharmacological profiles: TRV027, a beta-arrestin biased ligand of angiotensin II type 1 receptor, and TRV002, a G protein-biased ligand of the mu opioid receptor. These compounds highlight the concept, mechanism of action, and utility of biased ligands.

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

GPCR SCREENING CHALLENGES

10:40 Talk Title to be Announced

Mark Pausch, Ph.D., Director, *in vitro* Pharmacology, Merck

11:10 Sponsored Presentations (Opportunities Available)

11:40 Hit Identification and Hit Assessment for the Orphan G Protein-Coupled Receptor GPR88

Neil Burford, Ph.D., Senior Research Investigator II, Lead Discovery & Profiling, Bristol-Myers Squibb Company

GPR88 is highly expressed in brain regions and is implicated in the modulation of striatal dopamine function. GPR88 knockout mice exhibit a pro-psychotic behavioral phenotype suggesting that GPR88 agonists might be therapeutically beneficial as a treatment for schizophrenia. In this case study, the discovery of surrogate agonists

for GPR88 from high throughput screening will be described with emphasis on the challenges associated with screening an orphan GPCR.

12:10 pm Panel Discussion: Which Screening Strategy to Use?



Moderator:

Lisa K. Minor, Ph.D., President, *In vitro* Strategies, LLC

Panelists:

Neil Burford, Ph.D., Senior Research Investigator II, Lead Discovery & Profiling, Bristol-Myers Squibb Company

Annette Gilchrist, Ph.D., Assistant Professor, Department of Pharmaceutical Sciences, Midwestern University

Mark Pausch, Ph.D., Director, *in vitro* Pharmacology, Merck

Panelists will present their screening strategy and choice of assays in response to various mock drug discovery scenarios presented by the moderator.

12:40 Luncheon Presentation:

Sponsored by
DiscoverRx

Discovery of Novel, Biased Ligands Using a Suite of PathHunter® and HitHunter® GPCR Screening Platforms

Elizabeth R. Quinn, Ph.D., Senior Product Manager, GPCR Product Portfolio, DiscoverRx Corp.

Although G-protein dependent and independent pathways are often modulated in concert, a number of compounds having differential effects on these pathways have been reported. In order to gain further insight into this, a systematic characterization of GPCR targets and their associated ligands was done using: HitHunter® 2nd messenger signaling, PathHunter® arrestin activation, and PathHunter® receptor internalization. This talk focuses on how functional selectivity may be prevalent across receptor and ligand classes which could lead into discovery of compounds with novel characteristics.

SIGNALING COMPLEXITIES

2:20 Chairperson's Remarks

Graeme Semple, Ph.D., Vice President, Discovery Chemistry, Arena Pharmaceuticals, Inc.

2:25 Talk Title to be Announced

Thue Schwartz, Ph.D., Professor, The Novo-Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen

2:55 Regulators of Heterotrimeric G-protein Signaling

David Siderovski, Ph.D., Professor, Director, Chemical Biology, Department of Pharmacology, University of North Carolina at Chapel Hill

I discuss two distinct families of GPCR signaling modulators discovered in my laboratory: the 'regulators of G-protein signaling' (RGS) and GoLoco motif protein families. I will survey some of our latest findings on the physiological functions of RGS proteins and examine recent efforts to establish and validate proof-of-principle small molecule modulators of these proteins.

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

4:05 Antiparkinsonian and Anxiolytic Effects of a Novel Chemical Class of Positive Allosteric Modulators of Metabotropic Glutamate Receptor 4

Brice Campo, Ph.D., Group Leader, In vitro Pharma, Addex

Addex will disclose a novel chemical scaffold with a pharmacophore and structure activity relationship that is completely different from what it's known in the field. We also describe a proof-of-concept compound demonstrating efficacy in pre-clinical models of PD and anxiety disorders without any side effects (dyskinesias) associated with the existing frontline therapy L-DOPA. This work has been done in collaboration with Merck.

4:35 Generating Fully Human Antagonistic Antibodies against GPCR Targets

Sergej Kiprijanov, Ph.D., Vice President of Research and Preclinical Development, Affitech A/S

Using proprietary CBAS™ technology, Affitech generated a panel of antagonistic antibodies against GPCR targets involved in cancer progression and inflammation. The generated antibodies effectively competed with ligand binding, were able to block ligand-induced signaling and cell migration, and demonstrated high cell killing activity via ADCC. Data showing applicability of the GPCR targeting antibodies for treatment of cancer, inflammatory and autoimmune diseases will be presented.

5:05 Interactive Breakout Discussion Groups

6:15 – 7:15 Welcoming Reception in the Exhibit Hall with Poster Viewing

THURSDAY, NOVEMBER 3

7:30 am Breakfast Presentation (Sponsorship Opportunity Available) or Morning Coffee

GPCR-TARGETED DRUG CANDIDATE

8:15 Chairperson's Opening Remarks

Lisa K. Minor, Ph.D., President, In vitro Strategies, LLC.



8:20 Novel Mediators of Lymphocyte Trafficking

Klaus Seuwen, Ph.D., Principal Investigator, GPCR Biology, Developmental & Molecular Pathways, Novartis Institutes for Biomedical Research

The immune system depends critically on the ability of lymphocytes to perform directed migration and to move across vascular barriers. GPCRs play key roles in these processes. This presentation will discuss recent work in our group on the regulation of immune cell trafficking and endothelial function by the S1P1 receptor, and we report the identification of novel lymphocyte chemotactic oxysterols as ligands for the receptor EB12.



8:50 Identification of a New Class of GPCR Ligands through Receptor Deorphaning

Timothy W. Lovenberg, Ph.D., Johnson & Johnson Pharmaceutical Research and Development, LLC

The recent discovery that 7,25-dihydroxycholesterol is an endogenous ligand for an orphan GPCR has expanded our knowledge of biological signaling molecules and pathways and opens the door for a greater understanding of the humoral immune response system. Dr. Lovenberg's talk will highlight aspects of this recent discovery as well as review recent successes and challenges in the areas of orphan GPCR function.

9:20 Discovery of Potent and Selective Sphingosine-1-Phosphate [S1P1R] Agonists

Robert M. Jones, Ph.D., Senior Director, Medicinal Chemistry, Arena Pharmaceuticals

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

PROBING GPCR AND LIGAND STRUCTURE

10:40 Expression of Functional, Stable Isotope-Labeled Cannabinoid Receptor CB2 for Structural Studies

Alexei Yeliseev, Ph.D., Staff Scientist, NIH/ NIAAA

We developed an efficient procedure for preparation of functional GPCR labeled with stable isotopes in quantities sufficient to initiate high resolution NMR structural studies. The labeled receptor is incorporated into lipid bilayers of desired composition allowing studies of structure-function relationship of this protein at physiological conditions. Finally, we developed an efficient procedure to stabilize CB2 that did not require mutagenesis or any alteration of amino acid sequence of this receptor.

11:10 Ascorbate Enhancement of Adrenergic and Histaminergic Activity via Binding to the First Extracellular Loop of Their Receptors

Robert Root-Bernstein, Professor, Physiology, Michigan State University

We demonstrate that ascorbate and several structurally related compounds enhance the activity of a wide range of adrenergic and histaminergic drugs *in vitro* and in an animal model of asthma. The mechanism involves binding of enhancers to the first extracellular loop of the adrenergic and histaminergic receptors maintaining these receptors in their high-affinity conformation. The resulting allosteric changes appear to interfere with phosphorylation of the receptor as well, thereby preventing desensitization.

11:40 Crystal Structure of the Sphingosine-1 Phosphate Receptor

Mike Hanson, Ph.D., Associate Director, Structural Biology, Receptos, Inc.

The lyso-phospholipid sphingosine 1-phosphate modulates lymphocyte trafficking, endothelial development/integrity, heart rate, and vascular tone/maturation by activating G-protein-coupled sphingosine 1-phosphate receptors. The crystal structure of the sphingosine 1-phosphate receptor 1 (S1P1) in complex with a selective antagonist W146 providing a detailed view of the molecular recognition events that result in the modulation of immune and stromal cell responses therapeutically important for human diseases ranging from multiple sclerosis to influenza.

12:10 pm Close of Conference



Fifth Annual

Emerging Targets for the Kinase Inhibitor Pipeline

Novel Applications for the Kinase Community

WEDNESDAY, NOVEMBER 2**7:00 am Conference Registration and Morning Coffee**

DESIGN AND OPTIMIZATION OF INHIBITORS

8:30 Chairperson's Opening Remarks

8:40 Discovery of CX-4945, the First Clinical Stage Inhibitor of Protein Kinase CK2 for the Treatment of Cancer

Fabrice Pierre, Ph.D., Associate Director, Medicinal Chemistry, Cylene Pharmaceuticals, Inc.

Protein kinase CK2 expression and activity are elevated in many cancers, and the enzyme is known to regulate many oncogenic pathways, notably EGFR regulated pathways, PI3K-Akt-mTOR, WNT and NF- κ B cascades, angiogenesis and the DNA damage response. These properties make CK2 an attractive oncology target for single-agents or combination therapies. This talk will discuss the design, SAR and latest characterization of CX-4945, the first ATP-competitive inhibitor of CK2 currently in clinical trials.

9:10 Structure-Based Design of VEGFR-2 Inhibitors

Matthew Martin, Ph.D., Senior Scientist, Amgen, Inc.

Using the available structures of VEGFR-2 small molecule complexes, a novel series of inhibitors was identified. This talk will describe the design, optimization, and biological activity of a second generation VEGFR-2 inhibitor.

9:40 Structure-Based Identification of ATP-Competitive MK2 Inhibitors

Arthur Oubrie, CSO, Lead Pharma

MK2 kinase is a promising drug discovery target for the treatment of inflammatory diseases. In this talk, I will present the structure-based discovery of a novel MK2 inhibitor that exhibited *in vivo* efficacy in a short-term pre-clinical model. Optimization of this compound led to the identification of inhibitors with improved cellular potency and oral availability.

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

TARGETING PULMONARY DISORDERS

10:40 Inhibition of a Novel Serine/Threonine Kinase Over-Expressed in Chronic Obstructive Pulmonary Disorder

Stefen Boehme, Ph.D., Director, Immunology, Axikin Pharmaceuticals, Inc.

We have identified a novel serine/threonine kinase that is upregulated in the lung tissue of COPD patients. siRNA-mediated knock-down of this kinase decreases the secretion of inflammatory cytokines in *in vitro* experiments and strongly inhibits multiple aspects of the inflammatory response observed in various animal models of COPD. Using the crystal structure of the kinase to guide our screening and SAR efforts, we have identified multiple lead compounds. We will discuss our ongoing pre-clinical development of antagonists against this novel kinase and as a possible treatment for COPD.

11:10 Overcoming 'Rubbish In: Rubbish Out': Effectively Supporting Target Identification & Validation Using Target Insights, a New Product from Elsevier

Sponsored by



Jabe Wilson, MBA, Ph.D., Senior Product Development Manager, Elsevier (Pharma & Biotech Group)

In target identification/validation the fundamental questions are how is a target identified, and the hypothesis developed using the scientific literature? Reducing time & money investments in literature searching to get to a go-no go decision is crucial. Target Insights from Elsevier is a new online decision support tool for biologists dealing with these issues.

11:25 Biochemical and Cellular Profiling of Marketed Kinase Inhibitors

Sponsored by



Blaine N. Armbruster, Ph.D., Manager, Lead Discovery, EMD Millipore

This study elucidated the selectivity and cellular activity of several marketed kinase inhibitors, including Imatinib, Sunitinib, Lapatinib. We found that some inhibitors can have unsuspected cellular behavior based on their biochemical profiles.

11:40 Future Fields from Pharma Frustrations?

Dirk Leyesen, Ph.D., Founder & CSO, Amakem NV

Kinases are powerful biochemical targets with great potential to treat and modify many diseases. However most kinase inhibitors do not reach the market: systemic side effects limit the dose that can be applied and lead to narrow therapeutic windows and sub-therapeutic treatment regimens. Amakem developed a platform to circumvent these basic problems. Two cases will be presented in the field of ophthalmology and lung diseases that prove the validity of the concept and future value.

12:10 pm Panel Discussion

12:40 Luncheon Presentation:

Sponsored by



From cDNA Clones to Assays, A Genomic Approach

Xuan Liu, PhD, Senior Director, Marketing, OriGene Technologies, Inc.

Biomedical research demand quality tools for detection, measurement and perturbation of specific gene/protein targets. Built upon a solid foundation of genome wide full-length cDNA clone clones, OriGene has been developing products and service focusing on system biology approaches to gene function analysis. In this talk, we will showcase some of our novel technology platforms for analyze individual proteins as well as proteome in general.

STRATEGIES TO TARGET CANCER

2:20 Chairperson's Remarks

2:25 Epithelial-Mesenchymal Transition (EMT) as a Framework for Selection of Kinase Targets and Therapeutic Combinations for Oncology

Jonathan Pachter, Ph.D., Senior Research Director, Translational Research, OSI Pharmaceuticals

The activity of various Molecular Targeted Therapies, including

the IGF-1R/IR kinase inhibitor OSI-906 and the mTORC1/2 kinase inhibitor OSI-027 to inhibit tumor cell proliferation as a function of epithelial vs. mesenchymal phenotype will be discussed. A strategy to select and validate novel kinase targets that influence the EMT transition or survival/proliferation of mesenchymal-like tumor cells will be presented together with strategies for rational definition of effective drug combinations. Both pre-clinical and clinical data will be presented.

2:55 Identification of a New Class of c-Met Inhibitors with a Unique Mode of Action and a Distinct Profile Against Activating Mutations

Jason D. Katz, Chemistry Program Team Lead, Department of Chemistry, Merck Research Laboratories

c-Met is a transmembrane tyrosine kinase that mediates activation of several signaling pathways implicated in aggressive cancer phenotypes and several activating mutations in the kinase domain of c-Met have been described. This presentation will discuss the identification of MK-2461 and MK-8033, representative of a unique class of c-Met inhibitors that are efficacious in preclinical animal models of tumor progression. In addition, biochemical studies and X-ray analysis have revealed that this unique class of kinase inhibitors binds preferentially to the activated (phosphorylated) form of the kinase and displays a distinct profile against many of these activating mutations. This presentation will briefly describe the identification of these compounds and discuss potential advantages of their unique characteristics.

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

4:05 Multifaceted Intervention by the Hsp90 Inhibitor Ganetespib in Cancers with Activated JAK/STAT Signaling

David Proia, Ph.D., Senior Scientist, Synta Pharmaceuticals Corp.

Persistent JAK/STAT activation is oncogenic and characteristic of many human malignancies and thereby provides an attractive point of intervention for molecularly targeted therapeutics. In this presentation, we show that the Hsp90 inhibitor ganetespib has profound antitumor activity in an array of JAK/STAT-driven cancers and, importantly, can abrogate aberrant signaling through multiple mechanisms.

4:35 A New LIMK Inhibitor Stabilizes Microtubules and has Anticancer Activity

Laurence Lafanechère, Ph.D., Director of Research, CNRS, Team# 03, Polarity, Development & Cancer, Department of Cellular Differentiation and Transformation, Albert Bonniot Institute

We identified a highly selective cell permeable LIMK inhibitor that reversibly stabilized microtubules and blocked actin microfilament dynamics. We established that the microtubule stabilizing effect of the compound is the result of its inhibitory effect on LIMK, independently of its effect on the actin cytoskeleton. The compound inhibits cell motility and is effective on multidrug resistant cancerous cell lines. It is also effective in animals, where it delays tumors formation while showing a good tolerability.

5:05 Interactive Breakout Discussion Groups

6:15 – 7:15 Welcoming Reception in the Exhibit Hall with Poster Viewing

THURSDAY, NOVEMBER 3

7:30 am Breakfast Presentation (*Sponsorship Opportunity Available*) or **Morning Coffee**

NON-ONCOLOGY APPLICATIONS

8:15 Chairperson's Opening Remarks

8:20 Talk Title to be Announced

Jordan S. Fridman, Ph.D., Director, Pharmacology, Incyte Corp.

8:50 Diacylglycerol Kinases in Immune Function

Xiaoping Zhong, M.D., Associate Professor, Pediatrics, Duke University Medical Center

Diacylglycerol kinases (DGKs), a family of ten members in mammals, convert diacylglycerol (DAG) to phosphatidic acid (PA). By regulating the concentrations of DAG and PA, DGKs play important roles in development and function. We have found that DGK α and zeta synergistically regulate immune cell development and function. We propose that DGKs are potential targets for modulating immune responses for immunotherapy against cancer and microbial infection.

9:20 Sponsored Presentations (*Opportunities Available*)

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

10:40 Talk Title to be Announced

James Kempson, Ph.D., Senior Research Investigator, R&D, Bristol-Myers Squibb

11:10 Defining Novel Targets of Oxidant Stress with Kinase Signaling, Wingless, Sirtuins, and Forkhead Transcription Factors for Neurodegenerative and Vascular Disorders

Kenneth Maiese, M.D., Professor and Chair, Department of Neurology and Neurosciences, Chief of Service, University of Medicine & Dentistry of New Jersey, New Jersey Medical School

Complications of oxidative stress weigh heavily upon the nervous and vascular systems. As a result, focus upon innovative treatment strategies against disorders such as neurodegenerative disease, cardiac injury, cancer, or diabetes that employ targeted molecular pathways to balance sometimes opposing forces between cell protection and cell longevity are therefore required. Here we examine novel targets that involve kinase signaling, wingless, sirtuins, and forkhead transcription factors.

11:40 The Inhibition of CK1

Jeffrey F. Ohren, Ph.D., Principal Scientist, Pfizer Global R&D (tentative)

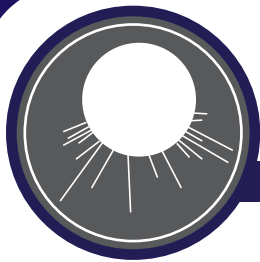
12:10 pm Close of Conference



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Inaugural

Cancer Cell Metabolism as Drug Target

Current Strategies of Starving Cancer Cells via Metabolic Interference

WEDNESDAY, NOVEMBER 2

7:00 am Conference Registration and Morning Coffee

8:30 Chairperson's Opening Remarks

NOVEL TARGETS

8:40 Malic Enzyme 2 (ME2) as a Novel Cancer Metabolic Target

Vikas Sukhatme, Professor, Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School

We have discovered that ME2 is widely overexpressed in a number of tumor types. Its inhibition can decrease tumor growth and induce differentiation *in vitro* and *in vivo*.

9:10 Targeting Atypical Glucose Transporter Regulation in Multiple Myeloma with HIV Protease Inhibitors

Mala Shanmugam, Ph.D., Research Assistant Professor, Robert H. Lurie Comprehensive Cancer Center, Northwestern University

Tumor cells, including the fatal B cell malignancy multiple myeloma, consume surprisingly high amounts of glucose. While elevated glucose utilization forms the basis for clinical imaging of various cancers, we are not yet able to target glucose utilization for therapy. We have identified a subset of glucose transporters (GLUTs) that are uniquely regulated in myeloma including the insulin-responsive glucose transporter GLUT4, providing targeting opportunities selective to these tumor cells. In addition we have identified an FDA approved HIV protease inhibitor that has an off-target effect on GLUT4, warranting repositioning of this class of compounds for the treatment of GLUT4-dependent cancers. Our studies range from target identification, *in vitro* cell line validation and *ex vivo* pre-clinical studies in myeloma patient samples providing novel approaches to treat this incurable cancer.

9:40 Targeting Carbonic Anhydrases IX and XII, Regulators of Cellular pH in Hypoxia

Shoukat Dedhar, Ph.D., Professor, Distinguished Scientist, University of British Columbia and BC Cancer Research Centre, Vancouver

Carbonic Anhydrase IX (CAIX) is a hypoxia inducible protein that regulates intra- and extra-cellular pH under hypoxic conditions and promotes tumor cell survival and invasion in hypoxic microenvironments. CAIX is specifically expressed in aggressive triple-negative and basal type breast tumors and is a poor patient prognostic marker. We have targeted CAIX with novel small molecule inhibitors and have shown that CAIX inhibition results in significant growth delay of orthotopic breast tumors, and also in significant inhibition of lung metastasis formation. New data on the role of CAIX in cancer stem cells will be discussed.

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

GLYCOLYSIS AND THE WARBURG EFFECT

10:40 Discovery of Novel Small Molecule Cancer Therapeutics Targeting the Glycolytic Pathway

Stephen T. Davis, Ph.D., Director, Biology, TransTech Pharma, Inc.

We have synthesized novel, potent selective inhibitors targeting the glycolytic pathway, and these molecules are showing promise as future anticancer agents. Our data show cancer cells require glycolysis for cell growth and survival. In addition, inhibition of glycolysis with our molecules makes the tumor cell very sensitive to inhibition of alternative pathways of energy metabolism, and produces enhancement of tumor cell killing.

11:10 Sponsored Presentations (Opportunities Available)

11:40 Targeting the Warburg Effect by Synthetic Lethality

Ray Tabibiazar, M.D., CEO, Ruga Corporation

Paul Pearson, Ph.D., VP, Pre-Clinical Development, Ruga Corporation

Identifying new molecular targeted therapies that specifically kill tumor cells while sparing normal tissue is the next major challenge of cancer research. We describe here strategies to target the Warburg Effect in a genetically defined patient population by utilizing synthetic lethality.

12:10 pm Interfering with Cancer Cell Signaling

Speaker to be Announced

12:40 tONCO: Taconic's Innovative Portfolio of Tools and Capabilities to Evaluate the Efficacy of Novel Cancer Therapeutics

David S. Grass, Ph.D., Vice President, Scientific Operations, Taconic

Sponsored by
Taconic

2:20 Chairperson's Remarks

2:25 Conserved Features of Cancer Cells Define their Sensitivity of HAMLET-Induced Death; C-Myc and the Warburg Effect

Petter Storm, Scientist, Laboratory Medicine, Microbiology, Immunology and Glycobiology (MIG), Lund University

HAMLET is the first member of a new family of tumoricidal protein-lipid complexes, and has shown great promise as a human drug candidate, with therapeutic efficacy against skin papillomas and rapid topical effects on human bladder cancers. The results of our research identify HAMLET as a novel anti-cancer agent that exploits unifying features of cancer cells for its activity, including c-Myc and the shift in glycolysis known as the "Warburg effect".

2:55 Targeting Mitochondria for Cancer Therapy: Role of Mitochondrial Hexokinase in Prevention of Apoptosis

Charles Wenner, Ph.D., Member, Department of Cell and Molecular Biology, Roswell Park Cancer Institute

Description-Historical perspective of the Warburg Effect with emphasis on modulation of high glycolytic rates in rapidly growing tumor cells for therapy. The need for a re-examination of the specific contributions of mitochondrial hexokinases and glucose metabolism is discussed in view of demonstrations that these hexokinases can antagonize apoptosis downstream of Bax activation despite metabolic disruption which suggests that metabolism per se is not obligatory for this process. These findings suggest that new approaches of targeting apoptotic susceptibility may be conceived.

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

4:05 Development of Chemical Probes to Study Cancer Metabolic Reprogramming

Sergey A. Kozmin, Ph.D., Associate Professor, Chemistry, University of Chicago

Understanding of the nature of reprogrammed energy metabolism in cancer cells is of significant current interest. We will describe the development of an arsenal of new small-molecule probes to study altered energy metabolism in cancer. This study is aimed at identifying the underlying reasons for major alterations in energy producing pathways employed by rapidly proliferating cells and testing the possibility of targeting such cells *in vitro* and *in vivo*.

4:35 Potent Anti-Cancer Lipoate Analogs Selectively Attack Tumor Cell Mitochondrial Metabolism

Paul Bingham, Ph.D., Vice President, Research, Cornerstone Pharmaceuticals

Among the enzymes whose regulation is reprogrammed in many tumor cells is the pyruvate dehydrogenase complex (PDH). The lipoate moieties of PDH

serve both catalytic and regulatory function. Non-redox active lipoate analogs apparently attack cancers-specific elements of this lipoate-sensitive regulatory apparatus, causing cancer cell death in cell culture and in human tumor xenograft models.

5:05 Interactive Breakout Discussion Groups

6:15 – 7:15 Welcoming Reception in the Exhibit Hall with Poster Viewing THURSDAY, NOVEMBER 3

7:30 am Breakfast Presentation (Sponsorship Opportunity Available) or Morning Coffee

8:15 Chairperson's Opening Remarks

8:20 Regulation of Glycolysis by SIRT3

Marcia C. Haigis, Ph.D., Assistant Professor, Pathology, Harvard Medical School

SIRT3 is a mitochondrial NAD-dependent deacetylase that is frequently down-regulated in human cancers. SIRT3 loss increases HIF1a activity and results in metabolic reprogramming to enhance glycolysis.

8:50 Autoimmune Disease Modulation through Mitochondrial Bioenergetics

Gary D. Glick, Ph.D., Werner E. Bachmann Professor, Chemistry, University of Michigan

In this presentation, Dr. Glick will discuss how modulation of the mitochondrial ATPase can provide a selective, non-immunosuppressive mechanism for the treatment of inflammation and autoimmune disease. In addition, he will describe the discovery of a novel series of orally available compounds that modulate the ATPase and exhibit therapeutic efficacy in murine disease models.

9:20 Comparative Metabolic Flux Profiling in Melanoma Cell Lines

Andrei Osterman, Ph.D., Associate Professor, Bioinformatics and Systems Biology Program, Sanford-Burnham Medical Research Institute

The presentation will provide: metabolic flux profiling methodology; metabolic signatures of different melanoma cell lines and melanocytes; metabolic response to hypoxia; and evaluation of potential therapeutic and diagnostic targets in central metabolism of melanoma.

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

10:40 Succinate Dehydrogenase Over-Expression Massively Increases Hydroxymethyl Cytosine Levels in Human Cells

Douglas Ruden, Ph.D., Director, Epigenomics, Obstetrics and Gynecology, Wayne State University

Gliomas often have a gain of function mutation in SDH1 or SDH2 that causes it to produce the cancer metabolite 2-HG at the expense of alpha-KG. Recently, it has been shown that 2-HG inhibits the TET enzyme that converts 5-mC to 5-hmC, thereby increasing global DNA methylation levels. We found that over-expression of wild-type SDH1 in human cells causes a 2-fold increase in modified cytosines greater than 2-fold above the levels of control cells. We propose a model wherein SDH1 over-expression increases alpha-KG levels which leads to a massive increase in both 5mC and 5hmC levels.

11:10 Modulating Cancer Metabolism with Small Molecule PKM2 Activators – A New Anti-Cancer Strategy

Oren Becker, Ph.D., CEO and President, Dynamix Pharmaceuticals

Using our DynamixFit™ technology, we discovered several series of small molecule PKM2 activators. These compounds exhibit potent PKM2 activation in vitro, anti-cancer activity in a variety of cell types, and a statistically significant in vivo anti-tumor efficacy in animal xenograft studies. Furthermore, the compounds have a highly favorable safety profile suggesting that clinical development can be initiated within the next year. Altogether, we show that cancer metabolism modulation with small molecule PKM2 activators is a promising novel anti-cancer strategy.

11:40 Panel Discussion: Targeting Mitochondrial Metabolism – Identifying New Strategies

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Agenda Presentations

Speak to a captive audience about your latest product or service. This sponsorship includes a 15-minute podium presentation within the scientific agenda as well as exhibit space, onsite branding and access to cooperative marketing efforts by CHI.

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Select invitees from the conference pre-registration list for an evening of networking at the hotel or a top local venue. CHI will extend invitations, conduct follow-up and monitor responses. Reminder cards will be placed in the badges of those delegates who will be attending.

Focus Groups

CHI will gladly provide you the opportunity of running a focus group on-site at Discovery on Target. This exclusive gathering can be useful to conduct market research, gather feedback on a new product idea and gather marketing intelligence from industry experts on a specific topic.

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

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Ninth Annual

RNAi for Functional Screens

Effectively Utilizing RNAi as a Tool for Screening Cellular Pathways and Drug Targets

November 3 - 4
Program 5

THURSDAY, NOVEMBER 3

ASSAY DESIGN AND SET-UP

1:30 pm Chairperson's Remarks

Christophe Echeverri, Ph.D., CEO & CSO, Cenix BioScience GmbH

1:40 Talk Title to be Announced

Alex Gaither, Ph.D., Research Investigator II, Developmental and Molecular Pathways, Novartis Institutes for Biomedical Research

2:10 Screening Approaches Towards Identifying Genes Associated with DNA Re-Replication in Cancer Cells

Scott Martin, Ph.D., Team Leader, RNAi Screening, NIH Chemical Genomics Center, NIH Center for Translational Therapeutics, NIH

The NIH Chemical Genomics Center has established an RNAi screening facility that performs screens in collaboration with investigators throughout the NIH intramural community. An initial genome-wide campaign involved screening for genes associated with aberrant DNA replication. Screening was conducted using libraries comprised of both pooled and individual siRNAs. Combining these approaches led to a thorough examination of genes associated with DNA replication and served as a way to compare the value of both platforms.

2:40 RNAi Screening Comes of Age: For the Love of My Target

Hakim Djaballah, Ph.D., Director, HTS Core Facility, Memorial Sloan Kettering Cancer Center

RNAi screening has offered the premise of performing several thousand simultaneous knockdowns leading to the discovery and validation of existing and novel targets. Several years on, has the technology matured enough to keep up with its premise?

3:10 Networking Refreshment Break in the Exhibit Hall with Poster Viewing

3:45 A Targeted Screen for Small Molecule Inhibitors of the Wnt/ β -catenin Pathway

Ramanuj DasGupta, Ph.D., Assistant Professor of Pharmacology and Director, RNAi Screening Facility, New York University School of Medicine/Cancer Institute

The Wnt/wingless (wg) pathway is one of a core set of evolutionarily conserved signaling pathways that regulate many aspects of metazoan development. One of the most important effectors of the Wnt pathway is encoded by the transcription factor, beta-catenin (β -cat)/armadillo (arm). Since Catenin Responsive Transcription (CRT) has been implicated in the genesis of many cancers, it makes a good target for developing therapeutics that could modulate the nuclear activity of β -cat. Recently, we employed a novel methodology of integrating a "sensitized" chemical genetic high-throughput RNAi screen to identify specific small molecule and microRNA modulators of CRT in *Drosophila* and human cell lines, both in the context of development and disease. I will discuss the potential functions and mechanism of action of these newly identified chemical and genetic regulators of the Wnt/wg pathway.

4:15 Sponsored Presentations (Opportunities Available)

» 4:45 KEYNOTE PANEL: Has RNAi Screening Delivered On Its Promise?

Moderator: Christophe Echeverri, Ph.D., CEO/CSO, Cenix BioScience GmbH

Panelists: Hakim Djaballah, Ph.D., Director, HTS Core Facility, Memorial Sloan Kettering Cancer Center

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

Alex Gaither, Ph.D., Research Investigator II, Developmental and Molecular Pathways, Novartis Institutes for Biomedical Research

Scott Martin, Ph.D., Team Leader, RNAi Screening, NIH Chemical Genomics Center, NIH Center for Translational Therapeutics, NIH

5:45 End of Day

FRIDAY, NOVEMBER 4

7:30 am Interactive Breakfast Breakout Discussion Groups

EXPLORING DIVERSE TARGETS

8:35 Chairperson's Opening Remarks

Hakim Djaballah, Ph.D., Director, HTS Core Facility, Memorial Sloan Kettering Cancer Center

8:40 Finding New Circadian Clock Components Using RNAi-Based Genetic Screens

Andrew Liu, Ph.D., Assistant Professor, Biological Sciences, The University of Memphis

Two decades of research identified a dozen clock genes and defined a biochemical feedback mechanism of circadian clock function, a recurring event at the cellular level that underlies our 24-hr rhythms in behavior and physiology. We applied kinetic bioluminescence recording in a genome-wide siRNA screen and identified hundreds of modifiers that impact clock function. Currently we are using lentiviral shRNAs to investigate the roles these modifiers play in the tissue-specific and ubiquitous molecular clock networks.

9:10 Identification of Myostatin Suppressors Using a Primary Myoblast Cell Line

Erica Stec, Ph.D., Research Biochemist, Screening and Protein Sciences Group, Merck Research Laboratories

Myostatin serves to negatively regulate stem cell activation, making it an obvious candidate for therapeutic intervention to promote muscle regeneration in Sarcopenia. A high content, genome-wide RNAi screen was performed to identify novel genes that suppress the myostatin signaling pathway. Human primary skeletal myoblasts were used as the primary screening system and stained for alpha-sarcomeric actin as a marker for differentiation. Follow up experiments included profiling additional human myoblast cell lines from both young and aged donors to validate targets of myostatin suppression.

9:40 Using High-Content, High-Throughput RNAi Screening to Discover Factors Involved in Viral Replication

Sara Cherry, Ph.D., Assistant Professor, Microbiology, Penn Genome Frontiers Institute, University of Pennsylvania School of Medicine

To discover cellularly encoded genes that impact viral replication we are using RNAi screening to identify innate immune mechanisms as well as cellular factors required for replication, with the hopes that they will reveal novel targets for antiviral therapeutics. By comparing and contrasting the factors identified using a panel of medically relevant human arboviruses we found three classes: those that impact replication of multiple virus families, others are virus family specific and a third group that are seemingly specific for a particular species of virus within a family.

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

10:55 Deciphering Cancer-Specific Pathways by Large-Scale RNAi Screens

Narendra Vajapeyee, Ph.D., Assistant Professor, Pathology, Member, Yale Cancer Center, Yale University School of Medicine

Among the many changes associated with cancer, the loss of tumor suppressor genes and their function are some of the most important. Here we present two shRNA-based large-scale RNAi screens: the first screen identifies new tumor suppressor genes and second one characterizes the apoptosis-inducing ability of a particular tumor suppressor.

11:25 A Genome-Wide siRNA Screen to Identify Modulators of Insulin Sensitivity and Gluconeogenesis

Ruojing Yang, Ph.D., Senior Research Biologist, Diabetes, Merck & Co.

A 4-gene High Throughput Genomics 384-well assay was developed that allowed concomitant measurements of G6PC and pyruvate dehydrogenase kinase 4 (PDK4) mRNA levels in AH-G6PC cells. Using this assay format, we screened an siRNA library containing pooled siRNA targeting 6650 druggable genes and identified 614 hits that lowered G6PC expression without increasing PDK4 mRNA levels. Our results support the proposition that the proteins encoded by the genes identified in our cell-based druggable genome siRNA screen hold the potential to serve as novel pharmacological targets for the treatment of T2D.

11:55 Panel Discussion: Common Pitfalls in Setting Up Effective RNAi Screens

Moderator: Hakim Djaballah, Ph.D., Director, HTS Core Facility, Memorial Sloan Kettering Cancer Center

12:25 pm Sponsored Presentation (Opportunity Available)

12:40 Luncheon Presentation (Sponsorship Opportunity Available) or Lunch on Your Own

SUCCESSFUL ANALYSIS AND INTERPRETATION

1:55 Chairperson's Remarks

Robert Hills, Ph.D., Senior Scientist, Lead Discovery, Janssen Pharmaceutical Companies of Johnson & Johnson

2:00 Elucidation of shRNA Off-Target Effects: A Multi-Vector, Multi-Cell Study

Robert Hills, Ph.D., Senior Scientist, Lead Discovery, Janssen Pharmaceutical Companies of Johnson & Johnson

Off target effects of siRNA are well documented, the usual suspect being the delivery method. However, the off target effects of viral delivery of shRNA are not as extensively documented. We therefore undertook a study comparing mouse and human cells transduced with two non-targeting shRNAs as well as a vector containing only a puro resistance element. Genome-wide coverage will be presented detailing differences of transduced cells compared to parental lines, as well as the effect of NT shRNAs on lineage development.

2:30 siRNA Off-Target Effects in Genome-Wide Screens Identify Signaling Pathway Members

Eugen Buehler, Ph.D., Senior Research Associate, Informatics IT, Merck & Co., Inc.

We describe a method for analyzing siRNA screens based entirely on off-target effects. Using a screen for members of the Wnt pathway, we demonstrate that this method identifies known pathway components, some of which are not present in the screening library. This technique can be applied to siRNA screen results retroactively to confirm positives and identify genes missed using conventional methods for on-target gene selection. This method is currently being used in the analysis of screens at Merck and the NIH.

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

3:40 Challenges in Managing Data from Genome-Scale siRNA Screening

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

Despite our expertise in carrying out high throughput screens of small molecule libraries, RNAi screening has posed many new challenges— not only in automating siRNA library handling and high throughput transfection protocols, but also in managing RNAi screening data and validating siRNA hits from primary screens. I will describe Screensaver, an open source, web-based lab information management system developed to address our informatics needs. Screensaver can support the storage and analysis of data from both genome-scale RNAi screening projects and small molecule screening projects.

4:10 Speaker to be Announced

4:40 Panel Discussion: Strategies for Improving Data Analysis and Hit Validation

Moderator: Robert Hills, Ph.D., Senior Scientist, Lead Discovery, Janssen Pharmaceutical Companies of Johnson & Johnson

5:10 Close of Conference



Inaugural

Allosteric Modulators

An Emerging Strategy for Drug Design

November 3 - 4
Program 6

THURSDAY, NOVEMBER 3

IDENTIFYING ALLOSTERIC MODULATORS: THEORY AND SCREENING APPROACHES

1:30 pm Chairperson's Remarks

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

» 1:40 KEYNOTE PRESENTATION:



7TM Receptor Drug Discovery: An Allosteric View of Shapeshifting Proteins

Terrence Kenakin, Ph.D., Director, Molecular Discovery, Assay Development, GlaxoSmithKline

As new drug screening increasingly uses functional rather than traditional binding assays, allosteric ligands often enter the drug discovery process through happenstance. However the need for specifically designed allosteric screens is growing. The therapeutic potential of allosteric molecules due to their unique properties of permissive, saturable and probe dependent activity is becoming well recognized. This talk discusses properties of allosteric ligands, how they can be detected and procedures for quantifying their activity for lead optimization.

2:40 A Case Study: Evaluating Allosteric Modulators of CCR1 for Multiple Myeloma

Annette Gilchrist, Ph.D., Assistant Professor, Pharmaceutical Sciences, Midwestern University

Osteolytic bone destruction is one of the most frequent complications of multiple myeloma (MM), a clonal B-cell disorder characterized by the accumulation of malignant plasma cells in the bone marrow. Studies have recently emerged that suggest a role for the chemokine receptor CCR1 in multiple myeloma progression. To evaluate the role of CCR1 in MM we used several previously described allosteric small molecule inhibitors. Results from radioactive binding assays, and beta-arrestin translocation assays will be presented.

3:10 Networking Refreshment Break in the Exhibit Hall with Poster Viewing

3:45 Opportunities and Challenges in Developing High-Throughput Screens for Allosteric Modulators of G Protein-Coupled Receptors

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

Allosteric modulation of G protein-coupled receptors is an emerging therapeutic strategy that can potentially provide improved selectivity and safety, along with maintenance of spatial and temporal regulation associated with native receptor signaling. Accordingly, drug discovery efforts at GPCR targets have increasingly focused on the identification of allosteric modulators. This presentation will focus on the special challenges, opportunities and current strategies for high-throughput screening for allosteric GPCR modulators, with particular focus on the identification of positive allosteric modulators.

4:15 Sponsored Presentations (Opportunities Available)

4:45 Positive Allosteric Modulation of Metabotropic Glutamate Receptors in Neurotransmission: Specific Activity-Dependent Regulation of Defined Synaptic Circuits *in vivo*

Thomas Salt, Ph.D., Professor, Visual Neuroscience, University College London Institute of Ophthalmology

This talk will review use of Positive Allosteric Modulators (PAMs) to enhance mGlu synaptic and extra-synaptic function. I will show how PAMs can affect synaptic function under different physiological and pathological conditions in the whole organism based on recent experimental data on PAM action in thalamic circuitry from various groups (including the presenter's). This will be placed in the context of how PAMs can affect sensory/pain processes, cognitive processes, schizophrenia, and epileptic mechanisms *in vivo*.



5:15 Panel Discussion: Screening for Allosteric Modulators

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

- What are the potential therapeutic advantages of PAMs (besides receptor subtype selectivity) and how can we exploit these?
- What is the meaning and relevance of the agonist activity that many PAMs exhibit in addition to their PAM activity *in vitro*? Is this an artifact of recombinant expression systems? Do mixed ago/PAMs have potential therapeutic advantages?
- Can allosteric modulators be used to modulate signaling bias? Can a PAM approach be used to avoid receptor desensitization?
- Are dynamic assays (specifically cAMP assays) different/better than accumulation assays for detecting allosteric modulators?
- Can expect to discover a large number of native allosteric modulators in the coming years?

5:45 End of Day

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7:30 am Interactive Breakfast Breakout Discussion Groups

Topic: Can Allosteric Modulators be Useful CNS Drugs?

Moderator: Thomas Salt, Ph.D., Professor, Visual Neuroscience, University College London Institute of Ophthalmology

- How can allosteric modulators regulate physiology *in vivo*?
- How specific are the effects of allosteric modulators in complex physiological systems?
- How effective can allosteric modulators be in pathological conditions?

Topic: Do Allosteric Modulators have Enough "OOMPH" to Produce Significant *In-vivo* Effects?

Moderator: John R. Atack, Ph.D., Senior Research Fellow, Neuroscience, Johnson & Johnson Pharmaceutical R&D

- Do positive allosteric modulators really offer advantages over agonists?
- Do agonists really produce desensitization *in vivo*?
- When and why is a tickle better than a sledgehammer?

**ALLOSTERIC MODULATORS
IN DEVELOPMENT**

8:35 Chairperson's Opening Remarks

Scott Kuduk, Ph.D., Senior Research Fellow, Medicinal Chemistry, Merck & Co.

8:40 Targeting Schizophrenia with Allosteric Modulators of Class A and Class C GPCRs

Craig Lindsley, Ph.D., Professor of Pharmacology and Chemistry; Director, Medicinal Chemistry, Vanderbilt Program in Drug Discovery, Vanderbilt University Medical Center

Allosteric modulation of either mGlu5 or M4 represent attractive new approaches for the treatment of the complex symptoms of schizophrenia. This talk will describe the HTS, lead optimization and *in vivo* efficacy of PAMs for both targets.

9:10 Identification of a Selective M1 Muscarinic Receptor Positive Allosteric Modulator

Scott Kuduk, Ph.D., Senior Research Fellow, Medicinal Chemistry, Merck & Co.

To combat the cognitive decline of Alzheimer's Disease, we search for positive allosteric modulators (PAMs) that activate the M1 muscarinic receptor sub-type of the cholinergic system in neurons of the basal forebrain. We targeted an allosteric site on the M1 receptor rather than the highly conserved orthosteric acetylcholine binding site. An HTS lead, quinolone carboxylic acid BQCA, evolved into a highly selective Quinolizidinone carboxylic acid PAM with enhanced CNS exposure and improved efficacy in a rodent model of cognition.



9:40 FEATURED PRESENTATION:

CCR5 Antagonists for HIV Therapy: The Discovery of Maraviroc

Tony Wood, Ph.D., Senior Vice President & Head, Worldwide Medicinal Chemistry, Pfizer

The lecture will describe the discovery of the CCR5 antagonist Maraviroc for the treatment of HIV. It will cover the medicinal chemistry of hit identification, optimization to overcome HERG binding risks, and candidate selection considerations.

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

10:55 Identification and Pharmacological Characterization of Multiple Allosteric Binding Sites on the Free Fatty Acid (FFA1) Receptor

Gayathri Swaminath, Ph.D., Senior Scientist, Metabolic Disorders, Amgen, Inc.

Activation of FFA1 (GPR40) is mediated by unsaturated fatty acids and importantly, can lead to amplification of glucose stimulated insulin secretion, suggesting a potential role of FFA1 as a target for type 2 diabetes. The focus of this talk will be on recent discovery of novel synthetic allosteric FFA1 agonists that display positive cooperativity and have the potential to deliver therapeutic benefits.

11:25 Discovery and Characterization of a Novel Chemical Class of GABA-BR Allosteric Potentiators

Sylvain Celanire, Ph.D., Group Leader, CNS Unit, Medicinal Chemistry, Addex Pharma

The allosteric modulation of GABA-BRs is offering an attractive and novel approach to identify new drug candidates for the treatment of disorders such as anxiety, depression, schizophrenia, pain or GERD, that are devoid of side effects associated with GABAB receptor agonists (e.g. baclofen), and represent a major advance in the drug discovery process. Addex has recently demonstrated *in vivo* efficacy of such novel PAMs in pre-clinical models of anxiety, inflammatory pain and osteoarthritis pain models.

11:55 GABA-A Receptor Subtype-Selective Modulators

John R. Atack, Ph.D., Senior Research Fellow, Neuroscience, Johnson & Johnson Pharmaceutical R&D

12:25 pm Sponsored Presentation (Opportunity Available)

12:40 Luncheon Presentation (Sponsorship Opportunity Available) or Lunch on Your Own

**NEW APPROACHES AND TARGETS FOR
ALLOSTERIC MODULATION**

1:55 Chairperson's Remarks

2:00 Pepducins: Allosteric Peptide Modulators of GPCRs

Kenneth Carlson, Ph.D., Vice President, Biology, Anchor Therapeutics

We will present on pepducins as novel allosteric modulators, using our CXCR4 allosteric agonist as an example. Pharmacological, mechanistic and *in vivo* data on this molecule will be discussed. Studies demonstrating that this molecule is a biased, allosteric agonist of CXCR4 with *in vivo* efficacy will also be presented.

2:30 Developing Assays and Discovery of VLA-4 Integrin Allosteric Antagonists

Alexandre Chigaev, Ph.D., Assistant Professor, Pathology, University of New Mexico

The VLA-4 integrin receptor is a single-pass membrane receptor that is involved in cell adhesion. This talk will provide the first report of a VLA-4 integrin allosteric antagonist. I will describe the assay development and screening for allosteric antagonists of VLA-4 integrin. Results of secondary validation and *in vivo* effects will be also presented.

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

3:40 Orthosteric and Allosteric Ligand Interactions within the Chemokine System - Implications for Future Drug Design

Mette M. Rosenkilde, M.D., Ph.D., Professor in Pharmacology, Department of Neuroscience and Pharmacology, Faculty of Health Sciences

Chemokine receptors control cell migration, and have consequently

been targets for drug development. Given the large size and extracellular receptor interaction of chemokines, small molecules often act more deeply in an allosteric mode. Using various CC-chemokine receptors including chimeras as model systems, the molecular interaction and conformational interchange required for proper action of various orthosteric chemokines and allosteric small molecules, including well-known CCR5 antagonists and different series of agonists and/or positive allosteric modulators was studied.

4:10 Allosteric Functional Switch of GPCRs: The Example of the Neurokinin NK2 Receptor

Jean-Luc Galzi, Ph.D., Research Director, School of Biotechnology, Strasbourg, Centre National de la Recherche Scientifique (CNRS)

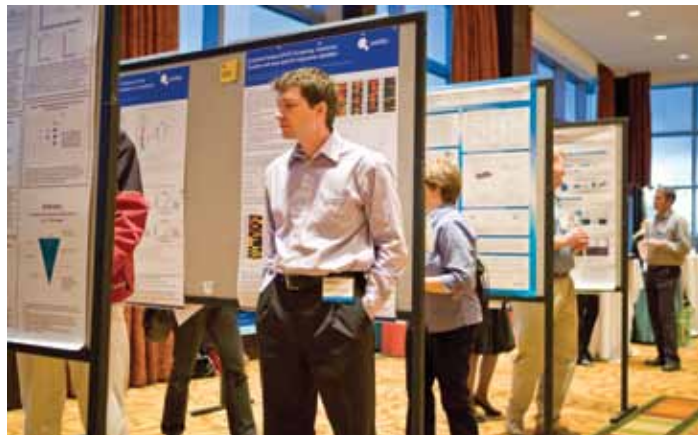
We describe receptor functional architecture according to three major phenotypes (affinity for ligands, interconversion between functional states, and biological activity associated with individual states) and combine experimental data with mathematical modelling to account for regulatory processes involving GPCRs and ligand gated ion channels. Our work illustrates that, depending on the agonist, NK2 receptors differentially couple to calcium and/or cAMP intracellular signalling and that an allosteric modulator can switch signalling from cAMP to calcium.

4:40 GPCR Allosteric Pharmacology in Endogenous Cell Lines & Primary Tissues

Joan Ballesteros, Ph.D., Chief Scientific Officer, Vivia Biotech SL

To circumvent the complex validation of GPCR Allosteric modulators we propose to validate these candidates directly in fresh primary tissues or endogenous cell lines. In these physiologically meaningful systems any potentiation or decrease in the endogenous ligand activity by the compound represents a credible validation of the compound's activity. We use our PAM candidate of the GLP1R to show the activity of 800 analog compounds in transfected vs cell lines that express endogenously the GLP1R. We also validate the candidate in isolated pancreatic islet cells. We compare both human and rat cells to compare species differences. The same set of endogenous human and rat endogenous cells is being developed for other insulin-releasing GPCRs like GPR40, GPR55, and GPR119. Heterodimer formation among these GPCRs can be readily assessed in these endogenous cell lines.

5:10 Close of Conference



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Advances in Targeting Phosphoinositide-3 Kinase (PI3K) Pathways

Novel Inhibitors for PI3K, Akt and mTOR

THURSDAY, NOVEMBER 3

TARGETING PI3K

1:30 pm Chairperson's Remarks

1:40 Inhibiting the PI3K Pathway in Cancer: Scalpels, Knives or Axes?

Joseph R. Garlich, Ph.D., CSO, Semafore Pharmaceuticals

Evolving cancer biology is revealing new information about the PI3K pathway that has tremendous implications for how best to block the pathway to maximize anticancer effects. For example different PI3K isoforms have been reported to be critical players in different types of cancer and non-PI3K pathways are found to become up-regulated which thwarts efficacy. The latest trends in this rapidly changing field will be discussed along with a case study of the clinical stage multi-kinase inhibitor SF1126 designed to maximally block the PI3K pathway.

2:10 Targeting PI3K Delta: A New Paradigm for the Treatment of B-Cell Malignancies that Involves the Tumor Cell and its Microenvironment

Brian Lannutti, Ph.D., Senior Scientist II, Oncology Research, Gilead Sciences

2:40 VPS34, A Class III PI3K: A Potential Novel Drug Target for Cancer Therapy

Wen Jin Wu, Principal Investigator, Division of Monoclonal Antibodies (DMA), Office of Biotechnology Products (OBP), FDA (tentative)

We find that Src, which plays an important role in the regulation of cancer development and progression, directly phosphorylates Vacuolar protein sorting 34 VPS34, and that this phosphorylation resulted in the activation of VPS34 to mediate cellular transformation. We also find that the levels of VPS34 expression and tyrosine phosphorylation are correlated with the tumorigenic activity of human breast cancer cells, suggesting that VPS34 may be involved in cancer development and a potential novel drug target for breast cancer therapy.

3:10 Networking Refreshment Break in the Exhibit Hall with Poster Viewing

PROGRESS IN TARGETING mTOR/mTORC

3:45 Discovery and Optimization of Selective ATP-Competitive mTOR Inhibitors

Emily Peterson, Ph.D., Scientist, Medicinal Chemistry, Amgen, Cambridge

4:15 The Identification of Clinical Candidate, AZD8055: A Potent, Selective Small Molecule Dual Inhibitor of mTORC1 and mTORC2

Kurt Pike, Ph.D., Team Leader, Medicinal Chemistry, AstraZeneca, UK
Two alternative approaches to identify selective inhibitors of the mTOR kinase domain resulted in the identification of two distinct lead series. The identification and optimization of these series will be described, culminating in the discovery of AZD8055, a potent and selective inhibitor of both mTORC1 and mTORC2. AZD8055 demonstrates dose-dependant tumor growth inhibition in xenograft studies and is currently undergoing clinical evaluation as a potential cancer therapy.

4:45 PWT33597, A Novel PI3 Kinase alpha/mTOR Inhibitor: Translation to the Clinic

David J. Matthews, Ph.D., Vice President, Drug Discovery and Exploratory Development, Pathway Therapeutics, Inc.

Dysregulation of both PI3 kinase and mTOR signaling is prevalent in cancer, prompting the discovery and development of drugs targeting these critical pathways. PWT33597 is a novel, highly selective inhibitor of PI3 kinase alpha and mTOR. The pre-clinical profile of PWT33597 will be discussed, together with data supporting the translation of these results into clinical studies.

5:15 Palomid 529 (P529), an Allosteric Dual TORC1/TORC2 Inhibitor of the PI3K/Akt/mTOR Pathway – Results from the Clinic

David Sherris, Ph.D., CEO, CSO, Paloma Pharmaceuticals

Aberrant up-regulation of the PI3K/Akt/mTOR pathway is involved in a variety of human diseases including retinal diseases of neovascularization and cancer. Normalization of the pathway could then be expected to potentially ameliorate such diseases. However as the pathway is complex with multiple branch points, cross-talk between other pathways and internal feedback inhibition, it is not a particularly simple task to adequately control the pathway to effect activity of disease states. We have shown in a variety of in vitro and in vivo animal models that disruption of both the TORC1 and TORC2 complexes by the allosteric inhibitor P529 could both normalize activation of the pathway and inhibit disease in a variety of animal models. We believe that allosteric inhibition of the TORC complexes via their dissociation as opposed to catalytic inhibition of mTOR is key to this activity. Here we will show in in vitro and in vivo studies activity of P529 as well as interim results in our Phase I human trial of P529 in age-related macular degeneration.

5:45 End of Day

FRIDAY, NOVEMBER 4

7:30 am Interactive Breakfast Breakout Discussion Groups

AN EMERGING, NOVEL MODULATOR

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SHIP1, a Phosphatidylinositide Phosphatase: From Basic Science to Therapeutic Applications

8:35 Chairperson's Opening Remarks

Csaba Szabo, M.D., Ph.D., CSO, Aquinox Pharmaceuticals

8:40 SHIP1: Cellular Functions and Pharmacological Activation

Alice Mui, Ph.D., Assistant Professor, Surgery; Co-Director, Centre for Surgical Research, University of British Columbia

SHIP1 is a normal physiologic counter-regulator of PI3K, which is expressed in immune/hematopoietic cells, that hydrolyzes the PI3K product PIP(3). The various regulatory roles of SHIP1 will be overviewed in the current presentation. Additionally, data will be presented with prototypical small-molecule activators of SHIP1.

These compounds activate recombinant SHIP1 enzyme *in vitro* and stimulate SHIP1 activity in intact macrophage and mast cells, *via* binding to an allosteric activation domain within SHIP1, with protective effects in mouse models of inflammation.

9:10 Development of AQX-1125, an Allosteric SHIP1 Activator: Pre-Clinical and Early-Stage Clinical Results

Csaba Szabo, M.D., Ph.D., CSO, Aquinox Pharmaceuticals

AQX-1125 is a clinical-stage small-molecule allosteric SHIP1 activator that is being developed for inflammatory pulmonary diseases. The present talk will summarize the *in vitro* effects of AQX-1125, in inhibiting leukocyte chemotaxis, Akt activation, pro-inflammatory mediator production, as well as its anti-inflammatory effects in various rodent models, including ovalbumin-, LPS-, and cigarette smoke - induced airway inflammation. In additional, Phase I clinical safety and pharmacokinetic data will be presented.

9:25 SHIP1: A Modulator of PI3K Metabolism and Functional Responses in Lymphocytes

Stephen G. Ward, Ph.D., Professor, Inflammatory Cell Biology Laboratory, Pharmacy and Pharmacology, University of Bath

The present lecture will outline the role of SHIP1 in regulating cell signalling pathways in immune cells (particularly peripheral T and B lymphocytes) that occur during the process of inflammation and allergy. An additional topic of the talk will focus on the regulation by SHIP1 of leukocyte motility and chemotaxis.

9:40 SHIP1 and Allergic Lung Diseases: Pre-Clinical and Clinical Aspects

Susan M. MacDonald, M.D., Professor; Associate Chair, Department of Medicine, Johns Hopkins University

Pre-clinical data demonstrate that genetic deletion of SHIP1 induces a pro-inflammatory phenotype in the lung, and sensitizes animals to various pro-inflammatory challenges. In basophils from asthmatic patients, a highly significant negative correlation exists between the amount of SHIP protein per cell equivalent and maximum histamine release to HrHRF. Furthermore, SHIP1 knockdown of human basophils increases their IgE-stimulated histamine release, whereas pharmacological SHIP1 activation decreases this response.

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

NOVEL STRATEGIES

10:55 mTOR siRNA/Antisense Can Deliver Better Potency than Rapamycin in HCC Cells

Yuxin Wang, Ph.D., Senior Scientist, Biology, Pfizer, Inc.

Rapamycin and analogues do not completely inhibit all components of the mTOR signaling complex potentially, leading to an mTOR dependent survival pathway that could lead to treatment failure. mTOR siRNA and antisense may represent better clinical opportunities than rapamycin in complete inhibition of mTOR signaling in cells by inhibiting both mTORC1 and mTORC2. In this experiment, we showed that siRNA molecules against mTOR can provide more potent and complete signaling and functional inhibition activities compare with rapamycin.

11:25 PI3K, AKT and mTORC1 – Potential New Targets for the Treatment of Alcohol-Related Disorders

Dorit Ron, Professor, Neurology, The Gallo Research Center, University of California, San Francisco

We recently found that the PI3K/AKT/mTORC1 signaling pathway is activated in the nucleus accumbens of rodents that consume large quantities of alcohol. The nucleus accumbens is a brain region that is heavily implicated in addiction and we show that inhibition of the PI3K/AKT/mTORC1 pathway with wortmannin, tricibirine and rapamycin in this brain region decreases excessive alcohol intake, seeking and reward in pre-clinical rodent models of alcohol abuse. Together, our results suggest that this pathway may be a novel contributor to molecular

mechanisms underlying alcohol addiction.

11:55 Progress in the Development of Novel, ATP-Competitive, Isoform-Selective PI3K Inhibitors for the Treatment of Inflammatory Diseases

Stephen J. Shuttleworth, Ph.D., CSO, Karus Therapeutics, Ltd.

12:25 pm Sponsored Presentation (Opportunity Available)

12:40 Luncheon Presentation (Sponsorship Opportunity Available) or Lunch on Your Own

1:55 Chairperson's Remarks

TARGETING PDK1

2:00 Targeting PDK1 in Cancer

Marco Falasca, Ph.D., Professor, Molecular Pharmacology, Inositide Signalling Laboratory, Queen Mary University of London

PDK1 activates a large number of proteins, including Akt, some PKC isoforms, S6K and SGK. Data also reveal that PDK1 is oncogenic and this is dependent on PI3K pathway. Therefore, accumulating evidence demonstrates that PDK1 is a valid therapeutic target and suggests that PDK1 inhibitors may be useful to prevent cancer progression and abnormal tissue dissemination. This talk will focus on our recent data on the role of PDK1 in cancer and approaches used to inhibit PDK1.

2:30 Structure-Based Optimization of Fragments into Potent and Highly Selective PDK1 Inhibitors

Jesus R. Medina, Ph.D., Senior Investigator, GlaxoSmithKline

One of the most difficult challenges in fragment-based lead discovery (FBLD) is the transformation of a validated fragment hit into a lead-like molecule, which is often guided by crystallography, modeling and docking. Once a lead-like molecule is discovered, the structural data becomes increasingly important to engineer potency and selectivity into the inhibitor. This presentation will describe our use of FBLD principles and structure-based design to transform a low MW fragment hit into novel, potent and selective aminoindazole inhibitors of phosphoinositide-dependent kinase 1 (PDK1), an attractive target for cancer therapy.

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

DRUG RESISTANCE

3:40 A Combined Synthetic Lethality and Drug Resistance Screen Identifies Mechanisms of Resistance and Synthetic Lethal Interactions in Breast Cancer

Sebastian Nijman, Ph.D., Principal Investigator, Functional Genomics, Center for Molecular Medicine (CeMM), Vienna

We performed a systematic drug-gene functional interaction screen to search for drug resistance mechanisms and synthetic lethal interactions between breast cancer genes and clinically relevant drugs. We identify an unexpected mechanism for resistance to PI3K inhibitors and several synthetic lethal interactions. These findings may have direct clinical implications for patient stratification and combination therapy.

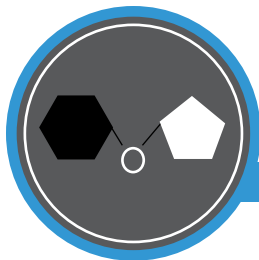
4:10 Panel Discussion: Designing Compounds Against Lipid Kinases: NVP-BKM120 - a Pan Class I PI3K Inhibitor

Mark Knapp, Ph.D., Structural Chemistry, Novartis Institutes for BioMedical Research (NIBR)

What approaches have proven more or less successful for identifying promising targets?

- What is the industry experience with moving forward into developing PI3K inhibitors as drug targets?
- What are promising novel targets to date?

5:10 Close of Conference



Fourth Annual

Diabetes Drug Discovery

New Diabetes Drug Targets and Candidates

November 3 - 4
Program 8

THURSDAY, NOVEMBER 3

DIABETES DRUG DEVELOPMENT FROM DIFFERENT VANTAGES

1:30 pm Chairperson's Remarks

1:40 FEATURED PRESENTATION:



Inhibiting Glucose Transporters via SGLT inhibitors – the Next New Diabetes Drug Family?

Michael Mark, Ph.D., Vice President, CardioMetabolic Diseases Research, Boehringer Ingelheim

This presentation will provide an update on diabetes drug candidates in late stage development, with a focus on compounds targeting sodium glucose transporters. Current challenges faced in the field of diabetes drug development will also be covered.

2:25 FEATURED PRESENTATION:



Diabetes Drug Targets from Gastric Bypass Surgery

Lee M. Kaplan, M.D., Ph.D., Professor, Harvard Medical School

3:10 Networking Refreshment Break in the Exhibit Hall with Poster Viewing



3:45 A Physician's Perspective on the Future of Diabetes Treatments

Rohit N. Kulkarni, M.D., Ph.D., Associate Professor, Medicine, Harvard Medical School; Investigator, Joslin Diabetes Center

This presentation will discuss the scope of the global diabetes problem and which types of diabetes treatments are most needed from a diabetes physician's and his patients' perspective to help provide a relevant context to scientists developing new diabetes treatments.

4:15 tONCO: Taconic's Innovative Portfolio of Tools and Capabilities to Evaluate the Efficacy of Novel Cancer Therapeutics

David S. Grass, Ph.D., Vice President, Scientific Operations, Taconic

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4:15 Sponsored Presentations (Opportunity Available)

4:45 Diabetes Market Landscape

Kelly Close, MBA, President, Close Concerns

5:15 Panel Discussion: Diabetes Drug Development



Moderator: Rebecca Taub, M.D., Senior Vice President, Research and Development, VIA Pharmaceuticals

*Panelists: Kelly Close, MBA, President, Close Concerns
Rohit N. Kulkarni, M.D., Ph.D., Associate Professor, Medicine, Harvard Medical School; Investigator, Joslin*

Diabetes Center

Lee M. Kaplan, M.D., Ph.D., Professor, Harvard Medical School

Michael Mark, Ph.D., Vice President, CardioMetabolic Diseases Research, Boehringer Ingelheim

Cristina Rondinone, Ph.D., Vice President, R&D, Head, Cardiovascular/Metabolic Diseases, MedImmune

- Developing diabetes drugs in Asia – how is it different? Is that the future?
- What will clinical trials look like five years from now?
- What is the ideal diabetes treatment regimen?

5:45 End of Day

FRIDAY, NOVEMBER 4

7:30 am Interactive Breakfast Breakout Discussion Groups

NEW TARGETS FOR DIABETES DRUG DEVELOPMENT

8:35 Chairperson's Opening Remarks

8:40 Biologics: The Future of Treatments for Cardiovascular and Metabolic Diseases?

Cristina Rondinone, Ph.D., Vice President, R&D, Head, Cardiovascular/ Metabolic Diseases, MedImmune



9:10 Targeting the Lipid Component of Diabetes

Rebecca Taub, M.D., Senior Vice President, Research and Development, VIA Pharmaceuticals

VIA's cardiometabolic drugs are directed to specific tissues to enhance efficacy and avoid safety issues. This presentation will discuss VIA compounds that specifically target thyroid hormone receptors in the liver involved in metabolism and cholesterol regulation. I will also show how THR beta lowers cholesterol by a different mechanism from statins and reduces triglycerides by increasing fat metabolism. VIA's pre-clinical intestinal Diacylglycerol Acyl Transferase 1 (DGAT1) inhibitor program for diabetes that has an upside potential in weight control and dyslipidemia will also be briefly presented.

9:40 Roux-en-Y in a Pill: Therapies of the Future

Sean Ross, Ph.D., Investigator, Enteroendocrine Discovery Performance Unit, GlaxoSmithKline

This presentation will highlight our strategy of identifying therapies to mimic the phenotypic changes seen in patients who have undergone Roux-en-Y surgery. The primary focus is the gastrointestinal system, targets that exist within and therapies that mimic the hormonal changes observed in Roux-en-Y patients.

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

10:55 GPR119

Peter Corneliuss, Ph.D., Former Project Leader/Associate Research Fellow, Cardiovascular, Metabolic and Endocrine Diseases, Pfizer
GPR119 is a Gs-coupled GPCR expressed in entero-endocrine cells of the gastrointestinal tract and in pancreatic islets. GPR119 agonists have potential as a new treatment for Type 2 Diabetes. To guide drug discovery efforts for GPR119 agonists, we developed in vitro assays for both rat and human GPR119. These assays uncovered unexpected functional SAR at human versus rat GPR119. Our results indicate that rodent models may not predict human GPR119 response, for particular chemical series.

11:25 AR-7947, a GPR119 Agonist with Durable Activity in Pre-Clinical Models of Type 2 Diabetes

Jay B. Fell, Research Investigator, Medicinal Chemistry GPR119 Project Lead, Array BioPharma Inc.

GPR119 agonists have the potential to work additively with DPP4 inhibitors leading to enhanced active GLP-1 levels, better glucose control and potential for weight loss in Type II diabetic patients. Array BioPharma has developed oral potent and selective GPR119 agonists that show durable glucose control and serum lipid lowering in animal models of diabetes. Treatment with AR-7947 in combination with a DPP4 inhibitor led to increased efficacy in OGTT and nonfasted glucose endpoints compared to monotherapy.

11:55 Design of Potent and Selective GPR119 Agonists for Type II Diabetes

H. Blair Wood, Ph.D., Director - Exploratory Chemistry Team Lead, Discovery and Preclinical Sciences, Merck Research Laboratories
Screening of the Merck sample collection identified a weakly potent GPR119 agonist hit. Hit to lead optimization afforded agonists with improved potency and selectivity. However, modest physical properties hindered the utility of this series. Design of a new lead series provided GPR119 agonists with improved physical properties.

12:25 pm Sponsored Presentation (Opportunity Available)

12:40 Luncheon Presentation (Sponsorship Opportunity Available) or Lunch on Your Own

DIABETES DRUG CANDIDATES

1:55 Chairperson's Remarks

2:00 DGAT1 Inhibitors for the Treatment of T2DM

Claire M. Steppan, Ph.D., Associate Research Fellow, Diabetes, Pfizer
DGAT1 (Acyl CoA:diacylglycerol acyltransferase 1) catalyzes the final step in the formation of triglyceride. DGAT1 inhibitors are being pursued for the treatment of metabolic disease including obesity, diabetes and dyslipidemia. This presentation will focus on the discovery of PF-04620110, a potent and selective inhibitor for the treatment of Type 2 diabetes.

2:30 Clinical and Pre-Clinical Experience with LX4211, a Dual Inhibitor of SGLT1 and SGLT2

David Powell, M.D., Vice President, Metabolism, Lexicon Pharmaceuticals
LX4211 is a potent inhibitor of SGLT1 and SGLT2. In patients with type 2 diabetes and in pre-clinical models, LX4211 treatment leads to rapid and impressive improvement in all glycemic parameters tested. LX4211 treatment not only increases urinary glucose excretion, it also increases circulating levels of GLP-1 which may contribute to the improved glycemic control observed in LX4211-treated diabetic patients.

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

3:40 Canagliflozin on Renal Glucose Re-Absorption and Blood Glucose Control in Diabetic Animals

Yin Liang, M.D., Ph.D., Head, in vivo Section, CVM Research, Johnson & Johnson Pharmaceutical Research & Development

The presentation will focus on: (1) Highlight the role of kidney in glucose re-absorption and explore inhibition of renal glucose re-absorption as a novel approach to treat type 2 diabetes; (2) Review canagliflozin pre-clinical pharmacology data to validate the new concept of increase urine glucose excretion as a potential anti-hyperglycemia strategy.

4:10 A Potential Novel SGLT2 Inhibitor for the Treatment of Metabolic Diseases - Pre-Clinical Development Status

Geraldine Deliencourt-Godefroy, Ph.D., Chief Scientific Officer, Sirona Biochem

SGLT2 Inhibitors, which block the reabsorption of glucose in the kidneys without interfering with glucose metabolism, hold real promise to solve unmet needs and could complement current therapies for Type 2 diabetes. Sirona Biochem through its subsidiary TFChem has developed a technology to mimic carbohydrates to unlock their potential for drug development. We have successfully applied our technology to a new family of SGLT inhibitors and identified a lead candidate that is currently undergoing preclinical development.

4:40 Rebalancing Inflammation in Type 2 Diabetes: CAT1000 New Chemical Entities

Michael Jirousek, Ph.D., Founder and Chief Scientific Officer, Catabasis Pharmaceuticals Inc.

Over the past decade subclinical chronic inflammation induced by obesity has been implicated as a key pathogenic factor in the development of insulin resistance and type 2 diabetes. The CAT1000 series of NCEs (new chemical entities) was designed to target key nodes in the inflammatory and cellular stress pathways. By selective inhibition of pro-inflammatory pathways and activation of endogenous anti-inflammatory pathways, the underlying inflammatory response in type 2 diabetes is rebalanced and resolved. The most exciting aspect of this approach is the potential for disease modifying therapy for the treatment of type 2 diabetes.

5:10 Close of Conference