The Leading Event on
NOVEL DRUG TARGETS

NINTH INTERNATIONAL

Discovery on TARGET

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

Register by July 15 and SAVE up to $450!
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-dependent 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

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 PIP3. 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.
The treatment of Alcohol-Related Disorders
mechanisms underlying alcohol addiction.
suggest that this pathway may be a novel contributor to molecular
in pre-clinical rodent models of alcohol abuse. Together, our results
this brain region decreases excessive alcohol intake, seeking and reward
a KT/mTORC1 pathway with wortmannin, tricibirine and rapamycin in
heavily implicated in addiction and we show that inhibition of the Pi3K/
quantities of alcohol. The nucleus accumbens is a brain region that is
activated in the nucleus accumbens of rodents that consume large
amounts of alcohol per cell equivalent and maximum histamine
release to HHRF. Furthermore, SHIP1 knockdown of human
basophils increases their IgE-stimulated histamine release, whereas
pharmacological SHIP1 activation decreases this response.

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 HHRF. 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
Signaling 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 Inhibitors 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