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

APRIL 16-17

4TH ANNUAL
Anti-Inflammatories

8TH ANNUAL
Fragment-Based Drug Discovery

INAGURAL
Constrained Peptides and Macrocylics Drug Discovery

APRIL 17-18

4TH ANNUAL
Kinase Inhibitor Chemistry

6TH ANNUAL
Protein-Protein Interactions

INAGURAL
GPCR-Based Drug Design
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

WELCOME RECEPTION IN THE EXHIBIT HALL WITH POSTER VIEWING

WEDNESDAY, APRIL 17

ANTI-INFLAMMATORIES

FRAGMENT-BASED DRUG DISCOVERY

CONSTRAINED PEPTIDES AND MACROCYCLICS DRUG DISCOVERY

KINASE INHIBITOR CHEMISTRY

PROTEIN-PROTEIN INTERACTIONS

GPCR-BASED DRUG DESIGN

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.
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 Bentzen, Ph.D., Scientist, Boehringer Ingelheim Pharmaceuticals, Inc.

This talk focuses on an ab initio approach to predict Ames activity with the highest quality. This is important because the quality of the data has a direct impact on the quality of the prediction.

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

Pharmacodynamic 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 feedback 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 LiPse or lipophilic ligand efficiency has become widely used. High quality compounds, those with a large LiPse, are essentially those that derive their binding affinity from factors other than hydrophobicity. Unfortunately, LiPse alone only provides a retrospective characterization of a series of compounds. It would be ideal to develop the ability to predict LiPse prospectively. Thermodynamic optimization plots (TOPs) provide such a tool since LiPse 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 LiPse.

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.

In silico vs experiment – is one set of data sufficient?

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

Symposium and Pre-Conference Workshops

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Please contact Suzanne Carroll at 781-972-5452 or at scarroll@healthtech.com for details.
Short Courses*

**MONDAY, APRIL 15 • 8:00-11:00 AM**

**Molecular Interactions and Drug Design**

*Tutor: Feng Shen, 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. Medicinal case studies are incorporated.

- Learn drug design principles generally applicable to all medicinal 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: Hsin Sung Chao, Ph.D., Chief Technical Officer, Amgen*

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 cytotoxic drugs.

- Design of novel linkers, payloads and ADCs 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**

*Tutors 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 biological defects
- Associated targets and their place in signal transduction pathways
- Current treatment landscape
- Review of current state of anti-cytokine therapies (mostly biologics)
- Biologics vs. Small Molecules
- What’s on the Horizon
- What's needed

**Antiviral Drug Discovery:**

**Small Molecule Candidates to Combat Human Viral Infections**

*Tutors: Randall Holcomb, Ph.D., Director, Medicinal Chemistry, Gilead Sciences; Dennis E. Hurby, Ph.D., CSO, Sigio Technologies; Robert Jordan, Ph.D., Director, Biology, Gilead Sciences; Christopher Hebner, Ph.D., Research Scientist II, HCV Clinical Virology, Gilead Sciences, Inc.*

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.

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

*Tutor: Mark L. Peterson, Ph.D., Vice President, Operations, Triazyme 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 macrocyclc 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

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

**Practical Aspects of Structure-Based Drug Discovery with GPCRd**

*Tutors: Robert Cooke, Ph.D., Head, Biomolecular Structure Department, Heptares; Michael Hansson, 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 (e.g. 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, DiscoverRx Corporation*

- Targeting Histone Methyl Transferases (HMTs)
- Inhibiting Demethylases (DMTs)
- Designing Histone Deacetylase Inhibitors (HDACs)
- Bromodomain and extra-terminal (BET) proteins
- Histone modification
- Impact on modeling activities
- Comparison with more established SBDD efforts (e.g. kinases)
- Incorporating data from purified protein assays
- A couple of case studies covering the process

*Separate registration is required*
TUESDAY, APRIL 16
Scientific Advisor: Martin Bradock, 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 & Development, LLC
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 autoantibodies. 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 Zok, 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?
Alison O’Mahony, Ph.D., Director, Inflammation Biology, BioSeek, a division of DiscoveRx
Sponsored by DrugdiscoveryChemistry.com/Anti-Inflammatories
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. Brutinib 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

Macrocylics (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
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. Brutinib 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.

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

4:00 Macrocycles for Drug Discovery - Identification of Small Molecule Synthetic Macrocyle 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 (Ensembilins™). Using this platform, small molecule macrocycle 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
Samajit 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 Giraudet, 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
James Olivas, Ph.D., CSO, LipaScience, Inc.
Efficiently-quantifiable NMR signals from the N-acetylgalactosamine/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 Oryukkel, 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
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

10:15 Fragment-Based Drug Design Using Molecular Dynamics
David Saracino del Amo, Ph.D., Head, Med. Chemistry, Acelleira 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
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 be 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
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, PhD, 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 Bowler, 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
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 PPIs, 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.

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.

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Case Studies

8:25 Chairperson's Opening Remarks
8:30 Beyond Consensus: Leveraging Biases Inherent in Different Fragment Based Screening Technologies
Peter S. Katchukian, 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 from various biological 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 techniques 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. Amara, 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
Fabiano Giordanetto, Ph.D., Project Leader, Principal Scientist, Medicinal Chemistry, CVG IlMed, 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 antplatelet effect. Despite the antplatelet action, no significantly increase in bleeding time was observed. Additionally, due to the engineered selectivity over p110α, 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...
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 Macrocylic Peptide Drug Discovery: Transforming Nature’s alpha-Helix into Breakthrough Medicines
Tom 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 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.
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.
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 amionopyrimidine 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. Plymowitz, 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.
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 affinity reagents 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
Hangtao 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 fragment 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 Asana, 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 has 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 tetrahydropyrazolopyrimidine 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
Lei Geng, 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

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

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 50-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
3:10 Computational Approaches to Antibody Modeling

Dora Warshawski, Ph.D., Applications Scientist, Applications Science, Schrodinger

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.

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)
SIXTH ANNUAL
Protein-Protein Interactions
Targeting PPI for Therapeutic Interventions

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., TNFα-R50, 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 populations 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/arrasible 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

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?
Oliver 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 (PPIs) 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 PPI 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 the ultimate aim of selecting PPI-compatible compounds to modulate PPI targets.

11:45 Sponsored Presentation (Opportunity Available)
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.
1:30 Chairperson’s Opening Remarks

Scientific Advisor: Michael Hanson, Ph.D., Director, Structural Biology, Receptos

**GPCR Structural Determinants**

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, yet 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 Cholesterol
Vladimir Cherezov, Ph.D., Assistant Professor, Department of Molecular Biology, The Scripps Research Institute

1.8 Å resolution structure of adenosine A2A receptor revealed a Na+ ion, 177 waters, 3 cholsterols 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.
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 ofGPCRs 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 conformational changes in 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
CHI offers comprehensive sponsorship packages which include presentation opportunities, exhibit space and branding, as well as the use of the pre and post-show delegate lists. Customizable sponsorship packages allow you to achieve your objectives before, during, and long after the event. Signing on early will allow you to maximize exposure to hard-to-reach decision makers!

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Sponsors will select their top prospects from the conference pre-registration list for an evening of networking at the hotel or at a choice local venue. CHI will extend invitations and deliver prospects. Evening will be customized according to sponsor’s objectives i.e.:  
• Purely social  
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*Inquire about additional branding opportunities!

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- If choosing a white paper program, we can offer editorial experience and provide an industry recognized author to write your white paper.

**To customize your participation at this event, please contact:**

Suzanne Carroll – Senior Business Development Manager  
781-972-5452 | scarroll@healthtech.com
Hotel & Travel Information

Conference Hotel:
Hilton San Diego Resort & Spa
1775 East Mission Bay Drive
San Diego, CA 92109
Phone: 619-276-4010
Discounted Room Rate: $199 s/d
Discounted Cut-off Date: March 15, 2013

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.

We understand that you have many choices when making your travel arrangements, and may ultimately decide to stay at another hotel. Please understand that reserving your room in the CHI room block allows you to take full advantage of the conference sessions, events and networking opportunities, and ensures that our staff will be available to help should you have any issues with your accommodations.

Flight Discounts:
Special discounts have been established with American Airlines for this conference:
• Call 1-800-433-1790 and use Conference code 9243BM
• Go to [www.aa.com/group](http://www.aa.com/group) and enter Conference code 9243BM in promotion discount box
• Contact our designated travel agent, Wendy Levine at 1-877-559-5549 or [wendy.levine@protravelinc.com](mailto:wendy.levine@protravelinc.com)

Car Rental Discounts:
Special discount rentals have been established with Hertz for this conference.
• [Click here](#) to make your reservation and use our Hertz Convention Number (CV): 04KL0004
Or Call Hertz directly at 800-654-3131 and reference our Discount Number 04KL0004

Visiting San Diego:
With its great weather, miles of sandy beaches, and major attractions, San Diego is known worldwide as one of the best tourist destinations. The San Diego Convention and Visitor’s Bureau is the official travel resource for the San Diego region such as maps and directions, visitor safety tips, where to stay, what to do and how to get around. International, and commercial air service for the region is provided by the San Diego International Airport.

• The San Diego Historical Society connects the past to the future so all generations will understand and appreciate the richness of San Diego’s regional history.
• The Gaslamp Quarter is Southern California’s premier dining, shopping and entertainment district, where you’ll find a truly eclectic blend of food, fun and culture all within one of San Diego’s most historic areas.
• At the world-famous San Diego Zoo, you will see some of the world’s rarest wildlife including giant pandas (and Hua Mei, the only panda cub in the U.S.), and koalas.
• QUALCOMM Stadium accommodates a variety of events, including major league sports and concerts.
• OTIS - The Online Transit Information System lets you find out how to get around San Diego using the Metropolitan Transit System’s buses, trolleys, or trains.
• A visit to the San Diego Wild Animal Park is like a safari to many of the world’s most exotic places.
• World-renowned Balboa Park is home to fifteen museums, various arts and international culture associations, as well as the San Diego Zoo, making it one of the nation’s largest cultural and entertainment complexes.
• SeaWorld San Diego: To entertain, amaze and educate, creating memories that last a lifetime. SeaWorld has hosted more than 100 million guests since opening in 1964.
How to Register: DrugDiscoveryChemistry.com

reg@healthtech.com • P: 781.972.5400 or Toll-free in the U.S. 888.999.6288
Please use keycode DCH F when registering

SHORT COURSES AND SYMPOSIA

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One-Day Symposium (April 15)
- Property-Based Drug Design
- Molecular Interactions and Drug Design
- Advancing Tools and Technologies for Fragment-Based Design
- Immunology Basics for Chemists
- An Intro to the Field of Antibody Drug Conjugates
- Enabling Macrocyclic Compounds for Drug Discovery
- Allosteric Modulation of GPCRs
- Antiviral Drug Discovery
- Epigenetic Targets: Chemical Tools
- Practical Aspects of Structure-Based Drug Discovery with GPCRs

CONFERENCE PRICING

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CONFERENCE SELECTIONS:
- April 16-17 (Tuesday-Wednesday)
  - Track 1: Anti-Inflammatories
  - Track 2: Fragment-Based Drug Discovery
  - Track 3: Constrained Peptides and Macrocyclics Drug Discovery

- April 17-18 (Wednesday-Thursday)
  - Track 4: Kinase Inhibitor Chemistry
  - Track 5: Protein-Protein Interactions
  - Track 6: GPCR Based Drug Design

CONFERENCE DISCOUNTS

POSTER DISCOUNT ($50 Off) Poster abstracts are due by March 15, 2013. Once your registration has been fully processed, we will send an email containing a unique link allowing you to submit your poster abstract. If you do not receive your link within 5 business days, please contact jting@healthtech.com. * CHI reserves the right to publish your poster title and abstract in various marketing materials and products.

REGISTER 3 - 4th IS FREE: Individuals must register for the same conference or conference combination and submit completed registration form together for discount to apply.

ALUMNI DISCOUNT: Cambridge Healthtech Institute (CHI) appreciates your past participation at Drug Discovery Chemistry. As a result of the great loyalty you have shown us, we are pleased to extend to you the exclusive opportunity to save an additional 20% off the registration rate. Please note: Our records must indicate you were an attendee of Drug Discovery Chemistry in the past in order to qualify.

GROUP DISCOUNTS: Discounts are available for multiple attendees from the same organization. For more information on group rates contact David Cunningham at +1-781-972-5472

Alumni, Group, and ‘Register 3 & 4th is Free’ discounts cannot be combined.