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Cambridge Healthtech Institute’s

Next-Gen Kinase Inhibitors

JUNE 4-6, 2012 | ROYAL SONESTA HOTEL BOSTON | CAMBRIDGE, MA

TOPIC HIGHLIGHTS:

• Strategies for Overcoming Resistance

• Targeting Cancer, Inflammation, Autoimmune Diseases, and CNS

• Conformational Changes in Protein Kinases

• Novel Paths towards Identifying Kinase Inhibitors

• Optimizing Leads and Inhibitors

Looking at the Path Ahead

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CO-LOCATED WITH:
12th Annual Structure-Based Drug Design Conference
Predicting Biological and Kinetic Profiles from Structure
June 6-8 | healthtech.com/SBD
Short Course: The Art and Science of Kinases

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.

Course Instructor:
Kent Stewart, Ph.D., Research Fellow; Structural Biology, Abbott & Maricel Torrent, Ph.D., Senior Scientist, Abbott

*Separate registration required

MONDAY, JUNE 4

8:00 - 9:00 am Pre-Conference Short Course Registration and Morning Coffee

11:00 am Main Conference Registration

1:30 pm Chairperson's Remarks

SELECTIVITY AND RESISTANCE

1:40 Multiple Strategies for Overcoming Kinase Inhibitor Resistance
Nathanael S. Gray, Ph.D., Professor, Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School

2:10 Resistance of Akt Kinases to Dephosphorylation through ATP-Dependent Conformational Plasticity
Roger S. Armen, Ph.D., Assistant Professor of Medicinal Chemistry, Department of Pharmaceutical Sciences, Thomas Jefferson University, School of Pharmacy

Phosphorylation of a threonine residue (T308 in Akt1) in the activation loop of Akt kinases is a prerequisite for deregulated Akt activity frequently observed in cancer. We describe that targeting Akt kinase to the cell membrane markedly reduced sensitivity of phosphorylated Akt to dephosphorylation, and that this effect was amplified by occupancy of the ATP binding pocket by either ATP or ATP competitive inhibitors. We describe a mechanism that provides an explanation for the "paradoxical" Akt hyperphosphorylation induced by certain ATP-competitive inhibitors.

2:40 A Broad Profiling Screen in Support of a Chemogenomic Map for Drug Discovery and Kinase Signaling
Kevin J. Harvey, Ph.D., Sr. Manager R&D, EMD Millipore

To better understand the nature of structure and activity across the kinome, and how they relate to off-target effects, we screened a well-defined collection of kinase inhibitors using "gold standard" radiometric assays for inhibitory activity toward 234 human kinases representing all branches of the kinome tree. We screened 158 small molecules initially identified in the literature as potent inhibitors of important signaling kinase targets and provide a framework for assessing their selectivity and potency.

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

NOVEL DEVELOPMENTS IN TARGETING TUMORS

3:40 Multifaceted Intervention by the Hsp90 Inhibitor Ganetespib in Cancers with Activated JAK/STAT Signaling
David Proia, Ph.D., Senior Scientist, Synta Pharmaceutical

4:10 Aptamers: A New Class of Tyrosine Kinase Inhibitors
Said Ismail, Ph.D., Associate Professor, Molecular Biology, Department of Biochemistry, Medical School, University of Jordan

Aptamers are short single stranded nucleic acids developed by the SELEX method to specifically target various molecules including proteins. Our lab has developed a large number of aptamers against several tyrosine kinase (TK) targets involved in different malignancies. Our aptamers have shown a great potential to specifically bind and inhibit their TK targets, which offers a great promise for their therapeutic uses.

4:40 Development and Activity of Inhibitors of the Atypical Mitotic Kinase Haspin
Jonathan Higgins, Ph.D., Assistant Professor, Medicine, Brigham & Women's Hospital, Harvard Medical School

Our work has defined the atypical kinase Haspin as a histone H3 kinase that is required for regulating Aurora B activity and chromosomes segregation in mitosis, and has suggested that Haspin is a suitable target for the development of anti-mitotic cancer therapies. Using high throughput screening, followed by medicinal chemistry guided by structural analysis and molecular modeling, we have identified and developed small molecule inhibitors of Haspin, and have also defined the mechanism of their anti-mitotic activity. These results and studies by others suggest that such compounds might have anti-tumor activity both as single agents and in combination with Aurora inhibitors.

5:10 Welcome Reception in the Exhibit Hall with Poster Viewing

6:45 Close of Day One
8:20 am Chairperson’s Remarks
Kelvin Lam, Ph.D., Vice President, Assay Services, Blue Sky Biotech

NOVEL PATHS TOWARDS IDENTIFYING KINASE INHIBITORS

8:30 Pathway-Based Identification of Biomarkers for Targeted Kinase Therapeutics
An Chi, Ph.D., Research Fellow, Molecular Biomarkers Department, Merck Research Laboratory

To enable the generation of drug-specific biomarker tools for kinase inhibitors, we discuss a differential phospho-proteomic approach to identify and quantify drug-regulated phosphorylation events. Recent examples of translational strategies for PI3K inhibitors would be highlighted.

9:00 Comprehensive Assay of Kinase Catalytic Activity Reveals Features of Kinase Inhibitor Selectivity and Novel Kinase-Inhibitor Interactions
Jeffrey R. Peterson, Ph.D., Associate Professor, Cancer Genetics and Signaling, Fox Chase Cancer Center

In the November issue of Nature Biotechnology, we reported the largest analysis of small molecule inhibition of kinase catalytic activity, testing 178 compounds against 300 recombinant human protein kinases using a high-throughput format of a substrate phosphorylation assay. The inhibitors tested include FDA-approved drugs, compounds in the clinical pipeline, and research tool compounds. Many off-target interactions were observed with seemingly unrelated kinases, revealing that large-scale profiling can identify multitargeted inhibitors of specific, diverse kinases. I will make the case for large-scale inhibitor profiling as a new approach to screening for drug candidates and will highlight many novel and surprising inhibitor-kinase interactions revealed by this study.

9:30 No Patent Left Behind - A Prerequisite in Kinase Inhibitors Competitive Intelligence
Parthiban Srinivasan, Ph.D., CEO & President, Parthys Reverse Informatics

Kinase research is accelerating every year. Retrieving complete list of kinase patents to remain up-to-date is a challenge. Patents use non-standard nomenclature. Searches performed with our kinase synonyms dictionary, retrieved even the obfuscated patents, generating actionable reports for you!

9:45 Sponsored Presentation (Opportunity Available)

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

10:45 Activation-State Dependent Conformational Differences in Protein Kinases and the Role of Hydrophobic Motifs in Inactive Kinases: Lessons Learned in Drug Discovery and Optimization
Mark Ashwell, Ph.D., Vice President, Chemistry, ArQule

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. Strategies will be presented and discussed for the identification and optimization of small molecule inhibitor of several kinases e.g., c-Met, FGFR, AKT and others. Characterization of the molecular interactions with inactive kinases will be described using biophysical, biochemical and cell-based assays together with X-ray crystallographic and mutational studies.

11:00 No Patent Left Behind - A Prerequisite in Kinase Inhibitors Competitive Intelligence
Parthiban Srinivasan, Ph.D., CEO & President, Parthys Reverse Informatics

11:15 Kinase Virtual Screening with Accuracy Comparable to Experiment
Eric Martin, Ph.D., Director, Computational Chemistry, Global Discovery Chemistry, Novartis Institutes for BioMedical Research

Three novel kinase virtual screening methods achieve unprecedented speed and accuracy by including massive amounts of IC50 and structural data from previous kinase targets into models for each new kinase: the 2D “Profile-QSAR” meta-QSAR, the Kinase-Kernel chemogenomic model, and 3D Surrogate AutoShim docking method. Between the 3 methods, 2 billion activity predictions have been made for 4 million internal and commercial compounds across 500+ kinases, so kinase virtual screening is now a table lookup. Applied to over 3 dozen active Novartis projects, at all stages of discovery, with external R2=0.35–0.7 and enrichments of 20x–70x. AutoShim and Profile-QSAR have also been extended to Serine and Cystine Proteases.

11:45 Identification of Novel Non ATP – Competitive Inhibitors against Human MAP Kinase Kinase1 (MEK1) and MEK2
Rambabu Gundla, Ph.D., Principal Scientist, Informatics, GVKBIO Sciences Pvt Ltd.

Virtual screening models were generated and validated utilizing a set of known human MAP kinase kinase1 (MEK1) and MEK2. The virtual screening models were successfully employed to discover a set of structurally diverse Non ATP – Competitive Inhibitors with growth inhibitory activity against MEK1 and MEK2. A search of a 3D database containing 6MM small molecules using the virtual models retrieved 734 potential hits. Of the 734 hits, 62 were selected for testing in vitro on the basis of structural novelty and desirable drug-like properties. Thirteen compounds inhibited with IC50 values <10 μM. These lead compounds have desirable physicochemical properties and are excellent candidates for further optimization.

12:15 pm Luncheon Presentation
Speaker to be Announced

1:35 Chairperson’s Remarks

NOVEL THERAPEUTIC APPLICATIONS

1:40 Template-Directed Assembly (TDATM) is an Enabling Technology to Overcome the Challenges of Targeting Membrane-Associated Kinases
Kelvin Lam, Ph.D., Vice President, Assay Services, Blue Sky BioServices

Membrane associated kinases are challenging class of targets because they are located and function adjacent to the hydrophobic natural lipid-bilayer environment. Traditionally, one studied these target class by isolating soluble catalytic domains, which lacks the proper physiological context. As a proof of principle TrkA was selected to validate the technology. TrkA receptor, which is part of the larger RTK (Receptor Tyrosine Kinase) receptor family, is activated by neurotrophins and implicated in neurodegeneration, pain, and cancer. We screened against a compound library and identified compounds with higher potency. We will show concordance between primary assay and secondary cell-based assays, including High Content Screen (HCS) assay. We will also discuss additional applications for the technology.

2:10 Inhibiting PI3K for Treating Inflammatory Diseases
Stephen J. Shuttlesworth, Ph.D., CSO, Karus Therapeutics, Ltd.
2:40 Targeting Infectious Diseases
Milton H., Ph.D., President & CEO, Inhibikase Therapeutics, Inc.

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

4:00 To Develop Novel Drak2 Inhibitors for the Treatment of Autoimmune Diseases
Jiangping Wu, Ph.D., Professor of Medicine, Medicine, University of Montreal
Drak2 is a novel therapeutic target for certain autoimmune diseases, and it is a safe one as Drak2 gene knockout mice have no gross anomalies. We obtained 2 highly potent inhibitors at less than 30 nM in IC50, after screening of 570,000 compounds. We also identified p70S kinase as Drak2’s substrate. This raises an interesting possibility that Drak2 and mTORC1 share a part of their signaling pathway.

4:30 The Resurgence of Covalent Drugs
Juswinder Singh, Ph.D., CSO, Avila Therapeutics

5:00 Developing an Inhibitor Scaffold for JAK2 and FAK Kinases
Bruce D. Dorsey, Ph.D., Senior Director, Chemistry, Cephalon

5:30 Close of Day Two

WEDNESDAY, JUNE 6

8:15 am Chairperson’s Remarks

OPTIMIZING LEADS AND INHIBITORS

8:20 Discovery of Potent, Selective, and Orally Bioavailable SIK2 Kinase Inhibitors for Multiple Disease Indications
Hariprasad Vankayalapati, Ph.D., Scientific Advisor, Arrien Pharmaceuticals
Salt Inducible Kinase 2 (SIK2) is a centrosome kinase required for bipolar mitotic spindle formation and is a Ser/Thr kinase family member. There are four SIK enzymes – SIK1, SIK2 and SIK3 are required for the signaling triggered by a number of factors and excessive signaling through SIK2-driven pathway is believed to play a critical role in the pathogenesis of large B-cell lymphoma, ovarian cancer, stroke, obesity and type-2diabetes. With the application of our proprietary FFDD approach led to the discovery of potent, selective, orally bioavailable first-in-class inhibitors of SIK2. The lead identification, optimization, SAR, PK and efficacy study details of ARN-3015 series of SIK2 inhibitors will be presented.

8:50 Development of a Mono-Selective CDK7 Inhibitor Lead
Jan Eickhoff, Ph.D., Head of Assay Development and Screening, Lead Discovery, Centrum GmBH
We generated picomolar and mono-selective CDK7 inhibitors through rationale design efforts. Inhibitors from our lead series demonstrated in vivo efficacy in a cancer xenograft model without causing toxic or adverse effects, and even more surprisingly, such highly selective CDK7 inhibitors showed a distinct responder profile of sensitive cell lines from a panel of more than 120 different human cancer cell lines. In addition, with the aid of highly selective CDK7 inhibitors, we were able to gain evidence that CDK7 has upside potential as a target in inflammation, as well as infectious diseases.

9:20 Talk Title to be Announced
Speaker to be announced, OSI Pharmaceuticals

9:50 Coffee Break
associated with typical idiopathic, late-onset PD. Here we report the identification of DYG-out inhibitors of LRRK2 based on the combined structural modeling and enzyme kinetic studies.

4:00 Determining the Crystal Structures of Allosteric Kinase Inhibitor Complexes
Barbara Brandhuber, Ph.D., Director, Early Drug Discovery, Biology, Array BioPharma
Upon discovery of a kinase inhibitor that does not appear to bind in the ATP-binding cleft, structural biologists are challenged to determine the crystal structure of the inhibitor-bound kinase to enable structure-based drug design. Frequently, the inhibitor does not crystallize with a canonical kinase construct and therefore a new crystallographic effort is launched. In this presentation, several biochemical, biophysical, and bioinformatic approaches will be discussed which enable and complement crystallographic studies. The use of multi-disciplinary approaches to crystallographically determine the unique binding mode of an allosteric inhibitor interacting with both the regulatory pleckstrin-homology and kinase domains of AKT-1 will be described.

4:30 Druggability and Ligandability: Structural Genomics Insights Suggest in Excess Of 10,000 Potentially Druggable Proteins in the Human Proteome
Florian Nigsch, Ph.D., Presidential Postdoctoral Fellow, Developmental and Molecular Pathways, Novartis Institutes for BioMedical Research
We present our recent efforts to exploit the information from comprehensive structural genomics and chemogenomics resources. To identify the set of currently ligandable domains we identified all InterPRO signatures that contain ligand-binding residues across all 75,000+ PDB structures. The occurrence of the identified InterPRO signatures in the human proteome suggests that for at least 25% of the human proteome there is chemical matter with high affinity available. We present applications of the derived data in target identification and chemical tractability assessment.

5:00 Close of Conference
Exhibit and Sponsor Information:

CHI can customize a sponsorship package to meet your company's needs and budget. We offer comprehensive packages that give your company exposure before, during and after the event. Sponsorship packages include a talk, exhibit space, conference registrations, branding, use of event mailing lists, and more.

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CHI Lead Generation:
CHI can help you with lead generation throughout the year. Our internal database includes over 800,000 prospects in the life sciences. By leveraging the database and mining for your specific requirements, we can produce multiple custom projects which will deliver your prospective buyers: Web Symposiums, Podcasts, White Papers, Custom Market Research Surveys and more!

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Exhibitors will enjoy facilitated networking opportunities with qualified decision makers at Next-Gen Kinase Inhibitors, making it the perfect platform to launch a new product, collect feedback and generate new leads. Exhibit space will sell out quickly, so reserve yours today!

Additional promotional and networking opportunities are available!

For sponsorship and exhibit information, please contact:
Jon Stroup
Business Development Manager
781-972-5483 | jstroup@healthtech.com

Hotel & Travel Information

Conference Hotel:
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Phone: 617-806-4200

Discounted Room Rate: $249 s/d
Discounted Room Rate Cut-off Date: May 8, 2012
Please visit our conference website to make your reservations online or call the hotel directly to reserve your sleeping accommodations. You will need to identify yourself as a Cambridge Healthtech Institute conference attendee to receive the discounted room rate with the host hotel. Reservations made after the cut-off date or after the group room block has been filled (whichever comes first) will be accepted on a space- and rate-availability basis. Rooms are limited, so please book early.

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781-972-5483 | jstroup@healthtech.com
If you are unable to attend but would like to purchase the Next-Gen Kinase Inhibitors CD for $350 (plus shipping), please visit healthtech.com/KIN. Massachusetts delivery will include sales tax.

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| Poster Submission-Discount ($50 Off) | Poster abstracts are due by May 9, 2012. Once your registration has been fully processed, we will send an email containing a unique link allowing you to submit your poster abstract. If you do not receive your link within 5 business days, please contact jring@healthtech.com. *CHI reserves the right to publish your poster title and abstract in various marketing materials and products. |

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