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Organized by Cambridge Healthtech Institute

CAMBRIDGE HEALTHTECH INSTITUTE'S EIGHTH ANNUAL

Drug Discovery Chemistry

RECORD ATTENDANCE EXPECTED THIS YEAR!

APRIL 16-18, 2013

HILTON SAN DIEGO RESORT & SPA · SAN DIEGO, CA

OPTIMIZING SMALL MOLECULES FOR TOMORROW'S THERAPEUTICS

NOBEL LAUREATE PLENARY KEYNOTE

APRIL 16 • 4:30PM

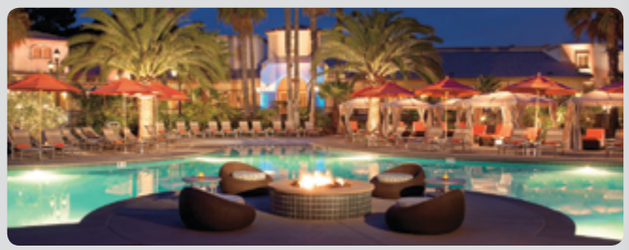
Jack W. Szostak, Ph.D.,
Investigator, Howard Hughes Medical Institute;
Professor of Genetics, Harvard Medical School

SYMPOSIUM

Property-Based Drug Design
Improving the Drug Discovery Process by Optimizing Bio-Physical Properties

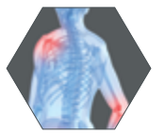
EVENT FEATURES

More than 100 Technical Presentations
10 Short Courses
Exclusive Exhibit & Poster Viewing Hours
Interactive Roundtable, Breakout & Panel Discussions
30+ Scientific Posters
400 High-Level Participants
Dedicated Networking Opportunities

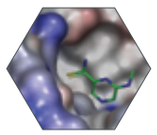


HILTON SAN DIEGO RESORT & SPA • SAN DIEGO, CA

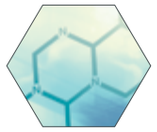
APRIL 16-17



4TH ANNUAL
Anti-Inflammatories

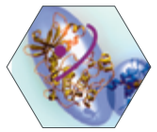


8TH ANNUAL
Fragment-Based Drug Discovery

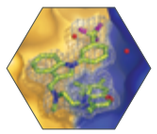


INAUGURAL
Constrained Peptides and Macrocyclics Drug Discovery

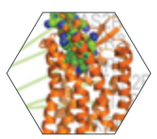
APRIL 17-18



4TH ANNUAL
Kinase Inhibitor Chemistry



6TH ANNUAL
Protein-Protein Interactions



INAUGURAL
GPCR-Based Drug Design

DrugDiscoveryChemistry.com

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CONFERENCE-AT-A-GLANCE

MONDAY, APRIL 15	SYMPOSIUM: PROPERTY-BASED DRUG DESIGN		SHORT COURSES
TUESDAY, APRIL 16	ANTI-INFLAMMATORIES	FRAGMENT-BASED DRUG DISCOVERY	CONSTRAINED PEPTIDES AND MACROCYCLICS DRUG DISCOVERY
	COMBINED PLENARY SESSION		
	WELCOME RECEPTION IN THE EXHIBIT HALL WITH POSTER VIEWING		
WEDNESDAY, APRIL 17	CONTINENTAL BREAKFAST & BREAKOUT DISCUSSIONS (IN SESSION ROOMS)		
	ANTI-INFLAMMATORIES	FRAGMENT-BASED DRUG DISCOVERY	CONSTRAINED PEPTIDES AND MACROCYCLICS DRUG DISCOVERY
	KINASE INHIBITOR CHEMISTRY	PROTEIN-PROTEIN INTERACTIONS	GPCR-BASED DRUG DESIGN
	DINNER SHORT COURSES		
THURSDAY, APRIL 18	KINASE INHIBITOR CHEMISTRY	PROTEIN-PROTEIN INTERACTIONS	GPCR-BASED DRUG DESIGN
	WALK AND TALK LUNCHEON IN THE EXHIBIT HALL WITH POSTER VIEWING		

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WELCOME
TO DRUG DISCOVERY CHEMISTRY

Cambridge Healthtech Institute's Drug Discovery Chemistry, now in its eighth year, is one of the few conferences geared towards medicinal chemists working in pharma and biotech. This four day event, focused on discovery and optimization challenges of small molecule drug candidates, offers many exciting opportunities for scientists to create a unique program according to personal interests.

New this year are two meeting tracks ("Constrained Peptides and Macrocyclics" and "GPCR-Based Drug Design") that represent areas of chemistry where new advances and technologies are leading to renewed interest. They nicely complement our most popular meetings from the past few years (Anti-Inflammatories, Fragment Based Drug Design, Kinase Inhibitor Chemistry and Protein-Protein Interactions).

To make the event even more cohesive but without leaving anyone's core focus out, we are offering a full day pre-conference symposium (Property-Based Drug Design). We have also expanded our scope by including more short courses to cover the specific therapeutic areas and approaches that many chemists find themselves moving towards or needing updated knowledge about.

We invite you to peruse this brochure to see for yourself the exciting science that is in store for you. Attendees' learning opportunities are not limited to the scientific and technology talks. Our audience and speakers participate in informal roundtable breakout sessions and expert panel discussions as part of the regular meeting tracks and discovery scientists at all levels and from different types of settings are able to interact with each other when the individual tracks join for poster and coffee breaks in the exhibit hall.

We look forward to meeting you in San Diego,

Edel O'Regan
Vice President

Anjani Shah, Ph.D.
Conference Director

NOBEL LAUREATE PLENARY KEYNOTE:

mRNA Display: From Basic Principles to Macrocycle Drug Discovery

Jack W. Szostak, Ph.D., Investigator, Howard Hughes Medical Institute; Professor of Genetics, Harvard Medical School; Alex Rich Distinguished Investigator, Department of Molecular Biology and the Center for Computational and Integrative Biology, Massachusetts General Hospital.

Dr. Szostak received the 2009 Nobel Prize in Physiology or Medicine for his fundamental contributions to our understanding of telomere structure and function, and the role of telomere maintenance in preventing cellular senescence. Dr. Szostak's early research on the genetics and biochemistry of DNA recombination led to the double-strand-break repair model for meiotic recombination. In the 1990s, Dr. Szostak and colleagues developed in vitro selection as a tool for the isolation of functional RNA, DNA and protein molecules from large pools of random sequences. His laboratory has used in vitro selection and directed evolution to isolate and characterize numerous nucleic acid sequences with specific ligand binding and catalytic properties.

Dr. Szostak is a member of the National Academy of Sciences and a Fellow of the New York Academy of Sciences, the American Academy of Arts and Sciences, and the American Association for the Advancement of Science. Dr. Szostak has published over 200 scientific papers and has been awarded 15 US patents.

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SECOND ANNUAL SYMPOSIUM • APRIL 15 • 8:30 AM - 4:30 PM

Property-Based Drug Design

Improving the Drug Discovery Process by Optimizing Bio-Physical Properties

The optimization of physical properties of a compound is fundamental to the drug discovery process, mainly due to their influence on absorption and distribution in vivo. They provide insight into the *in vivo* transport processes and knowing the properties will help with choosing the optimal compounds for the task. It saves costs and time when compounds are being properly analyzed in the design stage before they are moving into development, as it is important to consider questions such as how hydrophobicity will affect the solubility of a drug down the line or how the charge of the compound interacts with the absorption by a transport mechanism. Also, the use of predictive models is important, but again, without consideration of the actual physical chemical property of the new compound, the analyses will be based on a different set of data. This one-day symposium will discuss what it takes to create selective and efficacious compounds and to understand the biological data by analyzing the physicochemical properties early on.

8:30 Opening Remarks
Terry Stouch, Ph.D., President, R&D, Science for Solutions, LLC
Physicochemical properties and early ADME assays guide chemotype evaluation and rational scaffold alteration. This presentation will focus on the integration of these approaches with physiologically based pharmacokinetic modeling (PBPK) to enable the prediction of clinical outcomes and to optimize selection of development candidates.

8:40 Integrating Physicochemical Properties and PBPK for Improved Decision Making
Jan L. Wahlstrom, Ph.D., Principal Scientist, Pharmacokinetics and Drug Metabolism, Amgen, Inc.

9:20 *In Silico* Predictions of Ames Activities: The Nitrenium Hypothesis and Experiences with Crowd Computing
Jörg Bentzien, Ph.D., Scientist, Boehringer Ingelheim Pharmaceuticals, Inc.
This talk focuses on an ab initio approach to predict Ames activities of primary aromatic amines and recent experiences with a test example for predicting Ames activity via crowd computing using the Kaggle platform.

10:00 Morning Coffee Break

10:30 Important Considerations in the Interpretation of Pharmaceutical Data
Terry Stouch, Ph.D., President, R&D, Science for Solutions, LLC
Pharmaceutical Drug Discovery data can be surprisingly complex. Most of it is meant to be used immediately, in context with other temporally-related data, and with ready access to the informed commentary of the data provider. However, most companies have been archiving this data for years and it is often drawn on for use in development of predictive sciences and as as feedstock for "big data" efforts. Frequently, data is accumulated from diverse sources. However, few data are interpretable in isolation. Often involved meta data is essential to understand what a data item really means and how it relates to seemingly similar data. An especially important concern is that the precision of data is often overestimated by users. Actual error of the data items can be many times expected and may be sufficient to obviate the data for many uses. Along with examples, we will discuss issues to consider in the interpretation and use of data. We will discuss meta data of importance, magnitude and sources of error and resulting consequences for use, pitfalls in the use of historical data and accumulation of data from diverse sources.

11:00 Addressing Thermodynamic Properties
Ernesto Freire, Ph.D., Henry Walters Professor, Biology and Biophysics, Johns Hopkins University
The affinity and selectivity optimization of drug candidates is difficult because it needs to simultaneously maintain or improve the drug-like properties of the compound. Recently, different metrics have been proposed to assess the quality of drug candidates. Among them the LipE or lipophilic ligand efficiency has become widely used. High quality compounds, those with a large LipE, are essentially those that derive their binding affinity from factors other than hydrophobicity. Unfortunately, LipE alone only provides a retrospective characterization of a series of compounds. It would be ideal to develop the ability to predict LipE prospectively. Thermodynamic optimization plots (TOPs) provide such a tool since LipE is proportional to the enthalpy/entropy balance of a compound. TOPs provide an easy way of organizing enthalpy, entropy and binding affinity data obtained by isothermal titration calorimetry (ITC). While traditional structure/activity relationships rely solely on binding affinity, TOPs expand the range of correlations to enthalpic and entropic coordinates. TOPs allow prediction of the enthalpic and entropic consequences of chemical modifications at specific locations in a compound. As such, it provides a way to predict the effects of specific modifications on LipE.

11:30 Identifying Good Data for Structure-Based Design
Gregory Warren, Ph.D., OpenEye Scientific Software, Inc.
Structure-based design requires protein or protein-ligand structure data. This presentation discusses how to select data with the highest quality. This is important because the quality of the data has a direct impact on the quality of the prediction.

12:00 pm *In silico* Predictions of Metabolism
Marvin Waldman, Ph.D., Research Fellow, Simulations Plus, Inc.

12:30 Lunch on Your Own

2:00 Panel Discussion with Speakers: Considering Physicochemical Properties
- What drug properties are essential and when should they be determined?
- *In silico* vs experiment – is one set of data sufficient?
- Hydrophobicity in drug discovery – measurement or calculation?
- What's next for predictive methods?

3:00 Breakout Discussion Tables
These are moderated discussions with brainstorming and interactive problem solving, allowing conference participants from diverse backgrounds to exchange ideas, experiences, and develop future collaborations around a focused topic.
Moderators:
Terry Stouch, Ph.D., President, R&D, Science for Solutions, LLC
Jan L. Wahlstrom, Ph.D., Principal Scientist, Pharmacokinetics and Drug Metabolism, Amgen, Inc.

3:50 Closing Lecture
Speaker to be Announced

4:30 End of Symposium

**Separate registration is required*

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Short Courses*

**Separate registration is required*

MONDAY, APRIL 15 • 8:00-11:00 AM

Molecular Interactions and Drug Design

Tutor: Kent Stewart, Ph.D., Senior Research Fellow, Abbott Laboratories

This course provides an overview of protein-ligand interactions and drug design principles. The presentation is targeted to medicinal chemists. Part 1 covers hydrophobic, H-bonding and electrostatic interactions; Part 2 covers specialized topics such as conformation analysis, pi-stack, cation-pi, halogen bonding, protein-protein interface, and covalent inhibition. Medchem case studies are incorporated.

- Learn drug design principles generally applicable to all medchem programs.
- Interpret atomic-level protein X-ray and modeled structures of binding modes.
- Understand the relative amounts of potency gain from different interactions.
- Case studies illustrate all of the design strategies.

An Intro to the Field of Antibody-Drug Conjugates

Tutor: Ho Sung Cho, Ph.D., Chief Technical Officer, Ambrx

ADCs are an emerging modality in cancer. This course will give you an overview of the current advances being made in the clinic, review the design of novel payloads and linkers, and discuss some of the challenges being faced in developing future linkers and cytoxic drugs.

- Design of novel linkers, payloads and ADC's for Cancer
- Innovative chemistry strategies for ADC discovery
- Design, synthesis, and characterization of small molecule antibody therapeutics

MONDAY, APRIL 15 • 12:00 - 3:00 PM

Advancing Tools and Technologies for Fragment-Based Design

Tutor: Daniel A. Erlanson, Ph.D., Co-Founder, Carmot Therapeutics, Inc.

This short course will cover the basic ideas behind fragment discovery, outline the major tools for discovering fragments and provide case studies in the optimization of fragments to drug leads.

Immunology Basics for Chemists

Tutor to be Announced

- Review of inflammatory process and significant cellular and molecular players
  - cytokine biology
  - receptor pathways
- Autoimmune and Inflammation-related diseases
  - Which are most prevalent? Which have the greatest need for new therapies?
  - Underlying biologic defects
- Associated targets and their place in signal transduction pathways
- Current treatment landscape
  - Review of current state of anti-cytokine therapies (mostly biologics)
  - Biologics v. Small Molecules
  - What's on the Horizon
  - What is needed

MONDAY, APRIL 15 • 3:30 - 6:30 PM

Antiviral Drug Discovery:

Small Molecule Candidates to Combat Human Viral Infections

This course will bring together medicinal chemists who discover and develop new antiviral therapies. With the world becoming a smaller place, viral infections once contained to specific areas are now more wide-spread, increasing the need for novel therapies to combat once-rare viral infections. Thus, in addition to following the promising progress of new all-oral combination therapies to combat HCV, the meeting will also focus on treatments for human-targeted viruses that represent emerging unmet medical needs.

Instructors: Randall Halcomb, Ph.D., Director, Medicinal Chemistry, Gilead Sciences,
Dennis E. Hruby, Ph.D., CSO, Siga Technologies,
Robert Jordan, Ph.D., Director, Biology, Gilead Sciences,

Moderator: Christy Hebner, Ph.D., Research Scientist II, HCV Clinical Virology, Gilead Sciences, Inc.

Enabling Macrocyclic Compounds for Drug Discovery: Opportunities, Challenges and Strategies

Tutosr: Mark L. Peterson, Ph.D., Vice President, Operations, Tranzyme Pharma

Macrocyclic compounds fill an important chemical space between small molecules and biologics. This course will discuss the recent developments in the field of macrocycle synthesis and screening, as well as specific aspects of these compounds for drug discovery and development purposes. Topics to be Covered:

- Unique characteristics of macrocycles
- The challenges of macrocycle synthesis and screening
- Current methods for synthesizing and screening macrocyclic compound libraries
- Pros and cons of each methodology
- Drug discovery and development considerations for macrocyclic molecules
- Examples in the discovery of bioactive synthetic macrocycles
- Remaining challenges and possible solutions

Introduction to Allosteric Modulation of GPCRs

Tutor: Karen J. Gregory, Ph.D., Post-Doctoral Fellow, Jeffrey Conn Laboratory, Pharmacology, Vanderbilt University

Quantifying allosteric modulation

- Binding vs functional assays
- HTS and *in vitro* strategies
- *In vivo* experimental design

Complexities and challenges

- What to optimize for?
- Molecular switches and flat/steep SAR
- Modulation bias & context dependent pharmacology
- Multiple allosteric sites
- Probe dependence
- Some GPCRs are functional heterodimers

How can structural information aid modulator drug discovery?

- Mechanism validation (orthosteric, allosteric or bitopic?)
- Inform SAR
- Identify novel binding sites
- Virtual ligand screening

WEDNESDAY, APRIL 17 DINNER COURSES • 6:30 - 9:00 PM

Practical Aspects of Structure-Based Drug Discovery with GPCRs

Tutors: Robert Cooke, Ph.D., Head, Biomolecular Structure Department, Heptares
Michael Hanson, Ph.D., Director, Structural Biology, Receptos

- The quality of structures that can be expected and what can be done with the data.
- Expected throughput and turnaround times
- Working with fragments
- Dealing with conformational states
- Impact on modeling activities
- Comparison with more established SBDD efforts (eg kinases)
- Incorporating data from purified protein assays
- A couple of case studies covering the process

Epigenetic Targets: Chemical Tools

Tutors: Stephen Edgcomb, Ph.D., Senior Scientist, BPS Bioscience Inc.
Elizabeth Quinn, Ph.D., Director, Marketing Manager, LeadHunter Discovery Services, DiscoveRx Corporation
Terry Kelly, Ph.D. R&D Manager, Active Motif

This course will focus on what a chemist needs to know regarding epigenetic targets. It will start with a biology review of epigenetic modifications and then address challenges in designing probes and inhibitors for various EPG modifiers. Issues such as optimizing compounds for selectivity, potency and avoidance of toxicity will also be covered.

- Targeting Histone Methyl Transferases (HMTs)
- Inhibiting Demethylases (DMTs)
- Designing Histone Deacetylase Inhibitors (HDACi)
- Bromodomain and extra-terminal (BET) proteins

TUESDAY, APRIL 16

Scientific Advisor: Martin Braddock, Ph.D., Senior Principal Scientist, Inflammation, Neuroscience and Respiratory Global Medicines Development, AstraZeneca

7:00 am Registration and Morning Coffee

BTK and JAK Inhibitors for Inflammation

8:00 Chairperson's Opening Remarks

» 8:10 FEATURED PRESENTATION

Targeted Covalent-Reversible Inhibitors for Bruton's Tyrosine Kinase

Suvit Thaisrivongs, Ph.D., Executive Director, Chemistry, Pfizer

One strategy for optimizing pharmacological potency and selectivity for a number of challenging targets is to engage the non-catalytic cysteine residues with covalent inhibitors. Moreover, the utilization of a covalent inhibitor that reversibly forms an adduct is attractive as it may provide the pharmacodynamic benefit with reduced liability of long-lived irreversible protein adducts. 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 pre-clinical animal models of arthritis and autoimmune diseases. This offers promise as a therapeutic candidate for the treatment of autoimmune and inflammatory diseases.

8:50 Design and Characterization of Targeted Covalent Inhibitors of BTK

C. Eric Schwartz, Ph.D., Senior Director, Chemistry, Celgene Avilomics Research

One strategy for optimizing pharmacological potency and selectivity for a number of challenging targets is to engage the non-catalytic cysteine residues with covalent inhibitors. Moreover, the utilization of a covalent inhibitor that reversibly forms an adduct is attractive as it may provide the pharmacodynamic benefit with reduced liability of long-lived irreversible protein adducts. 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 pre-clinical animal models of arthritis and autoimmune diseases. This offers promise as a therapeutic candidate for the treatment of autoimmune and inflammatory diseases.

9:20 Potential of Selective BTK Inhibitors for Treating Autoimmune Diseases

Seng-Lai Tan, Ph.D., Global Medical Affairs, F-Hoffmann-La Roche Ltd.

BTK may contribute to the development of autoimmune diseases by mediating the production and effector function of (auto)antibodies. Consistently, a selective and reversible BTK inhibitor produces efficacy in models of rheumatoid arthritis and systemic lupus erythematosus. The data provide a proof-of-concept for developing BTK inhibitors as therapeutics for these diseases.

9:50 Networking Coffee Break

10:15 BTK Inhibitor

Longcheng Wang, Ph.D., Pharmacyclics

10:45 Discovery and Optimization of Selective JAK1 Inhibitors as Potential Treatments for Rheumatoid Arthritis

Mark Zak, Ph.D., Scientist, Discovery Chemistry, Genentech

JAK1 inhibitors exhibiting selectivity over JAK2 may hold the potential to maximize therapeutic efficacy against RA and other immune disorders, while minimizing unwanted anemia. Our strategies to identify selective and orally bioavailable JAK1 inhibitors will be presented, and the preclinical characterization of the lead molecule will be described.

11:15 Sponsored Presentation *(Opportunity Available)*

11:45 Luncheon Presentation: BioMAP® Profiling: To B or Not To B?

Sponsored by DiscoveRx

Alison O'Mahony, Ph.D., Director, Inflammation Biology, BioSeek, a division of DiscoveRx

Screening compounds in primary human cell BioMAP® systems designed to model diseased tissues reinstates a more physiological approach to drug discovery. Here, we present BioMAP® analysis of two BTK inhibitors revealing cell-selectivity, efficacy and safety related activities. Ibrutinib is broadly active on endothelial, epithelial, smooth muscle cells and fibroblast-based systems, while GDC-0834 is more selectively active in the BT system. Using these examples, we will show how BioMAP® can be used to guide pre-clinical development.

1:00 pm Session Break

Macrocyclics (Mostly) and Inflammation

1:25 Chairperson's Remarks

1:30 Discovery and Characterization of JAK1 Selective Macrocycles from a Cell-Based HTS Campaign

Jennifer Venable, Ph.D., Principal Scientist, Immunology Chemistry, Janssen Research & Development, LLC

2:00 Apremilast, a Targeted PDE4 Inhibitor in Development for Psoriatic Arthritis, Psoriasis, and Other Inflammatory Conditions

Peter H. Schafer, Ph.D., Senior Principal Investigator, Translational Development, Celgene Corporation

A premilast is an oral small molecule specific inhibitor of PDE4 with promising clinical efficacy in psoriasis and psoriatic arthritis. The expression of PDE4 in psoriatic skin and arthritic synovium, and the effects of apremilast on synovial fibroblasts, osteoclasts, osteoblasts, and osteocytes will be presented.

2:30 Nanocyclix: Potent and Selective Inhibitors for Novel Kinases in Cancer, CNS, Inflammation and Metabolic Diseases

Jan Hoflack, Ph.D., Head, Drug Discovery, ONCODESIGN Biotechnology

The Nanocyclix platform consists of low molecular weight macrocyclic kinase inhibitors that are exquisitely selective due to a high degree of shape complementarity with the ATP binding pocket. Multiple "First in Class" opportunities will be described in different therapeutic areas and will include detailed structural information on binding modes and selectivity generation.

3:00 Sponsored Presentation *(Opportunity Available)*

NEXT

3:15 Refreshment Break in the Exhibit Hall with Poster Viewing

4:00 Macrocycles for Drug Discovery - Identification of Small Molecule Synthetic Macrocycle Antagonists of Human IL17A

Nick Terrett, Ph.D., CSO, Ensemble Therapeutics Corporation

Ensemble Therapeutics has developed a DNA-programmed chemistry platform for the rapid synthesis and screening of macrocycles (Ensemblins™). Using this platform, small molecule macrocyclic compounds have been discovered that are nanomolar inhibitors of the interaction of the IL17A cytokine with its receptor. These compounds are anti-inflammatory in IL17-dependent animal inflammatory models and optimized for oral bioavailability.

» 4:30 PLENARY KEYNOTE

mRNA Display: From Basic Principles to Macrocycle Drug Discovery

Jack W. Szostak, Ph.D., Investigator, Howard Hughes Medical Institute; Professor of Genetics, Harvard Medical School; Nobel Laureate

The covalent attachment of a nascent protein or peptide to its own mRNA allows the *in vitro* selection of functional proteins and peptides from large libraries. This approach has recently been extended to the *in vitro* selection of highly modified cyclic peptides, a promising class of therapeutic agents.

5:30 Welcome Reception in the Exhibit Hall with Poster Viewing

6:30 End of Day

7:00 - 10:00 Complimentary Shuttle Bus Roundtrips to Downtown San Diego, Courtesy of Hilton San Diego Resort & Spa

WEDNESDAY, APRIL 17

7:45 am Continental Breakfast Breakout Discussions

In this interactive session, several topics will be offered for discussions and delegates are invited to choose a topic of interest and join the moderated discussion at hand. In this informal setting, participants are encouraged to share examples from their work, vet ideas with peers and be part of a group problem-solving endeavor. We emphasize that this is an informal exchange amongst scientists and is not meant to be, in any way, a product promoting session.

New Targets and Approaches for Inflammation

8:55 Chairperson's Opening Remarks

9:00 Anti-Chemokine Neutraligands as Potential Anti-inflammatory Drugs: From *in vitro* to *in vivo* Studies

Jean-Luc Galzi, Ph.D., Professor, Biotechnology and Cellular Signaling, University of Strasbourg

The discovery and use of small chemical compounds targeting chemokines -or neutraligands- will be described within the scope of anti-inflammatory therapeutic research. The potency of these chemokine neutralizing compounds in airway inflammation will be presented, illustrating new concepts in allergic disease treatment. The generality of the concept will be discussed.

9:30 Restoration of Phagocytic Function in Gaucher Macrophages by Non-Inhibitory Small Molecule Chaperones

Samarjit Patnaik, Ph.D., Research Scientist, National Center for Advancing Translational Sciences, NIH

Gaucher disease is a rare genetic disorder caused by lack of glucocerebrosidase enzymatic activity. This leads to pronounced lysosomal substrate storage and impaired function in macrophages, the crucial sentinel cells that initiate acute inflammation. We demonstrate effective reversal of disease phenotypes in advanced cellular models with non-inhibitory small molecule chaperones.

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

10:45 Discovery of Lesinurad, a URAT1 Inhibitor in Clinical Development for the Treatment of Gout

Jean-Luc Girardet, Ph.D., Vice President, Chemistry & Development Support, Ardea Biosciences, Inc.

Lesinurad is currently being developed for the treatment of hyperuricemia in gout patients. This molecule acts by inhibiting the reabsorption of uric acid in the kidney. It is being studied in phase 3 as combination therapy with xanthine oxidase inhibitors which reduce the production of serum uric acid.

11:15 GlycA and GlycB: Unique New Serum Markers of Systemic Inflammation Accessed by NMR Spectroscopy

Sponsored by LIPOSCIENCE

James Otvos, Ph.D., CSO, LipoScience, Inc.

Efficiently-quantifiable NMR signals from the N-acetylglucosamine/galactosamine (GlycA) and sialic acid (GlycB) moieties of glycosylated serum proteins can serve as unique new measures of systemic inflammation. Prospective clinical data indicate GlycA is more strongly associated with CHD, diabetes, CKD and other outcomes than traditional inflammation markers such as hs-CRP and fibrinogen.

11:30 Targeted Peptide Nanomedicine for Rheumatoid Arthritis

Hayat Onyuksel, Ph.D., Professor, Biopharmaceutical Sciences, University of Illinois at Chicago

Vasoactive intestinal peptide (VIP) is an endogenous neuropeptide with demonstrated anti-inflammatory activity. However, its intravenous use is limited due to its very short half life. We have developed a targeted, stable and safe nanomedicine of VIP using phospholipid micelles, and showed its high activity with no side effects on an animal model of RA.

12:00 End of Conference

BACK

Organized by
Cambridge Healthtech Institute

TUESDAY, APRIL, 16

7:00 am Registration and Morning Coffee

8:00 Chairperson's Opening Remarks

Roderick E. Hubbard, Ph.D., Senior Fellow, Vernalis (R&D) Ltd.; Professor, University of York, UK

» 8:10 KEYNOTE PRESENTATION

Alex MacKerell, Ph.D., Grollman-Glick Professor of Pharmaceutical Sciences; Director, Computer-Aided Drug Design Center School of Pharmacy University of Maryland

Using FBDD for Protein-Protein Interactions

8:50 Fragment-Based Approaches Targeting Protein-Protein Interactions

Richard Taylor, Ph.D., Principal Scientist, CADD, UCB

We will demonstrate an analysis of fragment hit rates against a range of novel Protein-Protein Interaction targets, using one of the largest fragment collections in the industry. We will show how this information can be used to guide the library design and the overlap with drug-like properties. Furthermore, some of the common problems associated with PPI targets and fragments will be discussed, and how the use of antibodies can overcome some of these issues.

9:20 Strategies for Fragment Evolution

Roderick E. Hubbard, Ph.D., Senior Fellow, Vernalis (R&D) Ltd.; Professor, University of York, UK

It is relatively straightforward to find fragments that bind to most proteins. The challenge is what to do with them, which to choose and how to evolve to higher affinity hits. I will discuss some new ideas which allow rapid and efficient exploration of the SAR attainable from fragment starting points and also summarise some recent experiences in using these and other techniques for developing leads against challenging targets.

9:50 Networking Coffee Break

Optimizing Hit-to-Leads

10:15 Fragment-Based Drug Design Using Molecular Dynamics

David Soriano del Amo, Ph.D., Head, Med. Chemistry, Acelelra Ltd.

Fragment-based drug design (FBDD) is an established method in drug discovery. *In silico* methods are a natural complement for biophysical assays and a variety of different approaches have been explored. In this study we apply recent advances in high-throughput molecular dynamics to assess the effectiveness of this simulation technique in selecting hits from a fragment library and predicting binding modes and affinities. A small 34-element fragment library was screened for binding to human factor Xa, using unbiased all-atom molecular dynamics simulations (Amber 99SB force field and ACEMD) performed at high ligand concentration and physiological conditions. The resultant trajectories were analyzed for fragment-protein interaction. Predicted hits compared favorably with a prior experimental assay using saturation transfer difference NMR spectroscopy.

10:45 Sponsored Presentation *(Opportunity Available)*

11:15 Rationalizing Non-Standard Interactions in Ligand Design: The Duality of Halogens

Sponsored by CHEMICAL COMPUTING GROUP

Chris Williams, Ph.D., Principal Scientist, Chemical Computing Group

Non-standard intermolecular interactions have been recognized as significant factors in protein-ligand binding, but their exploitation in ligand design can been difficult, because they are inadequately modeled using molecular mechanics based methods. Here we propose a model of intermolecular interactions based on Extended Hückel Theory (EHT), which accounts for electronic effects on interaction strength. The qualitative and semi-quantitative accuracy of the model is demonstrated using case studies that highlight the importance of these interactions.

11:45 To Affinity and Beyond: From Screened Fragments To Optimized Leads With SPR and ITC

Sponsored by GE Healthcare

Paul E. Belcher, Development Manager, GE Healthcare

This workshop outlines the fragment based drug discovery approach in the identification and optimization of potential drug candidates using label free techniques. We present results from case studies in which thousands of fragments are screened via SPR and well behaved binders rapidly selected via Biacore 4000 and an advanced Biacore T200 software. The fragment hits were then characterized and validated using a combination of SPR and ITC with binding site specificity and thermodynamic properties obtained.

1:00 pm Session Break

Computational Approaches and Library Design

1:25 Chairperson's Remarks

Edward T. Zartler, PhD, President & CSO, Quantum Tessera Consulting

1:30 "Fat, Drunk, and Stupid is No Way to Go through Life": (Re)Thinking Fragment Libraries

Edward T. Zartler, Ph.D., President, CSO, Quantum Tessera Consulting

Conventional thinking about fragment libraries tends to focus on size, partitioning in alcohol (clogP), and exploring a small portion of chemical space. This talk will present new points of view in regards to the size of molecules, solubility, and how best to interrogate 2D and 3D space.

2:00 DNA-Encoded Chemical Libraries for Fragment-Based Drug Discovery

Joerg Scheuermann, Ph.D., Senior Scientist, MoB, Pharmaceutical Sciences, ETH Zurich

In the implementation of Encoded Self-Assembling Chemical ("ESAC")-libraries, low-molecular weight compounds (fragments) are displayed on the 5' and 3' ends of DNA heteroduplexes which are formed upon hybridization of two small sized complementary DNA-encoded fragment sublibraries, thus yielding a large combinatorial library. Using these libraries for affinity-based selections enables the discovery of pairs of simultaneously binding fragments, which can subsequently be tested on DNA using standard techniques (e.g. SPR) and converted to high-affinity binders without DNA. The technology is perfectly suited for fragment-based lead-discovery and lead expansion (affinity maturation) of existing leads and case stories will be described.

2:30 Chemistry is the Key: Expanding the Diversity of Fragment Screening Libraries

Justin Bower, Ph.D., Head, Chemistry, Drug Discovery Programme, The Beatson Institute for Cancer Research

The target agnostic design of fragment libraries lends itself to screening against a range of potential targets and the gain in understanding of how PPI's exert their biological effects coupled with developments in structural biology, biophysical screening technologies and computational

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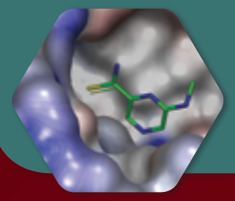

disciplines is increasingly bringing this class of target within the range of Fragment-Based Drug Design. This talk will explore the potential of using fragment -based methods to unearth hits against PPI's, detailing a discussion on fragment library composition along with suggestions of how future, more structurally diverse fragments which occupy different regions of chemical space to the vast majority of current fragment libraries can be designed and selected.

Sponsored by selcia

3:00 Successful Identification of Validated Fragment Hits Using Affinity Capillary Electrophoresis (ACE)

Carol Austin, Ph.D., Biology Group Leader, Selcia Ltd

ACE, in combination with the Selcia's fragment library, has been successfully used to identify fragment hits from different targets. The majority of hits have been validated using orthogonal techniques indicating a low false positive rate. The microscale technique does not require tethering of the target and is not dependent on protein size or high purity.

3:15 Refreshment Break in the Exhibit Hall with Poster Viewing

4:00 Impact of Novel Computational Approaches on Prospective FBDD Projects: From Screening Campaigns to *de novo* Design

Julen Oyarzabal, Ph.D., Director, Small Molecule Discovery Platform, Ctr for Applied Medical Research (CIMA), University of Navarra

I will present the impact of three novel computational approaches on prospective fragment-based drug discovery case studies: i.- Building a focused fragments library for screening campaign ii.- Fragment-hopping strategy to discover novel and chemically feasible scaffolds. iii.- Data mining and visualization tool to identify key fragments (R-groups) as well as ligand-receptor interactions from proprietary DBs, patents, … and transfer this knowledge to novel chemical series.

» 4:30 PLENARY KEYNOTE

mRNA Display: From Basic Principles to Macrocycle Drug Discovery

Jack W. Szostak, Ph.D., Investigator, Howard Hughes Medical Institute; Professor of Genetics, Harvard Medical School; Nobel Laureate

The covalent attachment of a nascent protein or peptide to its own mRNA allows the *in vitro* selection of functional proteins and peptides from large libraries. This approach has recently been extended to the *in vitro* selection of highly modified cyclic peptides, a promising class of therapeutic agents.

5:30 - 6:30 Welcome Reception in the Exhibit Hall and Poster Viewing

7:00 - 10:00 Complimentary Shuttle-Bus Roundtrips to Downtown San Diego, courtesy of Hilton San Diego Resort & Spa

WEDNESDAY, APRIL 17

7:30 am Continental Breakfast Breakout Discussions

In this interactive session, several topics will be offered for discussions and delegates are invited to join the moderated discussion at hand. In this informal setting, participants are encouraged to share examples from their work, vet ideas with peers and be part of a group problem-solving endeavor. We emphasize that this is an informal exchange amongst scientists and is not meant to be, in any way, a product promoting session.

Case Studies

8:25 Chairperson's Opening Remarks

8:30 Beyond Consensus: Leveraging Biases Inherent in Different Fragment Based Screening Technologies

Peter S. Kutchukian, Ph.D., Presidential Postdoctoral Fellow, Novartis Institutes for BioMedical Research, Cambridge, MA

A first step in FBDD often entails a fragment-based screen (FBS) to identify fragment "hits." While there are theoretical advantages of using FBDD at the earliest stages of a drug discovery program, hurdles such as the integration of conflicting results from orthogonal screens have hindered its success. We present the meta-analysis of 34 fragment based campaigns at Novartis, which used a generic 1,400 fragment library against diverse targets families using various biophysical and biochemical techniques. By statistically interrogating the multidimensional FBS data, we aim to answer three questions: 1) What makes a fragment amenable for FBS? 2) How do different FBS technologies compare with each other? 3) What is the best way to pair FBS assays? In addition to identifying properties that render fragments amenable for FBS, we compare in an unprecedented scale various screening technologies. Through our analysis we elucidate specific technology biases in detecting or missing fragment hits at a substructural level. Furthermore, we have developed a method to efficiently combine technologies based on these biases, in order to minimize the overall bias inherent in any screening campaign.

9:00 Enabling Chemical Discovery through the Lens of a Computational Microscope

Rommie E. Amaro, Ph.D., Assistant Professor, Department of Chemistry, University of California, San Diego

With exascale computing power on the horizon, computational studies have the opportunity to make unprecedented contributions to drug discovery efforts. Steady increases in computational power, coupled with improvements in the underlying algorithms and available structural experimental data, are enabling new paradigms for discovery, wherein computationally predicted ensembles from large-scale biophysical simulations are being used in rational drug design efforts. Such investigations are driving discovery efforts in collaboration with leading experimentalists. I will describe our work in this area that has provided key insights into the systematic incorporation of structural information resulting from state-of-the-art biophysical simulations into protocols for inhibitor and drug discovery, with emphasis on the discovery of novel druggable pockets that may not be apparent in crystal structures.

9:30 Fragment-Based Discovery of Novel, Selective PI3Kβ Inhibitors as Anti-Thrombotic Agents

Fabrizio Giordanetto, Ph.D., Project Leader, Principal Scientist, Medicinal Chemistry, CVGI iMed, AstraZeneca R&D

Structure-based evolution of the original fragment hits coupled with property-based design resulted in the identification of potent, selective Phosphoinositide 3-kinases (PI3K) p110β isoform inhibitors with favourable *in vivo* antiplatelet effect. Despite the antiplatelet action, no significantly increase in bleeding time was observed. Additionally, due to the engineered selectivity over p110β, no insulin resistance was induced.

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

10:45 The *de novo* Fragment-Based Drug Discovery of ITK Inhibitors

Heather Twin, Ph.D., Research Scientist, Vertex Pharmaceuticals

Interleukin-2 inducible T-cell kinase (Itk) is a member of the Tec family of non-receptor protein kinases which plays a central role in T-cell signalling. Inhibition of Itk presents an attractive approach for the treatment of

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TUESDAY, APRIL, 16

Scientific Advisor: Dinesh Patel, Ph.D., CEO, Protagonist Therapeutics

7:00 am Registration and Morning Coffee

Creating Constrained Peptides

8:00 Chairperson's Opening Remarks
Dinesh Patel, Ph.D., CEO, Protagonist Therapeutics

» 8:10 FEATURED PRESENTATION

A Renaissance of Constrained and Macrocyclic Peptide Drug Discovery: Transforming Nature's alpha-Helix into Breakthrough Medicines

Tomi Sawyer, Ph.D., CSO, Aileron Therapeutics

A renaissance of peptide drug discovery is leveraging innovative approaches to create constrained and macrocyclic analogs as novel modulators of extracellular and intracellular targets as well as tackle complex disease mechanisms. As a case study, advancements in stapled peptide technology to transform Nature's alpha-helix into breakthrough medicines will be presented.

8:50 Engineered Knottin Peptides: A New Class of Tumor Targeting and Molecular Imaging Agents
Jennifer Cochran, Ph.D., Associate Professor, Bioengineering, Stanford University
Cystine knot peptides (also known as knottins) are constrained by three interwoven disulfide bonds that confer high chemical, thermal, and proteolytic stability ideal for *in vivo* applications. We used rational and combinatorial methods to engineer knottin peptides that bind with low to sub-nanomolar affinity to tumor-associated receptors. In this talk, the evaluation of engineered knottin peptides in preclinical tumor models and their promise as diagnostic and therapeutic agents will be discussed.

9:20 Constrained Opioid Peptides
Steven Ballet, Ph.D., Research Group of Organic Chemistry, Departments of Bio-Engineering Sciences and Chemistry, Vrije Universiteit Brussel

9:50 Networking Coffee Break

10:15 Oral Disulfide Rich Peptide (DRP) Therapeutics
Dinesh Patel, Ph.D., CEO, Protagonist Therapeutics

10:45 EKO: A Method to Discover Small Molecules to Perturb Protein-Protein Interactions
Kevin Burgess, Ph.D., Professor, Department of Chemistry, Texas A&M University
Very recently, our group has devised a new approach to the problem of finding molecules that perturb specific PPIs; we call this Exploring Key Orientations. It involves defining a set of chemotypes for molecules that are ideally suited to this function (two examples are shown below), then matching their preferred conformations with structural features of PPI-interface regions on a massive scale. Significantly, it is a chemistry-centered method where small molecule design takes priority over bioassay considerations.

11:15 The Development of Linaclotide for the Treatment of Chronic Functional Gastrointestinal Disorders
Angelika Fretzen, Ph.D., VP of Pharmaceutical Chemistry and Development, Ironwood Pharmaceuticals

11:45 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Lunch on Your Own**

1:00 pm Session Break

Macrocyclic-Based Drug Candidates

1:25 Chairperson's Remarks

1:30 SOM230: A New Therapeutic Modality for Cushing's Disease
Ian Lewis, Ph.D., Research Chemist, Global Discovery Chemistry, Novartis
SOM230 has recently shown promise as the first effective pituitary directed medical treatment for Cushing's disease. Indeed, the multiple high affinity binding of SOM230 to somatostatin receptor subtypes enables much more effective inhibition of ACTH release *in vitro* and *in vivo*. Recent clinical studies involving treatment of Cushing's disease with SOM230 have demonstrated that SOM230 produced a decrease in urinary free cortisol (UFC) levels in 76% of patients during 15 days, with direct effects on ACTH release, establishing a new therapeutic modality for Cushing's disease.

2:00 Discovery of Stereochemically Complex Macrocyclic Hsp90 Inhibitors
Christoph Zapf, Ph.D., Principal Scientist, Worldwide Medicinal Chemistry, Pfizer
We wish to disclose the design and synthesis of a series of stereochemically complex, rule-of-five compliant small molecule macrocycles that were fine-tuned to be metabolically stable and devoid of hERG activity. The compounds showed impressive biomarker activity 24 hours post dosing in different cell lines. When studied in a lung cancer xenograft model, the macrocycles demonstrated prolonged exposure in tumors and significant tumor size reduction.

2:30 Discovery of TZP-102, a Macrocycle-Based Oral Ghrelin Receptor Agonist and GI Prokinetic Agent for the Treatment of Diabetic Gastroparesis
Helmut Thomas, Ph.D., Senior Vice President, Research and Preclinical Development, Tranzyme Pharma

3:00 Sponsored Presentation *(Opportunity Available)*

3:15 Refreshment Break in the Exhibit Hall with Poster Viewing

4:00 Macrocycles for Drug Discovery - Identification of Small Molecule Synthetic Macrocycle Antagonists of Human IL17A
Nick Terrett, Ph.D., CSO, Ensemble Therapeutics Corp.
Ensemble Therapeutics has developed a DNA-programmed chemistry platform for the rapid synthesis and screening of macrocycles (Ensemblins™). Using this platform, small molecule macrocyclic compounds have been discovered that are nanomolar inhibitors of the interaction of the IL17A cytokine with its

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receptor. These compounds are anti-inflammatory in IL17-dependent animal inflammatory models and optimized for oral bioavailability.

» 4:30 PLENARY KEYNOTE

mRNA Display: From Basic Principles to Macrocycle Drug Discovery

Jack W. Szostak, Ph.D., Investigator, Howard Hughes Medical Institute; Professor of Genetics, Harvard Medical School; Nobel Laureate

The covalent attachment of a nascent protein or peptide to its own mRNA allows the *in vitro* selection of functional proteins and peptides from large libraries. This approach has recently been extended to the *in vitro* selection of highly modified cyclic peptides, a promising class of therapeutic agents.

5:30 Welcome Reception in the Exhibit Hall with Poster Viewing

6:30 End of Day

7:00 - 10:00 Complimentary Shuttle Bus Roundtrips to Downtown San Diego, Courtesy of Hilton San Diego Resort & Spa

WEDNESDAY, APRIL 17

7:45 am Continental Breakfast Breakout Discussions

In this interactive session, several topics will be offered for discussions and delegates are invited to choose a topic of interest and join the moderated discussion at hand. In this informal setting, participants are encouraged to share examples from their work, vet ideas with peers and be part of a group problem-solving endeavor. We emphasize that this is an informal exchange amongst scientists and is not meant to be, in any way, a product promoting session.

Macrocyclics

8:55 Chairperson's Opening Remarks

9:00 Direct Selection of Cyclomimetics™ from *in Vitro* Display Libraries

Douglas A. Treco, Ph.D., President and CEO, Ra Pharmaceuticals

9:30 Successful Application of Novel Constrained Macrocycles in Drug Discovery

Daniel Obrecht, Ph.D., CSO, Polyphor, Ltd.

PEMfinder® (PEM=Protein Epitope Mimetics) and MacroFinder® are two complementary macrocycle-based platforms (MW= 400-2000) that have been developed by Polyphor as powerful tools to identify potent and selective modulators of intra- and extracellular protein-protein interactions (PPIs).This presentation will describe successful drug discovery case studies of applying PEMfinder® and MacroFinder® from discovery to the clinic.

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

10:45 Targeting Protein-Protein Interactions with Engineered Cyclotides

Julio Camarero, Ph.D., Associate Professor, Pharmacology and Chemistry, University of Southern California

I will present new data on the biosynthesis of cyclotides using bacterial and yeast expression systems for the generation of large genetically-encoded cyclotide-based libraries for high throughput cell-based screening and selection of cyclotides with novel biological activities. We will also report the design and biosynthesis of a MCoTI-grafted cyclotide with the ability to target intracellular and extracellular protein-protein interactions.

11:15 Bi-Cyclic Peptides to Target Endopeptidases

Christophe Bonny, Ph.D., CSO, Bicycle Therapeutics Limited

The Bicycle technology is based on repertoires of peptides displayed on the surface of bacteriophages which can be modified with an organochemical scaffold to create a diverse array of constrained peptides. These repertoires have been extensively used for iterative selections to identify high affinity binding peptides for a wide array of proteases. Results will be presented that exemplify the potential of the technology and its application to animal models of diseases.

11:45 End of Conference

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WEDNESDAY, APRIL 17

12:30 pm Registration

Optimizing Selectivity

1:30 Chairperson's Opening Remarks

Deborah J. Moshinsky, Ph.D., Founder and President, Cell Assay Innovations, LLC

1:40 Discovery of Highly Potent, Selective and Brain-Penetrable LRRK2 Inhibitors

Anthony Estrada, Ph.D., Scientist, Medicinal Chemistry, Genentech, Inc.

There is a high demand for potent, selective and brain-penetrable LRRK2 inhibitors to test whether inhibition of LRRK2 kinase activity will reduce the rate of disease progression in Parkinson's disease patients (PD) or animal models of PD. Starting from ligand efficient aminopyrimidine LRRK2 inhibitors, a thorough lead optimization process using property and structure-based drug design was executed. High throughput *in vivo* pharmacokinetic profiling enabled rapid validation of *in vitro* permeability and metabolic stability predictions. This resulted in the rapid discovery of inhibitors possessing an ideal balance of LRRK2 cellular potency, broad kinase selectivity, metabolic stability, and brain penetration across multiple species.

2:10 Structural and Biophysical Insights into an Allosteric Syk Kinase Inhibitor

Ann Aulabaugh, Ph.D., Senior Scientist, Structural Biology and Biophysics, Pfizer

2:40 Type II Protein Kinase Inhibitors for Increased Biochemical Efficiency and Kinome Selectivity: Experiences with PYK2 and SYK

Seungil Han, Ph.D., Senior Principal Scientist, Pfizer

In our pursuit to develop highly selective protein kinase inhibitors with increased biochemical efficiency in a cellular environment, we embarked on a systematic program to identify and characterize Type II inhibitors for two protein kinases, PYK2 and SYK. Application of different structural biology techniques along with sophisticated computational approaches have led to the identification of 'DFG-out' or 'C-helix-out' inhibitors of PYK2 and SYK. Crystal structures of these kinases with Type II inhibitors reveal the inherent dynamics within the kinase module of PYK2 and SYK that result in novel druggable binding sites outside of their adenine site. I will discuss our experiences in developing selective Type II inhibitors of protein kinases.

3:10 The SYK–BTK Axis as a Drug Target for Autoimmune Disorders

Seng-Lai Tan, Ph.D., Consultant, Global Medical Affairs, F- Hoffmann-La Roche Ltd., Basel, Switzerland

Spleen Tyrosine Kinase (SYK) and Bruton's Tyrosine Kinase (BTK) are non-receptor cytoplasmic tyrosine kinases that are primarily expressed in cells of hematopoietic lineage. Both are key mediators in coupling activated immunoreceptors to downstream signaling events that affect diverse biological functions, from cellular proliferation, differentiation and adhesion to innate and adaptive immune responses. As such, pharmacological inhibitors of SYK or BTK are being actively pursued as potential immunomodulatory agents for the treatment of autoimmune and inflammatory disorders. Here, we review and discuss recent insights into the emerging role of the SYK–BTK axis in innate immune cell functions, and our experience in developing selective SYK and BTK inhibitors.

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

4:20 Cell-Based Kinase Assays in Drug Discovery: Application to Selectivity Analysis and Personalized Medicine

Deborah J. Moshinsky, Ph.D., Founder and President, Cell Assay Innovations, LLC

This talk will focus on specific cellular model systems utilized in kinase drug discovery for potency, selectivity, and mechanism of action analyses. Examples of how these cell-based systems enable more physiologically relevant selectivity assessments will be given. Additionally, application of cellular kinase assays to personalized medicine will be outlined, with a particular emphasis on screening for inhibitors of drug-resistant mutant kinases.

4:50 Talk Title to be Announced

Kristine E. Frank, Ph.D., Senior Scientist III, Hit to Lead Chemistry, Abbvie

To date, ATP-mimetic kinase inhibitors have focused primarily on monocyclic and bicyclic heterocyclic cores. We sought to expand on the repertoire of potential cores for kinase inhibition by exploring tricyclic variants of classical bicyclic hinge binding motifs such as pyrrolopyridine and pyrrolopyrazine. A diverse collection of tricycles were prepared to investigate the electronics of each system and their ability to act as kinase hinge binders with differential selectivity. These structures have good calculated physicochemical properties and may have general use as scaffolds for kinase inhibitor projects.

5:20 Moderated Breakout Discussions

In this interactive session, several topics will be offered for discussions and delegates are invited to choose a topic of interest and join the moderated discussion at hand. In this informal setting, participants are encouraged to share examples from their work, vet ideas with peers and be part of a group problem-solving endeavor. We emphasize that this is an informal exchange amongst scientists and is not meant to be, in any way, a product promoting session.

6:20 End of Day

6:30 - 9:00 pm Dinner Short Courses *(Separate registration required, see page 3 for details.)*

THURSDAY, APRIL 18

7:45 am Breakfast Workshop Presentation *(Sponsorship Opportunity Available)* **or Morning Coffee**

Exploring the Chemical Space

8:15 Chairperson's Opening Remarks

» 8:20 FEATURED PRESENTATION

The Catalytic Domain of NF-kB Inducing Kinase Adopts an Active Conformation in the Absence of Phosphorylation

Sarah G. Hymowitz, Ph.D., Director, Department of Structural Biology, Genentech, Inc.

To better understand molecular basis of NF-kB inducing kinase (NIK) activity, we undertook a systematic expression and cloning effort to produce soluble and crystallizable NIK protein. This effort yielded crystal structures of apo human and murine NIK kinase domain as well as several structures of NIK bound to ATP-competitive inhibitors. These structures reveal the NIK kinase domain has an active-like conformation in the absence of phosphorylation and displays significant conformational variability.

NEXT

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9:00 Kinase Selectivity with Type 1 Inhibitors? Yes, we can!

Jan Hoflack, Ph.D., CSO, Oncodesign SA

Oncodesign's Nanocyclix platform of small macrocyclic kinase inhibitors allows to achieve high levels of selectivity across the kinome, without the need for reaching out to specificity pockets or targeting specific amino acids. The origin of this selectivity will be discussed using a number of experimental X-ray complexes. We will also detail the potential of these compound classes for rapid optimization based on highly consistent SAR, and discuss new data on unexplored kinases of high therapeutic interest.

9:30 Suitable Affinity Reagents for PAKs: Tight and Specific Binders from Rational Approaches

Ramesh Jha, Ph.D., Scientist, Bioscience Division, B10, MS M888, Los Alamos National Laboratory

PAKs are full of 'hotspot' regions for protein-protein interactions and play roles in several pathological conditions. This provides opportunities for design of affinity reagents and blockers. Using existing 3D structures of PAK1, specific binders that could distinguish 'open' and 'closed ' states were designed. The rational approaches used to design these affinityreagents will be discussed. Finally insights will be offered for targeting the regions on PAKs with unknown structure.

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

10:45 *In silico* Fragment-Based Discovery of Novel Classes of Potent and Selective Tyrosine Kinase Inhibitors

Hongtao Zhao, Ph.D., Scientist, Biochemistry, University of Zurich

We have developed an efficient *in silico* procedure called ALTA, which stays for anchor-based library tailoring approach, to interrogate a library of compounds for high throughput screening. First, small and mainly rigid virtual fragments are docked in the binding site. The fragments with most favorable calculated binding free energy (anchors) are used to identify the compounds with 2D structure containing one of these anchors, which are then submitted to flexible ligand docking. The essential of this ALTA approach is the novel fragmentation algorithm, which can generate fragments with high chemical richness that can serve as a starting point either directly for hit optimization or for identification of their "parent" compounds. This approach has led to identification of two novel classes of tyrosine kinase inhibitors, and the straightforward hit-to-lead optimization by addition of just one or two heavy atoms leads to two series of potent and selective inhibitors. The predicted binding modes were further confirmed by X-ray crystallography.

11:15 Discovery of AS1940477, a Highly Potent p38 MAPK Inhibitor

Toru Asano, Ph.D., Scientist, Drug Discovery Research, Astellas Pharma, Inc.

p38 mitogen-activated protein kinase (MAPK) plays a key role in immune responses through the production of cytokines such as TNF-alpha and IL-6. p38 MAPK is an attractive target for drugs to treat autoimmune diseases, although development of many p38 MAPK inhibitors have discontinued due to low efficacy and the need for high dosing. We have identified AS1940477 a highly potent p38 MAPK inhibitor with a novel tetrahydropyrazolopyrimidine structure. Data will be presented on the discovery and optimization of tetrahydropyrazolo-pyrimidine derivatives, including a favorable PK profile, and animal studies.

11:45 Kinase-Directed Phenotypic Screening: Identification of a Novel Target for Inflammatory Disease

David Chantry, Ph.D., Senior Director, Translational and Cellular Biology, Array BioPharma

Phenotypic screening is recognized as a powerful tool for drug discovery, but identification of molecular targets has proven challenging. We have established a phenotypic screening platform that allows for rapid identification and validation of novel kinase targets. We have assembled a collection of over 8 thousand compounds that cover >90% of the kinome. Using this platform we have identified a novel kinase target that regulates cytokine production by cells of the innate and adaptive immune system. Inhibitors of this kinase show anti-inflammatory activity *in vitro* and *in vivo*.

12:15 Sponsored Presentation *(Opportunity Available)*

12:30 Walk and Talk Luncheon in the Exhibit Hall (Last Chance for Poster and Exhibit Viewing)

Case Studies

1:55 Chairperson's Remarks

Tom Smithgall, Ph.D., William S. McEllroy Professor of Biochemistry; Chairman, Microbiology and Molecular Genetics, University of Pittsburgh School of Medicine

2:00 Discovery of a Novel and Highly Selective Series of JNK Inhibitors

Leyi Gong, Ph.D., Scientist, SRI International

A novel series of highly selective JNK inhibitors based on the 4-quinolone scaffold was designed and synthesized. Structure based drug design was utilized to guide the compound design as well as improvements in the physicochemical properties of the series. One of the lead compounds exhibits an IC50 of 62/170 nM for JNK1/2, excellent kinase selectivity and impressive efficacy in a rodent asthma model.

2:30 Small Molecule Inhibitors of the c-Fes Tyrosine Kinase: Potential Applications in Myeloid Leukemia and Myeloma

Tom Smithgall, Ph.D., William S. McEllroy Professor of Biochemistry; Chairman, Microbiology and Molecular Genetics, University of Pittsburgh School of Medicine

c-Fes is a cytoplasmic protein-tyrosine kinase that regulates normal cellular differentiation, the innate immune response, and vasculogenesis. Elevated c-Fes kinase activity is associated with Flt3+ AML and multiple myeloma. This talk will address the discovery and characterization of several classes of potent c-Fes inhibitors as well as their activity against these forms of cancer.

3:00 Chemistry to Unlock ROCK in Clinic

Olivier Defert, Ph.D., Amakem NV

Two case studies will be discussed in this lecture. First, we will focus on the design and the evaluation of a locally acting ROCK inhibitor as drug candidate for the treatment of glaucoma, AMA0076, which is currently in Phase 2 clinical development. Finally, the profile of the preclinical candidate for the treatment of respiratory diseases, AMA0247, will be shown. This compound showed efficacy in a variety of relevant *in vivo* models for asthma and COPD, with at least 500-fold lower exposure in the blood versus the lung tissues.

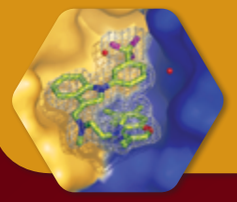
3:30 Selected Poster Presentation: Structure of the BRAF: MEK Complex Reveals Importance of Inhibitor Induced Protein Conformations for Downstream Signaling

Jawahar Sudhamsu, Ph.D., Postdoctoral Research Fellow, Structural Biology, Genentech Inc.

To understand the molecular basis of the RAF:MEK interaction, we solved the crystal structure of the BRAF:MEK1 complex. Our studies reveal the structural basis of diverse mechanisms of aberrant pathway activation by oncogenic variants of BRAF. In addition, this work also shows that inhibitor induced protein conformations can have unexpected consequences for downstream signaling.

4:00 End of Conference

BACK



WEDNESDAY, APRIL 17

12:30 pm Registration

PPI Drug Discovery - Novel Approaches

1:30 Chairperson's Opening Remarks

1:40 Systems and Network Pharmacology to Target Protein-Protein Interaction Networks in Cancer

Asfar Azmi, Ph.D., Research Scientist, Pathology and Oncology, Karmanos Cancer Institute, Wayne State University

To have an impact, interventions within a PPI network need to be multiple but highly selective. The major challenge is to design a promiscuous strategy that hits multiple weak nodes in cancer cell PPI without invoking undesirable side effects to normal cell network. The emergence of systems and network biology has enhanced our knowledge of PPIs and has allowed deeper evaluations of drug induced perturbations that has helped to decode the complex mechanisms of drug action. Emerging concepts such as 'Network Pharmacology' and 'Systems Pharmacology' are solidifying their position in cancer medicine.

2:10 PPI Drug Discovery - Peptide Mimicry and Fragment Approaches

David Fry, Ph.D., Head, Biostructural Research, Hoffman-La Roche

Modulating protein-protein interactions (PPIs) with small molecules is a difficult objective, but could potentially lead to a wide variety of novel and important therapeutics. PPI systems represent a unique class of drug target, and it has been shown that successful modulators of PPIs tend to have certain properties that distinguish them from drugs that act against more conventional target classes. One way toward understanding these key properties is to carefully study successful examples of PPI modulators and, at an atomic level, compare their binding strategies to those employed by the natural protein partners. Further, with regard to the fragment-based approach, we can learn by performing retrospective analyses of completed, successful programs - that is, deconstruct known PPI modulators into successively smaller fragments, and survey their potency and binding locations, and then compare these attributes to those of the parent compounds.

2:40 Bimolecular Fluorescence Complementation (Bifc) as a Novel Imaging-Based Screening for Inhibitors of Protein-Protein Interactions

Chang-Deng Hu, M.D., Ph.D., Associate Professor, Medicinal Chemistry and Molecular Pharmacology, Purdue University

Since the original report of BiFC in 2002, it has become a widely accepted method to study PPIs in various model organisms. Many critical PPIs have also been identified by the use of BiFC in living cells and animals. Further, recent improvements in the technology have also increased signal-to-noise ratio dramatically. Compared to other methods such as FRET, its higher signal-to-noise ratio (20 fold) is the most attractive feature for BiFC-based high throughput screening.

3:10 Computational Approaches to Antibody Modeling and PPI Hotspot Detection

Sponsored by SCHRÖDINGER

Dora Warshaviak, Ph.D., Applications Scientist, Applications Science, Schrödinger

Recent advances in computational methods have improved the predictive capabilities of modeling antibodies and protein-protein interaction energies. Here, we present recent work aimed at improving the speed and accuracy of antibody hypervariable loop prediction, and show high quality models can be generated for a large number of antibodies. In addition, we show that a more computationally intensive physics-based method is able to achieve a high degree of accuracy on the challenging H3 loop. Finally, we present results from a recent study on computational residue scanning to detect residue mutations at a protein-protein interface that contribute to significant favorable or unfavorable changes in binding energy.

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

Computational Methods

4:20 PocketQuery: Protein-Protein Interaction Inhibitor Starting Points from Protein-Protein Interaction Structure

David Koes, Ph.D., Research Assistant Professor, Computational and Systems Biology, University of Pittsburgh

PocketQuery is a web interface for exploring the properties of protein-protein interaction (PPI) interfaces with a focus on the discovery of promising starting points for small-molecule design. PocketQuery rapidly focuses attention on the key interacting residues of an interaction using a 'druggability' score that provides an estimate of how likely the chemical mimicry of a cluster of interface residues would result in a small-molecule inhibitor of an interaction. These residue clusters are chemical starting points that can be seamlessly exported to a pharmacophore-based drug discovery workflow.

4:50 Recent Advances in the Prediction of Protein Interaction Interfaces

Jarek Meller, Ph.D., Associate Professor, Environmental Health, University of Cincinnati

Computational methods to predict interaction sites using protein structure and sequence information are coming out of age. Recent developments in this field, accuracy of current prediction methods, inherent limitations and challenges are presented. Prediction of hot spots and druggable sites within interaction interfaces are also discussed.

5:20 - 6:20 Moderated Breakout Discussions

In this interactive session, several topics will be offered for discussions and delegates are invited to choose a topic of interest and join the moderated discussion at hand. In this informal setting, participants are encouraged to share examples from their work, vet ideas with peers and be part of a group problem-solving endeavor. We emphasize that this is an informal exchange amongst scientists and is not meant to be, in any way, a product promoting session.

6:30 - 9:00 Dinner Short Courses *(separate registration required, see page 3 for details)*

THURSDAY, APRIL 18

7:45 am Breakfast Workshop Presentation *(Sponsorship Opportunity Available)* **or Morning Coffee**

8:15 Chairperson's Opening Remarks

» 8:20 FEATURED PRESENTATION

Protein-Protein Interaction Drug Space: Stapled Peptide Drug Development

Tomi K. Sawyer, Ph.D., CSO, Aileron Therapeutics

Protein-protein interaction (PPI) drug space has become recognized as a promising new opportunity to advance a new modality of therapeutics for numerous diseases. The preponderance of such PPIs involve alpha-helical intermolecular recognition. This presentation will highlight recent advances in stapled peptide drug development.

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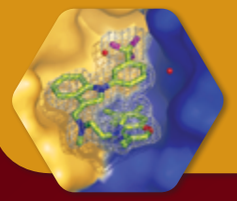

Rational Design

9:00 pH-Dependent Regulation of Cytokine-Receptor Interactions

Michael Hodsdon, M.D., Ph.D., Associate Professor, Laboratory Medicine, Yale University

Recognition of prolactin, a protein hormone and cytokine, by its receptor demonstrates a dramatic dependence on solution acidity across a physiologic range, such that acidification from pH 7.5 to 6.0 results in an approximately 500-fold decrease in affinity. This phenomenon has important implications for intracellular trafficking of endocytosed cytokine-receptor complexes. Biophysically, the pH-dependent behavior depends on a highly cooperative set of four histidine residues within the receptor-binding interface. A survey of cytokine-receptor complex tertiary structures reveals similar histidine-rich interfaces, which would be predicted to display similar pH dependence, along with histidine-free interfaces, expected to be pH independent. Site-directed mutagenesis can be used to rationally engineer pH-dependent behavior to both experimentally investigate its physiologic importance and also to potentially manipulate receptor trafficking.

9:30 Selective Protein-Protein Interactions Inhibition Result in Protection from Cardiac Ischemia and Reperfusion Injury

Nir Qvit, Ph.D., Research Associate, Chemical and Systems Biology, Stanford University

We rationally identified a peptide inhibitor of one of several functions mediated by delta-PKC. Our inhibitor is an allosteric inhibitor of the kinase and therefore, unlike inhibitors of the catalytic site, unlikely to affect other kinases. This peptide is an inhibitor of protein-protein interaction, thus a member of a novel family of pharmacological agents with therapeutic promise.

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

Strategies to Regulate PPIs

10:45 What Compounds for what PPI Target?

Olivier Sperandio, Ph.D., Drug Designer - CDithem Platform, Senior Research Associate, Inserm

I will describe our new iPPI-DB database that contains more than 1600 inhibitors of protein-protein interactions (iPPI) on about 15 classes of PPI targets with information on pharmacological activities, physico-chemical properties for the compounds, and biological descriptions about the PPI targets. The database was used to get some insight into the chemical space of iPPI with the ultimate aim of selecting PPI-friendly compounds to modulate PPI targets.

11:15 2P2I3D: A Focused Chemical Library Dedicated to Protein-Protein Interactions

Xavier Morelli, Ph.D., Group Leader & Principal Investigator, CRCM, CNRS

This talk will address some challenging questions: biological and chemical spaces of PPI with known orthosteric inhibitors, druggability assessment of protein-protein interactions, design and validation of chemical libraries dedicated to PPI.

11:45 Sponsored Presentation *(Opportunity Available)*

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12:15 Affinity Capillary Electrophoresis: An ACE method for Monitoring Protein-Protein Interactions (PPIs)

Carol Austin, Ph.D., Biology Group Leader, Selcia Ltd

Affinity Capillary Electrophoresis (ACE) is a high resolution, separation technique capable of readily detecting PPIs in solution. The technique does not require either protein to be immobilised and protein consumption is in the pM-nM range. Inhibitors from a range of starting points can be detected from fragments to natural product extracts.

12:30 Walk and Talk Luncheon in the Exhibit Hall (Last Chance for Poster and Exhibit Viewing)

1:55 Chairperson's Remarks

2:00 Promiscuous Small-Molecule Protein-Protein Interaction Inhibition: Could This Be a Real Concern?

Peter Buchwald, Ph.D., Director, Drug Discovery, Diabetes Research Institute, University of Miami

During our search for costimulatory interaction inhibitors, we have found poly-iodinated xanthene compounds that seem to be nonspecific promiscuous inhibitors of a number of PPIs within the tumor necrosis factor superfamily (e.g., (TNF-R–TNFalaf, CD40–CD154, RANK–RANKL, OX40–OX40L) as well as outside of it. For example, erythrosine B, and FDA-approved food colorant, acts as such an inhibitor with a remarkably consistent median inhibitory concentration (IC50) in the low micro-molar range. (approximately 2–20 mg/L) range.

2:30 Convergence of Mechanisms of Neuronal Injury and Cancer

James Bibb, M.D., Associate Professor, Psychiatry and Neurology and Neurotherapeutics, The University of Texas Southwestern Medical Center

Cdk5 is now being found in sparse poplulations of cells outside the nervous system. For example, we have found it in neuroendocrine C cells of the thyroid. Furthermore, it is highly expressed in medullary thyroid carcinoma (MTC), a cancer that is derived from these cells. Inhibition of Cdk5 arrests human sporadic and familial forms of MTC suggesting Cdk5 can cause MTC tumorigenesis. We have generated an inducible/arrestible mouse model of MTC and have derived a target library of downstream effectors of CDKs. We have validated one downstream effect as the Retinoblastoma protein. We are now working to screen this target library with the goal of identifying novel oncogenic and neuronal injury mechanisms that can serve as the basis for drug development. We will review these and our latest findings in this presentation.

3:00 Multiplex Analysis of Physiologic PPI Networks to Enable Identification of Signaling Signatures and Pharmacologic Targets

Adam G. Schrum, Ph.D., Assistant Professor of Immunology, Mayo Clinic College of Medicine

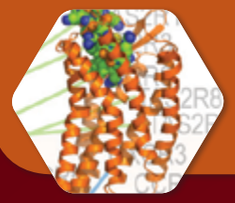
Physiologic signal transduction is thought to be mediated by sets of PPI that can operate together in modular networks. We present a novel multiplex microsphere based approach to analyze network PPI profiles for the T cell antigen receptor (TCR) signaling pathway. The unique signatures emerging in response to functionally distinct stimuli provide a new perspective on how to approach pharmacologic targeting of this immunologically important pathway.

3:30 Antagonism of Chromatin Interacting Proteins with Drug-Like Small Molecules

Cheryl Arrowsmith, Ph.D., Professor, Medical Biophysics; Canada Research Chair in Structural Proteomics, University of Toronto

4:00 End of Conference

BACK



WEDNESDAY, APRIL 17

12:30 pm Registration

GPCR Structural Determinants

1:30 Chairperson's Opening Remarks
Scientific Advisor: Michael Hanson, Ph.D., Director, Structural Biology, Receptos

» 1:40 KEYNOTE PRESENTATION

Adventures in S1P Receptor Therapeutics
Hugh Rosen, M.D., Ph.D., Professor, Chemical Physiology, Scripps Research Institute

2:40 Utilizing Structural Insights in GPCR Drug Discovery
Robert Cooke, Ph.D., Head, Biomolecular Structure Department, Heptares
The number of GPCRs for which structural information is available has increased dramatically in recent years, providing valuable insights into ligand recognition and mechanisms of activation, as well as additional starting points for homology modelling. Structure-based drug discovery is now a reality for this family, and the impact of new structures for family A and family B GPCRs will be reviewed.

3:10 Sponsored Presentation *(Opportunity Available)*

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

4:20 Delineating Determinants of Co-Operativity, Affinity and Bias for Allosteric Modulators of Metabotropic Glutamate Receptor 5
Karen J. Gregory, Ph.D., Post-Doctoral Fellow, Jeffrey Conn Laboratory, Pharmacology, Vanderbilt University; American Australian Association Merck Co. Foundation Fellow 2010; Drug Discovery Biology, MIPS & Department of Pharmacology, Monash University
Comparative modeling combined with the systematic mutagenesis has furthered our understanding of how metabotropic glutamate receptor 5 allosteric modulators exert their effects. We have identified key amino acids within the transmembrane domains that govern modulator affinity and/or cooperativity, as well as mutations that confer molecular switches in modulator pharmacology.

4:50 Mapping Allosteric Sites in GPCRs
Nagarajan Vaidehi, Ph.D., Professor, Immunology, Beckman Research Institute of the City of Hope
GPCRs are allosteric nanomachines that convey the ligand binding information on the extracellular surface to intracellular region. Experiments provide information on which residues are involved in either end of the allosteric communication but no information on the pathway of this communication. We have developed computational methods to map the allosteric pathway in GPCRs. These methods not only provide insights into the mechanism of communication but also provide new approaches to identifying allosteric druggable sites in GPCRs.

5:20 Moderated Breakout Discussions
In this interactive session, several topics will be offered for discussions and delegates are invited to choose a topic of interest and join the moderated discussion at hand. In this informal setting, participants are encouraged to share examples from their work, vet ideas with peers and be part of a group problem-solving endeavor. We emphasize that this is an informal exchange amongst scientists and is not meant to be, in any way, a product promoting session.

6:20 End of Day

6:30 - 9:00 pm Dinner Short Courses *(Separate registration required; see page 3 for details.)*

THURSDAY, APRIL 18

7:30 am Breakfast Workshop Presentation *(Sponsorship Opportunity Available)* **or Morning Coffee**

Probing GPCR Structure

8:15 Chairperson's Opening Remarks

8:20 FEATURED PRESENTATION

Structure of the Agonist-Bound Neurotensin Receptor NTS1
Reinhard Grisshammer, Ph.D., Investigator, National Institute of Neurological Disorders and Stroke (NINDS), NIH
Neurotensin is a peptide that functions as both a neurotransmitter and a hormone through activation of the neurotensin receptor NTS1, a G protein-coupled receptor (GPCR). I will present the structure at 2.8 Å resolution of NTS1 in an active-like state, bound to the peptide agonist. Our findings provide for the first time insight into the binding mode of a peptide agonist to a GPCR.

9:00 High-Resolution Structure of Human Adenosine A2A Receptor Reveals Allosteric Binding Sites for Sodium Ion and Cholesterols
Vadim Cherezov, Ph.D., Assistant Professor, Department of Molecular Biology, The Scripps Research Institute
1.8 A resolution structure of adenosine A2A receptor revealed a Na+ ion, 177 waters, 3 cholesterols and 26 lipids. Such unprecedented high-resolution details help to shed light on the role of waters in ligand binding and receptor activation, and to understand the allosteric effects of sodium, cholesterol and lipids on GPCR function.

9:30 Identifying an Alternate Antagonist Binding Site for a Diabetes Target: A GPCR Case Study
Carleton Sage, Ph.D., Fellow, Computational Systems, Arena

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

10:45 Probing Receptor Signaling Using Genetically-Encoded Unnatural Amino Acids
Thomas P. Sakmar, M.D., Professor, Laboratory of Chemical Biology & Signal Transduction, The Rockefeller University
Recent advances in molecular and structural studies of GPCRs have revolutionized drug discovery. Our aim is to elucidate the principles that underlie ligand recognition in GPCRs and to understand with chemical precision how receptors change conformation in the membrane bilayer when ligands bind. This lecture will describe new interdisciplinary technologies to study receptor dynamics and allosteric mechanisms.

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11:15 Nanobodies for the Structural and Functional Investigation of GPCR Transmembrane Signaling

Jan Steyaert, Ph.D., Executive Director and Professor, Molecular and Cellular Interactions, Vrije Univ Brussels

We generated Nanobodies that stabilize transient functional conformations of the human β2 adrenergic receptor. Nanobodies that faithfully mimic G protein binding were used to crystallize active agonist-bound states of this GPCR. Other nanobodies that stabilize the β2AR•Gs complex were instrumental to obtain the crystal structure of this complex, providing the first view of transmembrane signaling by a GPCR.

11:45 Structural Insights into Muscarinic Acetylcholine Receptor Function

Andrew C. Kruse, Graduate Student, Brian Kobilka (2012 Nobel Laureate) Lab, Department of Molecular and Cellular Physiology, Stanford University

I will present the recently determined structures of two muscarinic acetylcholine receptors, which offer new insight into ligand selectivity and allosteric modulation of muscarinic receptors and of GPCRs in general. In addition, I will discuss more recent work toward understanding the ligand binding and activation of these important receptors.

12:15 pm Sponsored Presentation *(Opportunity Available)*

12:30 Walk and Talk Luncheon in the Exhibit Hall (Last Chance for Poster and Exhibit Viewing)

Computational Approaches

1:55 Chairperson's Remarks

2:00 From GPCR Structure to Predictive Models

Ruben Abagyan, Ph.D., Professor, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego

As the number of GPCRs with known crystal structure approaches fifteen, the opportunities for structure based understanding of their function grow dramatically. Here we present the challenges and successes in predicting how orthosteric and allosteric ligands bind to GPCRs, as well as how protein and peptide ligands bind to family A and family B GPCRs.

2:30 Computational Approaches to GPCRs

Christopher A. Reynolds, Ph.D., MRC Fellow, Professor, School of Biological Sciences, University of Essex

Homology models of the calcitonin receptor-like receptor, a medically important class B GPCR; were constructed using a novel approach to the alignment and validated using experiment and theory. Distinct class B motifs and their class A equivalents have been identified. The relevance to drug design is discussed.

3:00 Hydrogen/Deuterium Exchange Captures Subtle Conformation Changes to GPCRs Upon Orthosteric Binding

Graham West, Ph.D., Postdoctoral Associate, Molecular Therapeutics, The Scripps Research Institute, Scripps Florida

Using hydrogen/deuterium exchange (HDX) coupled to mass spectrometry, we characterized conformation changes to the beta-2-adrenergic receptor in the presence of orthosteric ligands and absence of allosteric modulators (i.e. G proteins). Shifts to active GPCR conformations by orthosteric ligands alone have not been detected using crystallography. This work provides structural insight into GPCR signaling and presents a potential platform to structurally characterize GPCR-ligand interactions independent of tissue type.

3:30 Molecular Mechanisms of Vascular Alpha2C-adrenoreceptor Translocation

Marcin Pawlowski, Ph.D., Post-doctoral Scientist, Mathematical Medicine, The Research Institute at Nationwide Children's Hospital, Ohio

Alpha2C, a G protein-coupled receptor, has been recently found to act as a stress receptor of the vascular sympathetic system. Emerging evidence implicates this receptor in peripheral vascular conditions of Raynaud's phenomenon [1-4]. Based on preliminary studies, we hypothesize that the last 14 amino acids of Alpha2C carboxyl terminus mediate interaction with filamin-2. In the absence of a crystal structure for β2C-AR and filamin-2 region, we utilized amino acid homology searches, domain predictions, followed by protein-protein docking, to identify the residues that play a key role in Alpha2C-filamin-2 recognition and binding. This bioinformatics approach identified arginines R-454, R456, R-461 (within the arginine-rich region) and lysine 449 to be stabilized by negatively charged residues within the filamin-2 structure: E2004, E2059, D2060, and aspartic acid at position 2032, respectively

4:00 End of Conference

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Please **click here** or call the hotel directly to make your sleeping accommodations. You will need to identify yourself as a CHI 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 to take advantage of the discount we have negotiated.

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Property-Based Drug Design	Molecular Interactions and Drug Design	Enabling Macrocyclic Compounds for Drug Discovery	Epigenetic Targets: Chemical Tools
	Advancing Tools and Technologies for Fragment-Based Design	Allosteric Modulation of GPCRs	Practical Aspects of Structure-Based Drug Discovery with GPCRs
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April 16-17 (Tuesday-Wednesday)	April 17-18 (Wednesday-Thursday)
Track 1: Anti-Inflammatories	Track 4: Kinase Inhibitor Chemistry
Track 2: Fragment-Based Drug Discovery	Track 5: Protein-Protein Interactions
Track 3: Constrained Peptides and Macrocyclics Drug Discovery	Track 6: GPCR Based Drug Design

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