

Cambridge Healthtech Institute's Ninth Annual

Next-Gen Kinase Inhibitors

Across Multiple Therapeutic Areas

JUNE 6-8, 2011 | ROYAL SONESTA HOTEL BOSTON | CAMBRIDGE, MA

Specialized Panels:

I. Next Generation Kinases – Selectivity What Now?

II. Structure-Based Kinase Inhibitor Design

Presented by hand-selected panelists who have contributed more than a decade of research to the kinase field!

June 6th Half Day

Pre-Conference Short Course:

The Art and Science of Kinases – What you Need to Know

Kent Stewart, Ph.D. Research Fellow, Abbott

CO-LOCATED WITH:

11th Annual Structure-Based Drug Design Conference

June 8-10 | healthtech.com/SBD

TOPIC HIGHLIGHTS

- ▷ Designing, Screening and Assessing Selectivity
- ▷ Identifying and Assaying Allosteric Kinase Inhibitors
- ▷ Covalent Inhibition
- ▷ Kinases for CNS Indications – An Exciting Challenge
- ▷ Inflammation & Autoimmune – Leading Programs
- ▷ Kinases in Oncology – PI3, mTOR, cMet & More
- ▷ Novel Kinase Targets in Hot Pursuit
- ▷ Screening & Monitoring DMPK and Tox
- ▷ Advances in Computational Methods
- ▷ Resistance – Future Challenges

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FEATURED SPEAKERS



Doriano Fabbro, Ph.D.,
Head, Kinase Biology,
Expertise Platform Kinases,
Novartis Pharma AG



Carol Mackintosh, Ph.D.,
MRC Protein Phosphorylation
Unit, College of Life Sciences,
James Black Centre, University of
Dundee



Isabelle Dussault, Ph.D.,
Director, Oncology
Research, Amgen



Ravi Kurumbail, Ph.D.,
Research Fellow and
Structural Biology
Laboratory Head, Pfizer

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8:00 am Workshop Registration & Morning Coffee

9:00-12:00 pm Pre-Conference Short Course*

**THE ART AND SCIENCE OF KINASES –
WHAT YOU NEED TO KNOW**



Instructor: Kent Stewart, Ph.D., Research Fellow, Department of Structural Biology, Global Pharmaceutical Research and Development, Abbott

This instructional course has been designed for both chemists and biologists who are new to kinase research or have some experience in the field and would like to learn more. The Art and Science of Kinases course will cover topics that are critical to know for any kinase research program. This course will cover;

- Protein structure; structural basis for “inactive” and “active” (DFG-out/in) forms; active site residues and electrostatics; gatekeeper; hinge, back-pocket.
- Assays: different formats and readout; factors that control IC50 and Ki; ATP-concentration; off-rate; solubility; reasons for compound success and failure.
- Inhibitors: approved drugs; inhibitor types; Type1/2; ATP-site directed; allosteric; covalent; hot-spots for ligand potency; common chemotypes.
- Kinome selectivity: kinomics; visualizing and interpreting heat maps; conserved and variable active-site residues.
- Technologies: high-throughput screening; fragment-based design; structure-based drug design.
- Example case studies; late-stage challenges.

Instructor Biography: Dr. Kent Stewart has over 27 years experience in drug discovery, including contributions to over 15 kinase research programs at Abbott. Over 90 research publications in drug research with over 20 devoted to kinase research. Contributed to 8 candidate compounds, including 3 kinase candidates, with one in advanced clinical evaluation. Specialist in computer-aided drug design. Ph.D. in Organic Chemistry from University of California, Los Angeles, and post-doctoral work in biochemistry at the Rockefeller University.

* Separate Registration Required

12:00-1:30 Main Conference Registration

Main Conference

KINASE SELECTIVITY

1:30 Chairperson’s Remarks

Eli Wallace, Ph.D., Director, Medicinal Chemistry, Array BioPharma

1:40 Selective Small Molecule Kinase Inhibitors

Eli Wallace, Ph.D., Director, Medicinal Chemistry, Array BioPharma

Over the last decade, inhibition of various protein kinases has proven to be a successful therapeutic strategy to treat many diseases. While several multi-kinase inhibitors have demonstrated patient benefit, selective inhibitors are highly desirable from a safety and combination strategy prospective. Years ago, obtaining selective kinase inhibitors was a pipedream, as many researchers believed the conserved nature of the catalytic ATP binding pocket precluded design of truly selective small molecule inhibitors. However, these concerns have proven unfounded as many groups have designed and developed highly selective kinase inhibitors. This has been accomplished by both allosteric and ATP-competitive inhibitors. In this presentation, examples of selective allosteric and ATP-competitive kinase inhibitors of MEK, ErbB2, and others will be discussed.



14-3-3 Proteins Capture the Signaling Signatures of Hormones and Kinase Inhibitors

Carol MacKintosh, Ph.D., MRC Protein Phosphorylation Unit, College of Life Sciences, James Black Center, University of Dundee

We have devised a strategy to identify quantitative changes in the sets of proteins that are phosphorylated when PI 3-kinase/Akt, PKC/Erk/p90RSK and AMPK are activated in cells, and which are then captured by the 14-3-3 family of phosphoprotein-binding proteins. The differing response signatures of target proteins provide barcodes that report on how hormones and drugs affect these signaling pathways in cells and tissues.

2:40 Challenges and Opportunities with Kinase Inhibitor Selectivity

Peter Brandt, Ph.D., Principal Scientist, Beactica AB

In house assessment of kinase inhibitor promiscuity has previously been considered a challenge. However, a recent study of published kinase selectivity data suggests that inhibitor promiscuity can be assessed by selecting panels comprising a small set of non-redundant kinases. Thus, by determining the selectivity on a very limited but well chosen set of kinases, inhibitor promiscuity can be assessed in a very economical way. The methods used in this study and the conclusions drawn will be discussed in detail.

3:10 Creation of Novel Genetically Engineered Cell Lines Showing Single-Kinase-Specific Sensitivity to Inhibition by Fmk



Trevor Collingwood, Ph.D., Manager Technology Research, Research Biotech, Sigma-Aldrich

Target validation is critical to drug discovery. We have used zinc finger nuclease technology to genetically engineer human cell lines so that all endogenous protein kinases are insensitive to the inhibitor molecule fmk yet retain normal function. On this background we then “dial in” additional genetic mutations in individual endogenous kinase genes to render them uniquely sensitive to inhibition by fmk. This novel approach enables functional validation of target kinases at physiological levels.

3:40 Networking Refreshment Break in the Exhibit Hall with Poster Viewing

FROM ALLOSTERIC & COVALENT INHIBITORS TO TARGETING INACTIVE KINASES

4:20 The ABC’s of Kinase Conformations

Henrik Möbitz, Ph.D., Investigator III, Global Discovery Chemistry, Novartis Institutes of BioMedical Research

Protein kinases are of medical interest because their dysregulation is implicated in several diseases. We assemble and annotate the structural kinome from the Protein Data Bank on the basis of a universal residue nomenclature. Despite the inherent flexibility of kinases, a small set of clusters can be identified whose distribution shows a bias for the active conformation. A common rationale links the active and inactive state: stabilization of the active conformation, as well as inactivation by displacement of helix-C or the activation loop is governed by the interaction between helix-C and the DFG motif. In particular, the conformation of the DFG motif is tightly correlated with the propensity of helix-C displacement. Our analysis reveals detailed mechanisms for the displacement of helix-C and the DFG and improves our understanding of the role of individual residues. By pooling conformations from the whole structural kinome, the energetic contributions of sequence and extrinsic factors can be estimated in free energy analyses.

4:50 Targeting Alternative, Less Conserved Sites on Kinase Targets to Provide an Avenue for Greater Selectivity

Kenneth Comess, Ph.D., Senior Scientist III, Global Pharmaceutical Discovery, Abbott Laboratories

Unbiased, high throughput screening methods provide opportunities to identify novel, therapeutically relevant and selective small molecule ligands. Various techniques, including NMR, surface plasmon resonance and affinity selection-mass spectrometry, have been applied to serine/threonine and tyrosine kinase targets in our laboratories to seek alternative mechanisms of inhibition. Different

screening formats are deployed at different stages in the early drug discovery process to take advantage of their relative efficiencies and the robustness of the information they provide. While the predominant classes of inhibitory ligands found in both biased activity-based and unbiased affinity-based screens are active site directed, the latter techniques have allowed identification of novel ligand binding sites and novel, selective compounds. One example will be described in detail, the discovery and characterization of non-ATP site inhibitors of the Jnk-1 and p38 α MAP kinases.

5:20 Exploiting Activation-State Dependent Conformational Differences in Protein Kinases for Inhibitor Design and Optimization

Mark Ashwell, Ph.D., Vice President, Medicinal Chemistry, ArQule, Inc.

The presentation will describe the utilization of a new understanding of the role of hydrophobic residues within the ATP-binding cleft of inactive protein kinases in order to discover novel inhibitors. The inhibitory characteristics of these inhibitors in biophysical, biochemical and cell-based assays together with their binding mode characterization using X-ray crystallographic and mutational studies will be described.

5:50-7:00 Networking Cocktail Reception in the Exhibit Hall with Poster Viewing

TUESDAY, JUNE 7

RESISTANCE IN NEXT GEN KINASE INHIBITORS

8:30 am Chairperson's Remarks

David H. Drewry, Ph.D., Director, Department of Chemical Biology, GlaxoSmithKline

» 8:40 FEATURED SPEAKER



Resistance to Kinase Inhibitors: Mechanisms, Challenges and Opportunities

Isabelle Dussault, Ph.D., Director, Oncology Research, Amgen

Kinase inhibitors are important medicines for the treatment of several cancer types. Intrinsic or acquired resistance to these

medicines, however, has emerged as a significant barrier to clinical efficacy. The identification of several resistance mechanisms has opened the door to the development of next generation molecules. I will discuss examples of resistance mechanisms and future directions for novel kinase inhibitors.

9:10 Kinase Inhibitor Resistance: A Gateway to Drug Combinations

John D. Haley, Ph.D., Senior Research Director, Translational Research, OSI Pharmaceuticals

Receptor tyrosine kinases (RTKs) are key mediators of tumor cell survival, proliferation and migratory pathways, and inhibitors of RTKs have demonstrated anti-tumor efficacy in both the pre-clinical and clinical settings. RTK inhibitor resistance can be elicited through mutation within kinase domains, through pathway redundancy, seemingly through receptor crosstalk, through reciprocal RTK activation and through cell lineage switching.

NOVEL TARGETS

9:40 The Published Kinase Inhibitor Set: A Resource to Develop Probes for the Untargeted Kinome

David H. Drewry, Ph.D., Director, Department of Chemical Biology, GlaxoSmithKline

Protein kinases are chemically tractable drug targets, yet <10% of the human kinome has been thoroughly explored with selective small molecule inhibitors. It is likely that pharmacological evaluation of the whole kinome will uncover new opportunities for drug discovery. We will describe our strategy to probe the untargeted kinome via compound sharing and pre-competitive collaborations.

10:10 More Biologically Relevant Characterization of Kinase Inhibitors in a Simplified Assay Format

Kurt Vogel, Ph.D., R&D Director, Life Technologies

In addition to the facile identification of type I, II, and III kinase inhibitors and

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measurement of compound on/off rates, this talk will describe the ability to interrogate large, full length kinase proteins, such as RTKs, in a simple assay format.

10:25 Networking Coffee Break in the Exhibit Hall with Poster Viewing

11:10 Use of a High Content Screening Approach to Identify Neuroprotective Protein Kinase Inhibitors

Donald Zack, M.D., Ph.D., Professor, Ophthalmology and Neuroscience, Johns Hopkins University School of Medicine

Using a novel High Content Screening Approach we have identified protein kinase inhibitors (PKIs) that are neuroprotective for retinal neurons, and thus are potential therapeutic leads for the treatment of glaucoma and age-related macular degeneration. One of the most potent compounds identified is the receptor tyrosine kinase inhibitor sunitinib, which was a surprising find because sunitinib was not previously known to have neuroprotective activity, and in fact would be expected to be toxic to neurons. We have also identified other neuroprotective scaffolds with neuroprotective activity, and these are being optimized through a medicinal chemistry approach.

11:40 Longstanding Kinase Contributor Panel – Selectivity & Kinases Today

- How much selectivity is enough?
- How is selectivity being assessed?
- Differing results from *in vitro* and cell-based screens
- Novel screening formats to assess selectivity

Neil Wishart, Ph.D., Associate Director, Abbott

Kinase Bio: Over 10 years of experience leading multiple kinase programs from early hit-to-lead through to candidate status. Successfully navigated a number of kinase-related pitfalls on multiple classes of kinase targets (serine/threonine, tyrosine, pseudo and PI3 kinases) for Oncology and Immunology indications.

Daniel Goldberg, Ph.D., Senior Principal Scientist, Boehringer-Ingelheim Pharmaceuticals

Kinase Bio: Over 12 years of drug discovery experience, many spent in the field of kinase research. My focus has been on both autoimmune and cardiovascular disease targets from hit-to-lead through candidate selection. I have worked to balance the desired kinase selectivity through structure based approaches while being vigilant on maintaining desired drug like properties.

Isabelle Dussault, Ph.D., Director, Oncology Research, Amgen

Kinase Bio: Cancer Biologist, Team Leader and Director of multiple kinase programs. Experience spans from target identification to clinical candidate identification and early clinical development.

John D. Haley, Ph.D., Senior Research Director, Translational Research, OSI Pharmaceuticals

Kinase Bio: Over thirty years of experience in biochemical research. While at OSI, he has worked on multiple discovery and development programs targeting both tyrosine and serine-threonine directed protein kinases. Group is focused on drug target pathway identification, validation and biomarker discovery through a scientific understanding of epithelial-mesenchymal transition and cancer recurrence.

12:10 pm Luncheon Presentation

Speaker to be announced.

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KINASES IN ONCOLOGY – HOT TARGETS

1:30 Chairperson's Remarks

Kent Stewart, Ph.D., Research Fellow, Abbott

» 1:40 FEATURED SPEAKER



Non-ATP Competitive Kinase Inhibitors: Potential and Limitations

Dorian Fabbro, Ph.D., Head, Kinase Biology, Expertise Platform

Our knowledge on the structural determinants of kinase inhibition by small molecules binding to the ATP pocket has advanced steadily in the past years. Selectivity of ATP directed kinase inhibitors and the limited set of chemotypes targeting the ATP binding site - a highly crowded area - are issues in kinase drug discovery. In this lecture we will review inhibitors for the Abl as well as other kinases that do not bind to the ATP binding site and show improved target selectivity. The use of these inhibitors in various indications as well as in resistance formation will be discussed.

2:10 The Promise and Challenge of Raf Inhibitor

Joseette Carnahan, Ph.D., Principle Scientist, Oncology Research, Amgen

B-Raf kinase activating mutations are frequently found in several solid tumors, especially among melanoma patients. Moreover, expression of the most frequent and well studied activation loop mutation, V600E-B-Raf results in chronic MAPK pathway activation and tumor cell dependence for survival. As anticipated by an abundance of preclinical studies, B-Raf kinase inhibitors have recently shown remarkable clinical promise. However the emergence of resistance suggests that cancer cells rapidly reprogram signaling pathways that are critical for their survival. Understanding this plasticity will be critical to developing therapeutic regimens with more durable responses.

2:40 Discovery of GDC-0068: An ATP-Competitive Selective Akt Inhibitor for the Treatment of Human Tumors

James F. Blake, Ph.D., Principal Research Investigator, Computational Research, Array BioPharma, Inc.

Akt is a serine-threonine kinase, a downstream effector for phosphatidylinositol 3-kinase (PI3K), and comprises three closely related isoforms (Akt1, Akt2, and Akt3). Akt functions as a pivotal node in the PI3K-Akt-mTOR signaling pathway. Strategies for inhibiting Akt activity have included both kinase active site-directed inhibitors and non-ATP-competitive allosteric compounds. Herein, we report on the discovery and pre-clinical characterization of GDC-0068, a novel, potent, highly selective, oral, small molecule ATP-competitive Akt inhibitor. GDC-0068 demonstrates potent inhibition of Akt in biochemical assays and blocks phosphorylation of downstream substrates of Akt in cell-based assays. It induces growth arrest in human cancer cell lines and demonstrated robust antitumor activity in a range of cancer xenograft models, in particular those with activation of the PI3K-Akt pathway.

3:10 Kinases With a "Glowing" Future?

Simon Plyte, Ph.D, Scientific Director, Biology, Congenia Srl / European Institute of Oncology

The IEO is pursuing inhibitors of the spindle assembly checkpoint kinases. A single luminescent assay format is being used to develop both an HTS and IC50 determination assay that permits direct comparison of inhibitors between different kinases.

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

4:10 Bone Morphogenetic Protein Receptor Kinase Inhibitors

Paul Yu, M.D., Ph.D., Assistant Professor, Division of Cardiology, Brigham and Women's Hospital, Harvard Medical School

We have developed scaffolds which target the kinases of the Bone Morphogenetic Protein (BMP) type I Receptors, a subset of the Activin Like Kinase family. These compounds effectively inhibit maladaptive osteogenesis, including heterotopic ossification and vascular calcification. BMP signaling is implicated in the oncogenesis, metastasis, or invasiveness of a number of mesenchyme-derived tumors, and is a proposed target of oncologic therapy.

4:40 Next Generation ALK inhibitors and Personalized Medicine: The Next Frontier of Kinase Drug Discovery

Chris Liang, Ph.D., CSO & Executive Vice President, Xcovery, LLC

Recently, crizotinib has shown very impressive efficacy in NSCLC patients with ELM4-ALK fusion proteins. Unfortunately, after only 6-12 months of treatment, most patients develop resistance. Possible reasons for the short duration of efficacy and resistance are analyzed. Next generation of ALK inhibitors are developed to overcome resistance and to more effectively treat a variety of patients with ALK fusion, mutation, and amplification. This example is extended to highlight the importance of matching the right patient with the right inhibitor for most cost-effective treatments.

5:10 Structure-Guided Drug Design and its Use in the Discovery of Kinase Therapeutics

Dirksen Bussiere, Ph.D., M.B.A., Director, Structural Chemistry, Novartis Institutes for BioMedical Research

The use of structure-guided drug design in kinase lead optimization will be illustrated using examples from projects targeting serine/threonine kinases and tyrosine kinases, including the discovery of TKI258 (Dovitinib) which targets VEGFR, FGFR, and PDGFR kinases. A project targeting a lipid kinase, Phosphatidylinositol-3-Kinase, which led to the discovery of BKM120, will also be presented. The process, starting from gene-to-structure, and the use of co-structure information and molecular modeling in lead optimization will also be outlined.

5:40 Close of Day

WEDNESDAY, JUNE 8TH

KINASES IN ONCOLOGY – HOT TARGETS CONTINUED

8:30 Chairperson's Remarks

Erica Evans, Ph.D., Principal Scientist, Avila Therapeutics, Inc.

8:40 Case Study from AstraZeneca

Stephanos Ioannidis, Ph.D., Principal Scientist I, Cancer Chemistry, AstraZeneca

KINASE INHIBITORS IN INFLAMMATION & AUTOIMMUNE

9:00 Case Study from Incyte

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

9:20 Bruton's Tyrosine Kinase from Bench to Bedside: Covalently Silencing B Cells with AVL-292

Erica Evans, Ph.D., Principal Scientist, Avila Therapeutics, Inc.

Bruton's tyrosine kinase (Btk) plays a crucial role in the development and activation of B cells through the BCR signaling pathway and represents an exciting new target for therapeutic intervention in diseases characterized by inappropriate B cell activity. We will describe a targeted covalent drug design strategy that has enabled the discovery of a potent and highly selective inhibitor of Btk, AVL-292, which has recently entered clinical development.

9:40 Application of Functional Screening using Cultured Human Mast Cells for the Discovery and Optimization of SYK Kinase Inhibitors Leading to Fostamatinib

Rajinder Singh, Ph.D., Head, Medicinal Chemistry, Rigel Pharmaceuticals, Inc.

Use of cultured human mast cells in high throughput screening for identification of hits inhibiting immunoglobulin E (IgE) mediated activation of Fc receptor signaling leading to downstream inhibition of degranulation. Application of this paradigm to structure activity relationship (SAR) to one particular scaffold generated potent analogues and the discovery of orally bioavailable R406. Importantly R406 also blocks SYK-dependent Fc receptor mediated activation of monocytes, macrophages and neutrophils and B-cell receptor (BCR)-mediated activation of B lymphocytes. Formulation properties of R406 were further enhanced via synthesis of R788, fostamatinib, which has advanced to Phase 3 studies.

10:00 Sponsored Presentation (Sponsorship Opportunity Available)

10:15 Networking Coffee Break in the Exhibit Hall with Poster Viewing

KINASES FOR CNS INDICATIONS

» 11:00 FEATURED SPEAKER



Highly Selective Brain-Penetrant Inhibitors of Glycogen Synthase Kinase 3-β for Alzheimer's Disease

Ravi G. Kurumbail, Ph.D., Research Fellow and Structural Biology Laboratory Head, Pfizer

Glycogen synthase kinase 3- β (GSK-3 β) is an attractive target for the treatment of Alzheimer's disease. However, it has been a challenge to develop potent kinase inhibitors that are brain-penetrant because of almost the orthogonal attributes required for these two activities. We will discuss the discovery of a selective GSK-3 β inhibitor that demonstrates pharmacological modulation of phosphorylated-Tau in rat brain.

11:30 Elucidating the Role of LRRK2 in Parkinson's Disease

Greg Cuny, Ph.D., Assistant Professor, Harvard NeuroDiscovery Center, Brigham & Women's Hospital and Harvard Medical School

Leucine-rich repeat kinase 2 (LRRK2) has recently emerged as a potential contributor to Parkinson's disease pathophysiology. This presentation will provide a brief overview of LRRK2 biology and chemistry, highlight some of the challenges in tackling LRRK2 as a drug discovery target and illustrate several strategies at identifying modulators of LRRK2 kinase activity.

12:00 pm Luncheon Presentation (Sponsorship Opportunity Available) or Lunch on Your Own

STRUCTURE-BASED KINASE INHIBITOR DESIGN & KINASE SELECTIVITY

1:10 Chairperson's Remarks

Andrew C. Good, Ph.D., Distinguished Scientific Fellow, Medicinal Chemistry, Genzyme Corp.

1:15 Discovery of Crizotinib (PF-02341066)-A c-Met/ALK Dual Inhibitor for Oncology Applications

Jean Cui, Ph.D., Associate Research Fellow, Oncology Medicinal Chemistry, Pfizer, Inc.

Crizotinib (PF-02341066) has shown remarkable efficacy for lung cancer patients with EML4-ALK fusion gene and is currently in Phase III clinical trials. Crizotinib is created as a c-Met/Alk dual inhibitor using structure-based drug design in combination with medicinal chemistry principles.

1:45 A Role for Hydration in Interleukin-2 inducible T Cell Kinase Selectivity

Ronald Knegtel, Ph.D., Research Fellow I, Molecular Modeling, Vertex Pharmaceuticals (Europe) Ltd.

A series of Itk inhibitors that achieve selectivity through the introduction of a single, solvent exposed aromatic nitrogen atom without direct interactions with the enzyme is reported. By analyzing active site hydration using WaterMap, the selectivity profile can be explained in terms of the replacement of a thermodynamically unfavorable water molecule by the inhibitor and improved hydration of the bound ligand. This hydration site was successfully used to enrich virtual screening results in their content of selective Itk inhibitors.

2:15 Overcoming Drug-Resistant Mutations in Kinase Drug Discovery: Applying Lessons from Ponatinib (AP24534)

David C. Dalgarno, Ph.D., Vice President, Research Technologies, ARIAD Pharmaceuticals, Inc.

Ponatinib (AP24534) is a novel BCR-ABL inhibitor that inhibits both native and mutant BCR-ABL, including the T315I gatekeeper mutation, and hence acts as a pan-BCR-ABL inhibitor. We recently analyzed the structural basis for this pan-BCR-ABL activity. Here we discuss this analysis and how it can be applied to other kinase targets exhibiting mutation-based resistance, and how the lessons from ponatinib can be applied to the design of other mutant kinase inhibitors.

2:45 Structure-Based Kinase Inhibitor Design & Kinase Selectivity

Stephen A. Parent, Ph.D., Director of Business Development, Reaction Biology Corporation

RBC provides drug profiling and screening services using HotSpot technology, a high-throughput radioisotopic screening platform with more than 370 kinases. We will describe its application to kinase inhibitor development and kinase inhibitor selectivity.

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

3:30 Structure-Guided Fragment-Based Drug Discovery for Protein Kinase Targets

Stephen K. Burley, M.D., D.Phil., Distinguished Lilly Research Scholar, Lilly Biotechnology Center, Eli Lilly and Company

4:00 How Molecular Dynamics Simulation May be Applied in Structural Based Design of Kinase Drugs

Yibing Shan, Ph.D., Senior Scientist, Chemistry and Biology, D. E. Shaw Research

The understanding of the extensive conformational heterogeneity of protein kinases is crucial to the understanding of kinase drugs' binding and specificity. To this end, long molecular dynamics (MD) simulations, which for the first time reached the relevant timescale of micro- to milli-second, may prove a powerful tool. Our MD study of Abl, Src, and EGFR kinases will be discussed as examples of such effort in its early stage.

4:30 Recent Experience Establishing a New Lead ID Capability to Pursue Oncology Kinase Targets

Hans-Peter Biemann, Ph.D., Associate Scientific Director, In vitro Biology, Genzyme Corporation

Genzyme's small molecule discovery unit has incorporated fragment-based and x-ray structure-assisted technologies over the last three years. Ligands of 150-250 Daltons have undergone structure-assisted elaboration to identify novel potent and selective inhibitors of tyrosine and ser/thr kinases, including Pim-1. We progressed a tyrosine kinase to late lead optimization in 2.5 years and newer projects have productively commenced outside of the kinase and oncology sectors. This evolution of our HTS-based drug discovery unit to a multi-platform format enables us to address a number of target classes more expediently than before.

5:00 Longstanding Kinase Contributor Panel: Structure-Based Kinase Inhibitor Design

Topics

- Insights correlating kinase selectivity and toxicity
- Using co-crystal structures to generate novel kinase scaffolds
- Using structure to improve selectivity alongside potency

Andrew C. Good, Ph.D., Distinguished Scientific Fellow, Medicinal Chemistry, Genzyme Corp.

Kinase Bio: Highly experienced computational chemist involved in 3 projects that have brought compounds to the clinic. Exposure to multiple kinase projects at GlaxoWellcome, Bristol-Myers Squibb and Genzyme. Currently leading primary Genzyme kinase oncology project, shepherding the program from hit id through to late stage lead optimization.

Ravi G Kurumbail, Ph.D., Research Fellow and Structural Biology Laboratory Head, Pfizer

Kinase Bio: Experience in structure-based drug design in over half a dozen kinase projects in the pharmaceutical industry; have contributed to the development of clinical candidates; experience in evaluation of kinase inhibitors for CNS indications; championed a kinase project for Alzheimer's disease; trained as a protein X-ray crystallographer; currently leading a structural biology lab at Pfizer.

Dirksen Bussiére, Ph.D., M.B.A., Director, Structural Chemistry, Novartis Institutes for BioMedical Research

Kinase Bio: Fifteen years experience in structure-based drug design, including more than ten projects targeting kinases for diabetes and cancer, several of which led to compounds currently in development; trained in protein biochemistry, biophysics, structural biology, and computational chemistry/biology; currently leading a structural biology group at Novartis.

5:30 Close of Day

HOTEL & TRAVEL INFORMATION

Royal Sonesta Hotel Boston
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Discounted Room Rate: \$249 s/d
Discounted Room Rate Cut-off Date: May 10, 2011

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Reservations made after the cut-off date or after the group room block has been filled (whichever comes first) will be accepted on a space- and rate-availability basis. Rooms are limited, so please book early.

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Rational Molecular Approaches to Targeted Therapeutics -
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TOPICS INCLUDE:

- Protein Flexibility
- Fully Synthetic Protein-Protein Interaction Inhibitor
- Fragment-to-Lead Optimization
- High Performance Computing and Collaborative Drug Design
- State-of-the-Art Molecular Dynamics Simulations

Special Package Pricing is Available to Attend Both Conferences!

SPONSORED PRESENTATIONS:

Give a 15 or 30 minute podium presentation within the Next-Gen Kinase Inhibitors program, ensuring your audience is seated and ready to listen. Additional benefits include exhibit booth space, on-site signage denoting your company as a Corporate Sponsor, branding on the conference website and brochure (contingent on CHI printing deadlines) and more.

LUNCHEON WORKSHOPS

Invite session delegates to enjoy lunch on your company's behalf while you give a 30-minute presentation. Your workshop is concluded with 15 minutes of Q&A, allowing you to interact with your customer base.

INVITATION ONLY NETWORKING RECEPTIONS

CHI will invite Next-Gen Kinase Inhibitors delegates to a private reception at the host hotel. Cocktails and hors d'oeuvres will be served in a setting conducive to networking. These receptions are available on a first-come, first served basis.

Presentation opportunities are limited, so reserve your talk today to ensure participation!

EXHIBITOR INFORMATION

Why Exhibit? This is the biggest and most focused Kinase event of the year! Exhibitors will have ample opportunity to network and create relationships with 150+ qualified delegates. Don't miss your chance to demonstrate your company's expertise to the world's prominent scientists striving to discover novel kinase inhibitors and to explore novel technologies and platforms.

ADDITIONAL PROMOTIONAL OPPORTUNITIES INCLUDE:

- Branded Badge Lanyard – Exclusive!
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- Attendee Coffee Mugs – Exclusive!
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Next-Gen Kinase Inhibitors

Across Multiple Therapeutic Areas

JUNE 6-8, 2011 | ROYAL SONESTA HOTEL BOSTON | CAMBRIDGE, MA

PRICING AND REGISTRATION INFORMATION

PROGRAM PRICING

	Commercial	Academic, Government, Hospital-Affiliated
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NEXT-GEN KINASE INHIBITORS (JUNE 6-8)

Early Registration until March 11, 2011	\$1645	\$795
Advance Registration until April 29, 2011	\$1795	\$875
Registration after April 29, 2011 and on site	\$1995	\$945

NEXT-GEN KINASE INHIBITORS & STRUCTURE-BASED DRUG DESIGN (JUNE 6-10)

Early Registration until March 11, 2011	\$2540	\$1270
Advance Registration until April 29, 2011	\$2690	\$1340
Registration after April 29, 2011 and on site	\$2890	\$1390

PRE-CONFERENCE PRICING (JUNE 6)

Pre-Conference Morning Short Course	\$695	\$395
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ADDITIONAL REGISTRATION DETAILS

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