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Final Agenda

Eleventh Annual

MASTERING MEDICINAL CHEMISTRY

Improving Drug Discovery Success Rates

May 21-22, 2014
Westin Waterfront | Boston, MA

Coverage Includes

- The Future Role of Medicinal Chemistry – An Executive Perspective
- Tissue Targeting by Design: From ADCs to Nanoparticles
- Allosteric Inhibitors to Enhance Profiles or Modulate Difficult Targets
- Beyond Rule of Five - Peptides and Macrocycles and PPIs
- Receptor Kinetics and Residence Time
- Case Studies from AbbVie, Bristol-Myers Squib Pfizer, Inc., Sanofi-Aventis, Stony Brook University

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Pre-Conference Short Course*

TUESDAY, MAY 20, 2014 | 2:00 – 5:00PM

Receptor Kinetics and Residence Time – What the Medicinal Chemist Needs to Know

Stewart L. Fisher, Ph.D., Principal, SL Fisher Consulting, LLC

Peter J. Tonge, Ph.D., Professor, Chemistry, Institute for Chemical Biology & Drug Discovery, Stony Brook University

Participants will be introduced to the fundamentals of time-dependent inhibition and how these factors can impact drug discovery and development. The course will cover a range of topics from an introduction to the basic principles, to practical methods for measuring and using time-dependent inhibition data, to the factors that determine the best use of these data to enable medicinal chemistry driven projects. Case studies, derived from the literature and ranging from lead discovery to marketed drugs, will be used to reinforce and provide real-world examples of the practical application of these concepts.

Topics to be covered include:

- Differences between open and closed systems
- Kinetic mechanisms driving time-dependent inhibition behavior
- Techniques to measure and utilize time-dependent inhibition data in drug discovery projects
- Examples demonstrating the impact of residence time data to advance lead series

*Separate Registration Required

WEDNESDAY, MAY 21, 2014

THE FUTURE ROLE OF MEDICINAL CHEMISTRY– AN EXECUTIVE PERSPECTIVE

7:00 am Registration and Morning Coffee

8:00 Chairperson's Opening Remarks

Eddine Saiah, Ph.D., Atlas Venture

8:05 The Future Role of Small Molecule Research

Hans-Joachim Boehm, Ph.D., Global Head, Small Molecule Research, Roche

There remain challenges in medicinal chemistry, such as tackling protein-protein interactions, targeting certain cell types or organs and developing new strategies to avoid off-target toxicity. I will present work from Roche trying to address these issues and will provide an outlook about the future of small molecule research.

8:35 Medicinal Chemistry v2.0

Mark Bunnage, D.Phil., Vice President, Head, Chemistry, Biotherapeutics Research, Pfizer, Inc.

Pharmaceutical R&D has been undergoing significant change in recent years in response to its productivity challenges. This presentation will discuss the role of medicinal chemistry in this evolving R&D ecosystem and highlight new areas of opportunity for medicinal chemists to enable future drug discovery.

9:05 Strategic, Organizational and Cultural Considerations for Medicinal Chemistry Practices

Mike Hann, Ph.D., Director, Chemical Sciences, R&D Platform Technology & Sciences, GlaxoSmithKline

Medicinal chemistry is sometimes seen as the cause rather than the solution to the problems we face in the pharma industry of low return on investment. This presentation takes a look at some issues that have influenced this debate and discuss how we can ensure medicinal chemistry remains at the core of drug discovery and alive to the opportunity that high attrition continues to challenge us with.

9:35 Coffee Break in the Exhibit Hall with Poster Viewing

10:20 Driving Medicinal Chemistry through Collaborative Networks

Jorg Holenz, Ph.D., Director, Discovery & Preclinical Sciences, AstraZeneca Pharmaceuticals

In 2012, AstraZeneca pioneered a novel externally facing approach of driving R&D projects via collaborative networks with academic and industry partners. This talk will introduce this approach and focus on how medicinal chemistry is flexibly organized within our model to successfully drive the Design-Make-Test cycle within preclinical projects.

10:40 PANEL DISCUSSION: The Future Role of Medicinal Chemistry

Moderator: Michael Block, Ph.D., former Executive Director, Chemistry, AstraZeneca Boston

Panelists:

Hans-Joachim Boehm, Ph.D., Global Head, Small Molecule Research, Roche

Mark Bunnage, D.Phil., Vice President, Head, Chemistry, Biotherapeutics Research, Pfizer, Inc.

Mike Hann, Ph.D., Director, Chemical Sciences, R&D Platform Technology & Sciences, GlaxoSmithKline

Jorg Holenz, Ph.D., Director Discovery & Preclinical Sciences, AstraZeneca Pharmaceuticals

- New organizational models driving medicinal chemistry virtual models, outsourcing, collaborative tools, partnerships
- Re-focus on receptor kinetics, difficult targets with peptides, allosteric and covalent inhibition, tissue targeting by design, neglected diseases and natural products

CASE STUDY SESSION: PART I

11:00 Chairperson's Remarks

11:05 Marketed and Clinical Macrocycles – Food for Thought

Fabrizio Giordanetto, Ph.D., Director, Medicinal Chemistry, Taros Chemicals GmbH & Co. KG

Macrocycles have gained renewed popularity for drug discovery applications in recent years due to perceived advantages in terms of affinity, selectivity, metabolic stability and especially oral absorption. An analysis of currently marketed macrocycles and macrocycles in clinical development is presented to investigate such advantage claims.

11:25 The Discovery and Profile of Narrow Spectrum Kinase Inhibitors as Novel Treatments for Inflammatory Pulmonary Diseases

Sponsored by SYGNATURE discovery

Stuart Onions, Ph.D., Director, Research Management, Sygnature Discovery Ltd

COPD affects 65 million people worldwide and by 2030 could be the third largest cause of death. Corticosteroids remain the front line intervention, but a widespread insensitivity and inability to effect disease progression with these agents is driving the need for new, improved therapies. This presentation details the discovery of narrow spectrum kinase inhibitors which maximize the beneficial effect on the target organ, promote optimal duration of action and reduce the potential for toxicity by minimizing systemic exposure.

11:55 Natural Products in Medicinal Chemistry

Peter Hamley, Ph.D., Global Head, Parallel Synthesis and Natural Products, Sanofi-Aventis

Natural products can be used directly as starting points for new drugs, and indirectly, for example by deorphaning new targets or revealing unexpected binding modes. This talk describes Sanofi's capabilities, recent successful applications, future technological directions and shows how public-private partnerships are being used for this area.

12:25 pm Covalent Inhibition in Medicinal Chemistry Drug Design: Reversible Covalent Inhibitors of Bruton's Tyrosine Kinase for Autoimmune Diseases

Suvit Thaisrivongs, Ph.D., Head, Immunoscience Research Unit Chemistry, Worldwide Medicinal Chemistry, Pfizer, Inc.

One drug design strategy for achieving pharmacological potency and selectivity for kinase targets is to engage the non-catalytic cysteine residues with covalent inhibitors. Structure-based design led to the discovery of such a class of inhibitors for BTK. The optimized compound has been shown to be efficacious in several preclinical animal models of arthritis and autoimmune diseases.

12:55 Luncheon Presentation

Sponsored by SCHRÖDINGER.

Speaker to be Announced

1:30 Session Break

CASE STUDY SESSION: PART II

2:00 Chairperson's Remarks

Stewart L. Fisher, Ph.D., Principal, SL Fisher Consulting, LLC

2:05 Inhalation by Design – p38 Inhibitors for COPD

John Mathias, Ph.D., Senior Director & Head, Medicinal Chemistry, Inflammation & Remodeling, Pfizer, Inc.

This talk details the medicinal chemistry design of our PII inhaled p38 inhibitors in 3 key areas: 1. Engineering in slow onset/offset kinetics and some kinetic-structure relationships we derived to maximize lung efficacy following inhalation, 2. Lung targeting to ensure physical residence in target organ, 3. Designing to drive low systemic bioavailability and low potential active metabolite burden following inhalation.

TISSUE TARGETING BY DESIGN: FROM ADCs TO NANOPARTICLES

2:35 Medicinal Chemistry Approaches to the Design of Novel Linkers, Payloads and Antibody-Drug Conjugates for the Treatment of Cancer

Christopher J. O'Donnell, Ph.D., Senior Director, Oncology Medicinal Chemistry, Pfizer, Inc.

Antibody drug conjugates (ADCs) are an established modality for the treatment of cancer. This talk will focus on Pfizer's chemistry strategy to discover and develop new linker-payload classes and conjugation methods that yield more efficacious and potentially better tolerated ADC that are being advanced to the clinic.

3:05 Novel Linker-Duocarmycin Payloads for Next-Generation Antibody-Drug Conjugates

Patrick Beusker, Ph.D., Director, Antibody-Drug Conjugates, Synthon

ADCs are emerging as a new modality for cancer treatment. Despite the impressive results obtained thus far, there is still need for improvement. Our novel linker-duocarmycin payloads have been designed to provide ADCs with excellent efficacy and a high therapeutic index. Design and application of this linker-drug technology will be discussed.

3:35 Incorporating Macrocyclic Expertise into Protein-Protein Interaction Ligand Design

Sponsored by ASINEX

Roman Kombarov, Ph.D., Project Manager, ASINEX

Protein-Protein interactions have great potential as therapeutic targets but are currently one of the most challenging areas in drug discovery. At Asinex, we have developed a platform that uses macrocyclic elements to facilitate the efficient design of novel alpha-helix mimetics which are decorated with poly-substituted hydrophobic substituents. These structures have the correct geometry and substitution characteristics to align the requisite functional groups in three dimensions and are thus able to disrupt key elements of the PPI interface. This talk will focus on how this strategy addresses an unmet need in drug discovery.

3:50 Sponsored Presentation

Sponsored by CHEMICAL COMPUTING GROUP

Speaker to be Announced

4:05 Refreshment Break in the Exhibit Hall with Poster Viewing

TOUGH TARGETS: ALLOSTERIC INHIBITORS TO ENHANCE PROFILES OR MODULATE DIFFICULT TARGETS

5:00 Allosteric Modulation of Phospholipase D: Oncology, Virology and Beyond

Craig W. Lindsley, Ph.D., Director, Medicinal Chemistry, Vanderbilt University Medical Center

This talk describes the chemical optimization of allosteric, isoform selective PLD inhibitors and the challenges therein. With highly selective tools, it was now possible to dissect the physiological roles of PLD1 and PLD2. Data presented will make a compelling case for PLD inhibition as a novel mechanism for therapeutic intervention across a spectrum of diseases.

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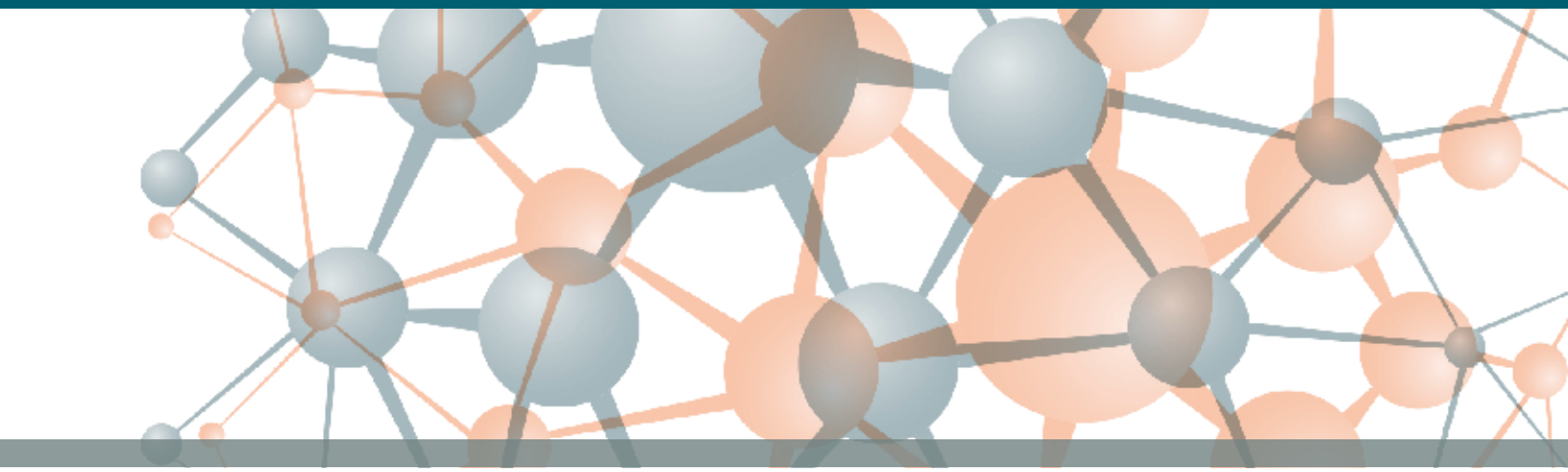

5:30 Molecular Mechanism of SSR128129E, an Extracellularly Acting Small Molecule Allosteric Inhibitor of FGF Receptor Signaling

Chantal Alcouffe, Medicinal Chemistry Team Leader, Early to Candidate, Sanofi

Cellular assays, signal transduction analysis, crystallization, Fourier transform infrared spectroscopy, mutagenesis, molecular dynamics simulations and metadynamics free energy calculations experiments participate in the elucidation of SSR128129's allosteric mode of action. SSR128129 is the first reported small molecule allosteric inhibitor of FGF/FGFR signaling, acting via binding to the extracellular part of the FGFR.

6:00 Welcome Reception in the Exhibit Hall with Poster Viewing

7:00 End of Day

THURSDAY, MAY 22, 2014

7:30 am Interactive Breakout Discussion Groups

RECEPTOR KINETICS AND RESIDENCE TIME

8:35 Chairperson's Remarks

Renato Skerlj, Ph.D., Founder, Drug Discovery Consulting LLC; former Head, Small Molecule Discovery, Genzyme, a sanofi company

8:45 Modulating Drug-Target Residence Time and Assessing Target Vulnerability

Peter J. Tonge, Ph.D., Professor, Chemistry, Institute for Chemical Biology & Drug Discovery, Stony Brook University

We are currently exploring the molecular factors that control the life-time of the drug-target complex and are using this information to rationally alter residence time. The translation of residence time effects through biological systems of increasing complexity reveals that drug-target kinetics can provide insight into target vulnerability.

9:05 CRTh2: Can Residence Time Help?

Rick Roberts, Ph.D., Senior Scientist, Medicinal Chemistry, Almirall

This talk outlines some of the results of our efforts to develop potent, orally bioavailable CRTh2 antagonists with long receptor residence time to prolong the pharmacodynamic effect. Structure residence relationships revealed the requirement of specific functional groups which bestowed long dissociation half-lives.

9:25 Translating Slow-Binding Inhibition Kinetics into Cellular and *in vivo* Effects

Stewart L. Fisher, Ph.D., Principal, SL Fisher Consulting, LLC

This seminar will discuss the concept of target:ligand residence time and the current challenges in translating routine *in vitro* measurements to more complex cellular and *in vivo* models. The development of mechanistic pharmacodynamic models that incorporate these features will be presented and demonstrated using data from an antibacterial drug discovery program.

9:45 Sponsored Presentation

Sponsored by AnalytiCon discovery

Speaker to be Announced

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

10:45 Protein Methyltransferase Inhibitors as Personalized Cancer Therapeutics: DOT1L and EPZ-5676

P. Ann Boriack-Sjodin, Ph.D., Director, Protein and Structural Sciences, Epizyme, Inc.

The enzymatic activity of DOT1L is associated with a chromosomal translocation that is universally found in patients with MLL-rearranged leukemia. Drug discovery efforts have yielded a potent, selective inhibitor of DOT1L (EPZ-5676) that affects the appropriate histone methyl marks in cells and affects tumor growth inhibition in xenograft models.

CASE STUDIES SESSION: PART III

11:05 BCL Case Study – From Fragment to Clinical Candidate

Vincent S. Stoll, Ph.D., Associate Director, Structural Biology, AbbVie

This presentation will describe the Discovery of Bcl drug candidates, from fragments to orally bioavailable drug candidates. The use of High-Throughput Chemistry, and dedicated Medicinal Chemistry in the optimization of fragment leads into potent molecules with the property optimized features for oral administration will be described.

11:25 Solving hERG Channel Inhibition

Kap-Sun Yeung, Ph.D., Principal Scientist, Discovery Chemistry, Bristol-Myers Squibb

A better understanding of the molecular characteristics of the hERG channel binding pocket and the ambiguous function of a basic amine, optimization of lipophilic ligand efficiency, as well as an appreciation of hERG trafficking inhibition are essential in mitigating the blockade of this cardiac potassium channel during the drug discovery process.

11:45 Close of Conference

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For more information, please contact:

Joseph Vacca
Business Development Manager
781-972-5431 | jvacca@healthtech.com

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CONFERENCE VENUE AND HOST HOTEL:

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Boston, MA 02210
T: 617-532-4600

Room Rate: $269 s/d
Reservation Cutoff: April 23, 2014

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