FINAL AGENDA

The *Leading Event* on

# NOVEL DRUG TARGETS

*NINTH INTERNATIONAL*

# Discovery on TARGET

Register by July 15 and SAVE up to $450!

**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**

## PREMIER SPONSOR

Aquinox

## 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

Cambridge Healthtech Institute
250 First Avenue, Suite 300, Needham, MA 02494
Telephone: 781-972-5400 or Toll-free in the U.S. 888-999-6288 | Fax: 781-972-5425

DiscoveryOnTarget.com

*Second Annual*

# Advances in Targeting Phosphinositide-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**

### PROGESS 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 TPWT33597, 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 Talk Title to be Announced**

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

**5:45 End of Day**

## FRIDAY, NOVEMBER 4

**7:30 am Interactive Breakfast Breakout Discussion Groups**

### AN EMERGING, NOVEL MODULATOR

*Sponsored by* Aquinox

**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: PI3K Inhibitiors to Drugs**

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**