

The Boston Society

*Presents*



Applied  
Pharmaceutical  
Chemistry

**2009 CONFERENCE**

May 21 - 22, 2009

Merck Research Laboratories Boston Amphitheater

Boston, MA

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Co-Sponsor



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Exhibitors



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Pharmaceutical



Welcome to the Applied Pharmaceutical Chemistry 2009 conference. The organizers of APC have gathered an outstanding group of speakers and have arranged the program to allow for extensive audience participation and discussion. We hope that all conference attendees will take the opportunity to engage in discussion to benefit fully from the APC experience. Thank you for your participation.

### Organizers

#### Co-Chairs:

Julian Adams, *Infinity*  
Mark Goulet, *Merck*  
*Research Laboratories*

#### Organization Members:

Mark Duggan, *Link Medicine Inc.*  
Youssef Bennani, *Vertex*

### Speakers

Julian Adams, Ben Cravatt, Pat Walters, Ann Weber, Ed Scolnick, Mark Bilodeau, Mark Wittman, Travis Wager, David Rees, Jeffrey Albert, Steve Swann, Anna Bowman, Nick Terrett

### Conference at a Glance

#### THURSDAY

**Approaches and Lessons in Lead ID**

**Approaches and Lessons in Lead Optimization**

**Insights into Psychiatric Genetics and Biology**

**Case Studies & Overcoming Hurdles**

#### FRIDAY

**New Technologies & Techniques**

**Approaches and Lessons in Lead Optimization**

## Thursday May 21, 2009

### Lead ID Session I

#### Approaches and Lessons in Lead ID

Moderator: Mark Goulet, Merck Research Laboratories

- 08:00 AM - 08:30 AM Registration and Coffee
- 08:30 AM - 08:40 AM Conference Opening, *Julian Adams*
- 08:40 AM - 08:50 AM Introduction, *Mark Goulet*
- 08:50 AM - 09:20 AM Fragment based discovery of novel allosteric kinase inhibitors, *Steve Swann*
- 09:20 AM - 09:50 AM Fragment-based lead generation: challenges and successes. Discovery of high affinity beta-secretase inhibitors, *Jeffrey Albert*
- 09:50 AM - 10:00 PM **Break**
- 10:00 AM - 10:30 AM Fragment Based Drug Discovery: Case Histories, *David Rees*
- 10:30 AM - 11:00 AM *Panel Discussion*
- 11:00 AM - 11:15 PM **Break**
- 11:15 AM - 12:00 AM Discovery of JANUVIA™ (Sitagliptin), a Selective Dipeptidyl Peptidase-4 Inhibitor for the treatment of Type 2 Diabetes, *Ann Weber*
- 12:00 AM - 01:00 PM **Lunch**

### Lead Opt Session II

#### Approaches and Lessons in Lead Optimization

Moderator: Mark Duggan, Link Medicine

- 01:00 PM - 01:10 PM Introduction, *Mark Duggan*
- 01:10 PM - 01:40 PM Kv1.5 blockers: Invention of an ion channel selective and peripherally restricted clinical candidate, *Mark Bilodeau*
- 01:40 PM - 02:10 PM Development of a CNS Multi Parameter Optimization (MPO) Design Tool Increasing the Prob Compound Survival by Aligning Metabolism, Permeability, and Safety Properties in One Mole, *Travis Wager*
- 02:10 PM - 02:25 PM **Break**
- 02:25 PM - 02:55 PM The Road to BMS-754807, A Small Molecule Inhibitor of IGF-1R in Clinical Trials, *Mark Wittman*
- 02:55 PM - 03:40 PM *Panel Discussion*
- 03:40 PM - 03:55 PM **Break**
- 03:55 PM - 04:40 PM Discovery and Development of the First Proteasome Inhibitor: The Velcade Story, *Julian Adams*
- 04:40 PM - 05:30 PM **Keynote Address**, *Edward Scolnick*
- 05:30 PM End of Day

Friday May 22, 2009

## New Tech Session

### New Technologies & Techniques

Moderator: **Youssef Bennani, Vertex**

- 08:30 AM - 08:40 AM Introduction, *Youssef Bennani*
- 08:40 AM - 09:10 AM Activity-based proteomics and its application for enzyme and inhibitor discovery, Benjamin Cravatt
- 09:10 AM - 09:40 AM ASAP - Emphasizing Multidimensional Drug Discovery, *Pat Walters*
- 09:40 AM - 10:10 AM **Break**
- 10:10 AM - 10:40 AM A DNA-Programmed Chemistry Approach to Macrocyclic Lead Compounds, *Nick Terrett*
- 10:40 AM - 11:10 AM Small molecule inhibitors of the MDM2-p53 interaction discovered through the multiple protein structure (MPS) method, *Anna Bowman*

Friday - Agenda

## Thursday Workshop

### **Discovery and Development of the First Proteasome Inhibitor: The Velcade Story, Julian Adams**

Basic research on the proteasome in the early 90's revealed that there was a highly regulated biology governing cellular protein regulation. In addition there were early associations that the proteasome was implicated in the regulation of many pathways that are activated in cancer. A start-up biotech company, Myogenics (later changing its name to ProScript), was formed to study inhibitors of the proteasome. This talk will document the early discovery and ultimate development of PS-341 aka bortezomib and commercially sold as VELCADE. The complexity of introducing a new chemotype, for a new target for a relatively unknown disease, multiple myeloma, was rather challenging and the story is perhaps instructive to scientists in drug discovery and development.

### **Fragment based discovery of novel allosteric kinase inhibitors, Steve Swann**

Allosteric inhibition of kinases has emerged as an intriguing approach to drug discovery because it is believed targeting domains outside of the ATP binding region may afford increased selectivity and reduced toxicity. Using Affinity Selection followed by Mass Spectroscopy(AS/MS) along with NMR, we have identified ligands that bind to novel allosteric sites on members of the mitogen activated protein kinase family (MAPKs): the c-Jun N-terminal kinase 1 (Jnk-1) and p38. Detailed NMR analyses confirmed that these small molecules bind to sites on the protein distinct from the ATP site, and high resolution crystallographic analyses revealed that the inhibitors bind to sites associated with the MAP insertion within the structure of Jnk-1 and p38. These compounds represent novel approaches for targeting the inactive form of MAP kinases with the potential for improved selectivity, cellular potency, and safety.

### **Fragment-based lead generation: challenges and successes. Discovery of high affinity beta-secretase inhibitors, Jeffrey Albert**

Fragment based lead generation (FBLG) has recently emerged as an alternative to traditional high throughput screening (HTS) to identify chemistry starting points for drug discovery programs. In comparison to HTS screening libraries, the screening sets for FBLG tend to contain orders of magnitude fewer compounds, and the compounds themselves are less structurally complex and have lower molecular weight. We will describe challenges and successes across several projects at AstraZeneca, with particular emphasis on the discovery of high affinity beta-secretase inhibitors for Alzheimer's disease. Using NMR methods, we screened a library of low molecular weight compounds to identify hits that bound to the active site of beta-secretase with affinities (IC<sub>50</sub>) of 1-5 mM. X-ray crystallography and structure-based design facilitated the rapid evolution of these weak hits into high affinity (IC<sub>50</sub> <100 nM) drug leads

### **Fragment Based Drug Discovery: Case Histories, David Rees**

Five years ago most scientists did not consider low molecular weight fragments (MW = 120-250) with corresponding binding affinities of only mM to uM to be attractive starting points for drug discovery programs. However, today there is widespread acceptance that these fragments can be progressed into nM lead series and on into clinical trials. Reported examples include candidates that target different protein families such as kinases (CDK, Aurora, Akt, raf), protein-protein interactions (Bcl-XL), ATPases (HSP-90) and proteases (MMP 2&9).

Fragment based drug discovery uses biophysical screening to identify the initial fragments. Subsequently, in the fragments-to-leads stage a detailed structural understanding of the binding interactions between the fragment and its target protein utilizing X-ray crystallography or NMR is critical. Starting with different fragments allows several lead series to be identified, often by synthesizing only small numbers of compounds.

This presentation has two parts. Firstly, a general overview of the techniques associated with fragment based drug discovery and secondly some specific examples from Astex's laboratories of fragments that have been progressed into candidates for clinical trials.

## Thursday Workshop

### ***Kv1.5 blockers: Invention of an ion channel selective and peripherally restricted clinical candidate, Mark Bilodeau***

Existing treatments for atrial fibrillation that maintain or restore sinus rhythm (rhythm control) have deleterious effects on the ventricle. The potassium current  $I_{Kur}$  and its underlying protein Kv1.5 represent a cardiac repolarization mechanism that is present in the atrium and not in the ventricle and thus has been a prime target for the invention of new AF agents. The presentation will divulge our efforts from the discovery of a novel lead series through the identification of the clinical candidate. The talk will highlight the lead identification process and our strategies for the optimization of pharmacodynamics and pharmacokinetics. Ion channel selectivity proved to be a key issue for working around cardiac and central side-effects. Our strategies for creating peripherally restricted compounds to minimize central effects and for in vitro and in vivo screening to optimize cardiac parameters will be presented.

### ***Development of a CNS Multi Parameter Optimization (MPO) Design Tool Increasing the Prob Compound Survival by Aligning Metabolism, Permeability, and Safety Properties in One Mole, Travis Wager***

As the cost to develop pharmaceutical drugs increases and the regulatory environment for them becomes more conservative it is imperative that clinical candidates are designed with an improved probability of success. CNS MPO provides a prospective holistic assessment of a compound with respect to metabolism, permeability, safety, and drug-likeness. The CNS MPO algorithm designed by incorporating knowledge from CNS drug space, general medicinal chemistry, exp safety and ADME analyses. Six physicochemical properties were selected to be the foundation of the MPO algorithm. Looking at the in-vitro metabolism, permeability, and efflux, data from thousands of compounds and in-vivo safety data from CNS candidates, the CNS MPO has improved the probability of aligning and optimizing these parameters in one molecule. The overall MPO score defines the design space and correlates with Pfizer CNS clinical candidate survival. The power of this MPO is that it is prospective, expands drug design space versus hard property cut-offs, and can predict probable outcomes prior to compound synthesis.

### ***The Road to BMS-754807, A Small Molecule Inhibitor of IGF-1R in Clinical Trials, Mark Wittman***

Considerable interest in the pharmaceutical industry has been generated around the challenges of developing inhibitors of IGF-1R. As monoclonal antibodies targeting the extra-cellular binding domain of IGF-1R have advanced in the clinic, the potential of this target is being demonstrated. Following closely on the heels of these advances, small molecule inhibitors are just beginning to be investigated in the clinic. The lead optimization efforts to address the development issues surrounding a series of 1H-(Benzoimidazol-2-yl)-1H-pyridin-2-one pyridine inhibitors will be discussed and how a discovery strategy was developed that eventually led to BMS-754807. The preclinical characterization and early clinical experience with this novel pyrrolo [1,2-f][1,2,4] triazine will also be presented.

## Friday Workshop

**Activity-based proteomics and its application for enzyme and inhibitor discovery,****Benjamin Cravatt**

Genome sequencing projects have revealed that eukaryotic and prokaryotic organisms universally possess a huge number of uncharacterized enzymes. The functional annotation of uncharacterized enzymatic pathways, thus, represents a grand challenge for researchers in the post-genomic era. To address this problem, global molecular profiling methods hold great promise, as they provide a relatively unbiased portrait of the biochemical composition of cells and tissues and can reveal unanticipated alterations in their metabolic and signaling networks. Nonetheless, the identification and functional characterization of enzymatic pathways that support human physiology and pathology have, to date, been hindered by a lack of “systems biology” techniques that can evaluate their activity in complex biological samples. To address this problem, we have introduced functional proteomic and metabolomic technologies that record dynamics in enzyme activity in directly in native biological systems. For example, the activity-based protein profiling (ABPP) technology utilizes active site-directed chemical probes to determine the functional state of large numbers of enzymes in proteomes. In this presentation, I will describe the integrated application of ABPP and complementary functional proteomic/metabolomic methods to discover and functionally annotate enzyme activities in mammalian (patho)physiological processes. I will also present competitive ABPP platforms for developing selective inhibitors for enzymes.

**ASAP - Emphasizing Multidimensional Drug Discovery, Pat Walters**

One of the biggest challenges facing drug discovery teams is extracting information from the large volume of data generated in the course of a lead optimization effort, and using this information to make decisions. A typical lead optimization project can track between 15 and 30 assays (enzyme, cell, properties, PK, etc), and identifying trends in this data can be difficult. In an effort to address this problem and help scientists to make better decisions, we have developed a new software platform called ASAP. ASAP provides an intuitive overview of the data that also allows scientists to easily “drill down” and examine the details of particular experiments. A combination of “filters” and heat maps allows teams to focus on aspects of the data while remaining aware of the “big picture”.

**A DNA-Programmed Chemistry Approach to Macrocyclic Lead Compounds, Nick Terrett**

We have developed an integrated platform for the synthesis and screening of macrocyclic molecules (Ensemblins<sup>TM</sup>) that can interact with protein-protein drug discovery targets. The platform incorporates both a DNA-programmed chemistry (DPC) approach to compound libraries as well as more conventional medicinal chemistry. DPC permits the synthesis of thousands of macrocyclic molecules using predefined DNA sequences to control individual synthetic steps. The platform has been used successfully for the discovery of compounds that interact with the oncology target BCL-XL. In a separate program, we have discovered a series of macrocyclic compounds that competitively antagonize the activity of TNF- $\alpha$  on TNF receptors in both biochemical and cell-based assays. Agents that can prevent binding of TNF- $\alpha$  to its receptors have utility in the treatment of rheumatoid arthritis, Crohn's disease, psoriasis and ankylosing spondylitis. Currently marketed drugs are biologicals that target sequestration of TNF- $\alpha$ , and there are very few small molecule TNF- $\alpha$  antagonists at any stage of development. We have recently demonstrated that our small molecule TNF- $\alpha$  antagonist macrocycles have drug-like properties and show anti-inflammatory activity in vivo.

## Friday Workshop

### ***Small molecule inhibitors of the MDM2-p53 interaction discovered through the multiple protein structure (MPS) method, Anna Bowman***

Inhibiting protein-protein interactions with small molecules is an attractive proposal due to the pharmacological advantages small molecule drugs hold over larger molecules such as peptides. However, because of their large and often shallow interfaces protein-protein interactions are notoriously difficult to inhibit with small molecules. One system which presents a deep well-defined binding cleft favorable to inhibition with small molecules is MDM2-p53. Stabilization of p53 by small molecule inhibition of the MDM2-p53 interaction may offer a novel approach for initiating or enhancing cancer cell death. Dynamic pharmacophore models of MDM2 were developed using the multiple protein structure (MPS) method. The MPS method incorporates flexibility into a receptor based pharmacophore model that identifies appropriate hotspots of binding. A high-throughput virtual screen of a modest database identified five novel scaffolds which inhibit the MDM2-p53 interaction. The results demonstrate the power of the MPS method in expanding relevant chemical space and identifying diverse, new inhibitors

### ***Discovery of JANUVIA™ (Sitagliptin), a Selective Dipeptidyl Peptidase-4 Inhibitor for the treatment of Type 2 Diabetes, Ann Weber***

Dipeptidyl peptidase-4 (DPP-4), a member of a family of proline selective serine dipeptidases, is responsible for the N-terminal inactivation of GLP-1 and GIP, incretin hormones that evoke glucose dependent secretion of insulin and inhibition of glucagon release. Inhibitors of DPP-4 have been shown to increase circulating levels of GLP-1 and GIP, both in animal models and in the clinic, resulting in improved glucose tolerance. Thus, DPP-4 inhibitors represent a potential new therapy for type 2 diabetes. Early-amino acid-derived DPP-4 inhibitors that were not selective over related family members, in particular DPP-8 and DPP-9, induced profound toxicities in preclinical species. SAR studies on two novel screening hits provided a series of -amino acid-derived inhibitors that were highly selective over these enzymes. Optimization of this series led to the discovery of JANUVIA™ (sitagliptin), a selective DPP-4 inhibitor that was recently approved by the FDA for the treatment of type 2 diabetes.

### Julian Adams

Dr. Adams is President of Research and Development and Chief Scientific Officer. Prior to joining Infinity, Dr. Adams was the Senior Vice President, Drug Discovery and Development at Millennium Pharmaceuticals. In this capacity, he had global responsibility for multiple drug discovery programs, including the successful discovery and development of VELCADE®, a proteasome inhibitor for cancer therapy. He joined Millennium through its acquisition of LeukoSite in 1999 where he was Senior Vice President, Research and Development. Dr. Adams joined LeukoSite as a result of its acquisition of ProScript, Inc., where he had served as a member of the founding management team, Executive Vice President of Research and Development, and a member of the Board of Directors. Earlier in his career, Dr. Adams served in various positions, including Director, Medicinal Chemistry at Boehringer Ingelheim, where he successfully discovered the drug Viramune® for HIV. Also, from 1982-1987, he was a Medicinal Chemist at Merck.

Dr. Adams received a B.S. from McGill University and a Ph.D. from the Massachusetts Institute of Technology in the field of synthetic organic chemistry. He has received many awards, including the 2006 AACR Bruce F. Cain Memorial Award and the 2001 Ribbon of Hope Award for VELCADE® from the International Myeloma Foundation. Dr. Adams is an inventor of over 40 patents and has authored over 100 papers and book chapters in peer-reviewed journals. He is the editor of Proteasome Inhibition in Cancer Therapy published in July 2004.

### Ben Cravatt

Dr. Cravatt is a Professor in the Skaggs Institute for Chemical Biology and Department of Chemical Physiology at The Scripps Research Institute. His research group is interested in understanding the roles that enzymes play in physiological and pathological processes, especially as pertains to the nervous system and cancer. To address this challenge, they develop and apply an array of biochemical, chemical, and genetic technologies. The Cravatt group has obtained fundamental insights into the chemical, biochemical, and physiological workings of several important mammalian serine hydrolases, including enzymes involved in the neurobiology of pain and in proteases associated with tumor progression.

Dr. Cravatt obtained his undergraduate education at Stanford University, receiving a B.S. in the Biological Sciences and a B.A. in History. He then trained with Drs. Dale Boger and Richard Lerner and received a Ph.D. in Macromolecular and Cellular Structure and Chemistry from The Scripps Research Institute (TSRI) in 1996. Professor Cravatt joined the faculty at TSRI in 1997 as a member of the Skaggs Institute for Chemical Biology and the departments of Cell Biology and Chemistry. His honors include a Searle Scholar Award (1998-2001), the Eli Lilly Award in Biological Chemistry (2004), a Cope Scholar Award (2005), the Irving Sigal Young Investigator Award (2007), and the Tetrahedron Young Investigator Award in Bioorganic and Medicinal Chemistry (2008).

### Pat Walters

Pat Walters has been a member of the Molecular Modelling group at Vertex Pharmaceuticals since 1995. He currently heads this group, whose research focuses on the development of novel computational tools to support drug discovery. Before joining Vertex, Dr. Walters earned his Ph.D. in Organic Chemistry from the University of Arizona where he studied the application of artificial intelligence in conformational analysis. Prior to obtaining his Ph.D., he worked at Varian Instruments as both a chemist and a software developer. Dr. Walters received his B.S. in Chemistry from the University of California, Santa Barbara.

### Ann Weber

Dr. Ann E. Weber obtained her B.S. degree in chemistry summa cum laude from the University of Notre Dame. She earned her Ph.D. degree from Harvard University, studying synthetic organic chemistry in the laboratories of Professor David A. Evans. Following completion of her degree in 1987, Dr. Weber joined Merck Research Laboratories in Rahway, NJ as a Senior Research Chemist. She is currently Executive Director of medicinal chemistry.

Dr. Weber's research interests include the design and synthesis of ligands for G-protein coupled receptors, ion channels and enzymes. She has worked in the area of obesity research where her group identified a 3-adrenergic receptor agonist that was used for key proof of concept studies in the clinic, demonstrating that stimulation of this target did not induce weight loss in humans. She went on to co-lead a cross functional team of chemists and biologists that discovered JANUVIA™ (sitagliptin phosphate), which was approved by the United States Food and Drug Administration in 2006 as a new treatment for patients with Type 2 diabetes. JANUMET™, a fixed dose combination of sitagliptin and metformin, was approved by the FDA in March 2007. Currently, efforts in her group target new treatments for patients with diabetes and obesity.

Dr. Weber is the author or co-author of over 65 publications. She is co-inventor on 25 issued US patents with 11 additional applications pending. In 2002 she was named Women at the Forefront of Chemistry by the American Chemical Society Women Chemists Committee. She received the 2007 Thomas Alva Edison Patent Award from the Research and Development Council of New Jersey and a Directors' Award from Merck for her contributions to the discovery of JANUVIA™. She was part of a team that received the 2007 Prix Galien USA for JANUVIA™, and was named among the 2008 Outstanding Women in Science by the New Jersey Association for Biomedical Research.

### Ed Scolnick

Dr. Edward Scolnick earned his M.D. degree from Harvard Medical School and received 2 years of Internal Medicine Training at the Massachusetts General Hospital. He spent 15 years at the National Institute of Health where he made seminal discoveries on the nature of genes that cause cancer in humans. He then spent 22 years at Merck Research Laboratories where he was head of Research from 1985 to 2002. Dr. Scolnick was elected to the National Academy of Sciences in 1984 and to the American Academy of Arts and Sciences in 1993. Since leaving Merck he has been at the Broad Institute of MIT and Harvard as Director of the Psychiatric Disease Program and the Stanley Center for Psychiatric Research, which is focused on understanding the causes of schizophrenia and bipolar illness and finding new ways to treat these diseases.

### Mark Bilodeau

Mark Bilodeau was born in Newton, MA. He earned his B.S. in Chemistry at Boston College in 1988 where he did undergraduate research in the laboratory of Prof. T. Ross Kelly. He then did his doctoral studies with Prof. David Evans at Harvard University where he earned his Ph. D. in 1993. He then did a two year NIH post-doctoral fellowship with Prof. Samuel Danishefsky at the Memorial Sloan-Kettering Cancer Center. Since 1995 he has been in the Medicinal Chemistry Department of the Merck Research Laboratories where he currently holds the position of Director.

Education:

- BS in chemistry; Houghton College (1983)
- PhD in synthetic organic chemistry; James Kallmerten, Syracuse University (1988)
- Development of the glycolate-enolate Claisen rearrangement and the 2, 3 Wittig rearrangement as a vehicle for controlling acyclic stereochemistry.
- Application of these methods to natural product synthesis
- Post-doctoral fellow; Sam Danishefsky, Yale University (1990)
- Development of methods to prepare hydroxyl amine containing sugars using dimethyldioxirane
- Development of methodology for preparing allal and gulals using a 2,3 rearrangement of glycols
- Application of these methods to the synthesis of the trisaccharide of Esperamicin/Calicheamicin. Bristol-Myers Squibb (1990- present)
- Senior scientist/project leader; Oncology Discovery Chemistry
- Natural product synthesis and semi-synthesis (ene-diyene and taxane antitumor agents)
- Small molecule inhibitors of growth factor receptor targets

### Travis Wager

Travis T. Wager received his Ph.D in 1998 at the University of Utah working in the laboratory Keck, PhD. His research at that time involved the total synthesis of naturally occurring Amary alkaloids. He subsequently accepted a Pfizer postdoctoral fellowship at the University of Utah Keck where he focused on the synthesis Rhizoxin D. After coming to Pfizer in August of 1999 several years working on novel Alzheimer's approaches, particularly CDK-5 & GSK-3b. As a discovery Medicinal Chemist he focuses on early safety de-risking strategies which he believe deliver high quality products to the clinic and ultimately to the market. He is a proud recipient Upjohn Award (2007) for his innovative work on an early safety strategy targeting the removal phospholipidosis adverse findings in vivo. He has two active clinical candidates and is an author of 28 peer-reviewed papers, reviews and patents. Travis lives in New London, CT with his wife C their two children Genevieve (6) and Cecelia (4). Major interests are racquetball, water skiing generally anything outdoors

### David Rees

David Rees joined Astex 6 years ago and is Senior Vice-President of Medicinal Chemistry. Prior to Astex, he had 19 years experience as a drug discovery chemist in the pharmaceutical industry, working with Parke-Davis, Organon and, most recently, AstraZeneca where he held the position of Director and Head of the Medicinal Chemistry Department with some 140 staff at the research and development laboratories, Mölndal, Sweden. He has served on various University positions, editorial boards and international conference committees, he has over 75 publications and patents and is a joint recipient of the Royal Society of Chemistry's Malcolm Campbell prize in 2007 for the discovery of the anesthesia drug, sugammadex (Bridion).

### Jeffrey Albert

Jeffrey Albert did his Ph.D. with Prof. Andrew Hamilton at the University of Pittsburgh and post-doc with Prof. Peter Dervan at the California Institute of Technology. He joined AstraZeneca Pharmaceuticals in 1998. He and his project teams work in the early phases of drug discovery by identifying important new targets for psychiatric diseases and then developing chemical starting points to evolve toward drugs.

Today's presentation will focus on the use of fragment-based methods across AstraZeneca and focus on application to beta-secretase as a target for Alzheimer's disease.

Steve received his Ph.D. in Organic Chemistry under John Koh, at the University of Delaware in 2002 where he used molecular modeling to design and synthesize potentially therapeutic vitamin D analogs. He then moved onto to Dupont Discovery research where he used computer-aided design to develop novel fungicides and insecticides. After 5 years, Steve moved to Abbott in 2006 where he continued to use molecular modeling and synthesis to optimize fragment hits generated from NMR screening, as well as the de novo design of inhibitors for lead optimization programs. In his brief career at Abbott, Steve has generated 3 patents around de novo designed kinase inhibitors as well as personally advancing 2 fragment hits to lead optimization.

### Anna Bowman

Anna Bowman read chemistry at the University of Bristol, followed by a Ph.D. in Computational Chemistry also at the University of Bristol, investigating enzyme catalyzed reactions with QM/MM methods. She then joined Prof. Heather Carlson's lab at the University of Michigan where she worked on incorporating protein flexibility into structure-based drug discovery. Now at the Centre for Drug Discovery at Northeastern University, she applies computational approaches to the endocannabinoid signaling system

### Nick Terrett

Nick Terrett was born in London and educated at the University of Cambridge. On completing a PhD in organic chemistry, he joined Pfizer in Sandwich, UK where he worked as a medicinal chemist initially on cardiovascular disease that resulted in the discovery of candoxatrilat, and later, the discovery and development of Viagra and Revatio. Shortly after this, Nick established Pfizer's combinatorial chemistry group and authored related papers and a textbook. From 2003, Nick was Senior Director of Chemical Sciences at the Pfizer Research Technology Center in Cambridge, Massachusetts, before moving in 2006 to Ensemble Discovery to take up his current role of Chief Scientific Officer.

## Notes

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# Parking

For your convenience we have included details on the public parking garages within walking distance to the facility. These rates are subject to change. Updated 1/1/08

### Trilogy

180 Brookline Ave  
 (10 min. walk, 7 blocks)  
 Boston, MA 02115 Early Bird Special  
 (In by 8am out by 7pm) - \$15  
 Hourly Rate - \$5 per hour  
 Daily Maximum - \$20

### Pilgrim Parking, Inc.

Longwood Galleria Parking Garage  
 (3 blocks)  
 350 Longwood Ave.  
 Boston, MA 02115 3hrs. - \$15  
 4hrs. - \$18    5hrs. - \$20  
 6hrs. - \$23    Over 6hrs. - \$30

### Standard Parking

(Located at Harvard COOP, 2 blocks)  
 333 Longwood Ave.  
 Boston, MA 02115  
 3hrs. - \$13  
 4-5hrs. - \$25    5hrs.+ - \$30  
 Daily Maximum - \$30

### Children's Hospital Parking

Available to External Parkers Depending on Daily Volume  
 300 Longwood Ave.  
 Boston, MA 02115  
 3hrs. - \$15    4hrs. - \$18  
 5hrs. - \$20    Over 5hrs - \$30

# Taxi Cabs

| Taxicab Company      | Phone Number | Protocol                            | Payment Method  |
|----------------------|--------------|-------------------------------------|-----------------|
| Boston Cab           | 617-262-2227 | Call with 1/2 to 1 hour notice      | Cash or *Credit |
| City Cab             | 617-536-5100 | Call with 1/2 to 1 hour notice      | Cash or *Credit |
| MetroCab (John Ward) | 617-242-8000 | Call with 20 min to 1/2 hour notice | Cash or *Credit |
| Town Taxi            | 617-536-5000 | Call with 20 min to 1/2 hour notice | Cash or *Credit |

\*If paying by credit card please inform when calling.

# Limousine Services

### Hello Limo

24 Hour Service to airport  
 617-953-7969

### ABC Shuttle & Limo Service

24 Hour Service to airport  
 Call 1 hour in advance  
 781-244-8998

## Restaurants

Restaurants in Boston with varying cuisines are listed below. For more information and reviews visit one of the following links: <http://calendar.boston.com/restaurants> or <http://www.phantomgourmet.com/>

### **Al Dente**

Snuggled in the heart of the world famous North End, Al Dente Restaurant lets you feast on a bountiful array of Italian specialties. The outstanding menu, featuring pasta, chicken, veal and seafood, highlights a spectrum of lavish Italian specialties that are sure to please discriminating palates. The open kitchen lets you in on the action behind the superb dishes, and you'll enjoy their lavish fare amid a cozy, casual setting. | Italian | 109 Salem St., Boston, MA, 02113 (617) 523-0990

### **La Galleria 33**

The hot top spot for swank Italian dining in Boston. Tucked away on Salem Street in the heart of the North End – well off the boisterous, beaten track of Hanover Street – this cozy, warm and romantic restaurant serves some of the best, reasonably priced Italian food found anywhere. | Italian | 125 Salem St., Boston, MA, 02113 (617) 723-7233

### **Boston Public**

Located in the Louis Boston building, this used to be Restaurant L. Chef Pino Maffeo, now an owner, is still at the helm, and the place has been revamped as Boston Public. | Steak House | 234 Berkeley St., Boston MA, (617) 266-4680

### **Bouchee Boston**

The menu at this lively place spans classic brasserie to lighter, updated fish dishes. Open early till late all week long, it's a great addition to Boston's favorite shopping street. | French | 159 Newbury St., Boston MA, (617) 450-4343

### **Ko Prime Nine Zero Hotel**

Ken Oringer's steakhouse does what you'd expect a Ken Oringer steakhouse to do: serve high-quality meat prepared in ways you won't see at Outback. Filet mignon goes to Argentina with a topping of chimichurri; thin slices of skirt steak are edged in North African spices. | Steak House | 90 Tremont St., Boston MA, (617) 772-0202

### **Skipjack's Boston**

The staff is cool. The food is cool, as in "rad." The decor is perfectly upscale "mod." And the chef knows how to cook fish. We've never gone wrong here with the likes of Atlantic salmon and juicy broiled scallops. | Seafood | 199 Clarendon St., Boston MA, (617) 536-3500

### **Mantra Restaurant**

Stunning architecture and a glittery crowd almost overshadow chef Thomas John's French and Indian cuisine. But his subtle and sure way with spices prevails. | American/Indian/French/Fusion/Eclectic | 52 Temple Pl., Boston MA, (617) 542-8111

### **Northend Pomodoro**

The food and personal service far outweigh the decor at this small but inviting spot specializing in creative veal, fresh seafood, and pasta dishes. There's no bar, but during long waits you get sidewalk delivery of the best fried calamari in Boston. | Italian | 319 Hanover St., Boston MA, (617) 367-4348

### **No. 9 Park**

Taking a slightly different approach to the bar menu idea, the cafe at No. 9 Park has an extensive menu of very ambitious dishes, only slightly scaled down in portion size and changing with the season, making it a good way to sample chef-owner Barbara Lynch's cuisine. (Boston Globe) | Mediterranean, French, Italian / Pasta | 9 Park St., Boston MA, (617) 742-9991

### **Pho Thien Thien**

This new Vietnamese restaurant has a gracious owner who learned cooking in her mother's kitchen and later in native restaurants. The fresh vegetables taste as if they've come from a garden out back. | Vietnamese / Southeast Asian | 8 Kneeland St., Boston MA, (617) 357-5536

### **The Capital Grille**

Dry aged steaks have earned high praise from the nation's toughest food critics, and their seafood is flown in daily. Award-winning collection of over 400 wines is an experience in itself. | Steak/Seafood | 359 Newbury Street, Boston, MA 02115, (617) 262-8900

### **Chart House Restaurant**

An incredible landmark location on Boston's Long Wharf. The Chart House is situated in the Gardiner Building - the restored 18th-century offices of American Patriot John Hancock. Combine the extraordinary setting with outstanding cuisine & it's not hard to see why the restaurant is a longtime favorite. | Steak/Seafood | 60 Long Wharf, Boston, MA, 02110, (617) 227-1576

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