Symposium Schedule

• 8:30 Breakfast – Spark Reception Area
  All talks are in Spark G 45

• 9:00 Welcome and Introductory Remarks- Phil Garner, Ph.D. (WSU) and Phil Cox, Ph.D. (AbbVie & WSU)

• 9:10 Vincent S. Stoll, Ph.D., Research Fellow, Associate Director of Structural Biology, R&D, AbbVie Inc.

• 10:00 Michael Michaelides, Ph.D., Senior Research Fellow and Head of Oncology Chemistry, AbbVie

• 10:50 Coffee Break

• 11:10 Russell Thomas, Ph.D., Director of Strategic Alliances, Axxam SpA, Milan, Italy

• 12:00 Lunch – Spark Reception Area

• 1:00 David DeGoey, Ph.D., Research Fellow, Discovery Chemistry and Technology, AbbVie

• 1:50 Coffee Break

• 2:10 Adrian Hobson, Ph.D., Research Fellow, Global Biologics, AbbVie

• 3:00 Paul Leeson, Ph.D., Director, Leeson Consulting and former Head of Medicinal Chemistry at Astra Zeneca, Charnwood, UK.

• 3:50 Donald Matteson, Ph.D., Emeritus Professor, Washington State University

• 4:15 Social – Elson S. Floyd Cultural Center

• 5:15 Dinner – Elson S. Floyd Cultural Center
Principles and Case Studies of Structure-based and Fragment-based Drug Design

Vincent Stoll, Ph.D.
Research Fellow, Associate Director of Structural Biology, R&D, AbbVie Inc

Abstract

This talk will cover some of the basic principles of structure-based drug design, the strengths and limitations of structure. Several case studies will be used to highlight effective use of Structure-based drug design and reinforce the principles described.

Vincent Stoll earned his B.A. from Bard College in 1985 and his Ph.D. in Biochemistry from Albert Einstein College of Medicine in 1990 where he studied with Prof. John Blanchard on the use of multiple kinetic isotope effects studies to determine the chemical mechanism of NADH peroxidase. He initiated his postdoctoral research in protein X-ray crystallography at the Max Planck institute for medical and biophysical research in Heidelberg Germany with Prof. Emil Pai 1990-1992, studying the crystal structures and chemical mechanisms of flavoprotein oxidoreductases. He continued his postdoctoral studies with Prof. Pai at the University of Toronto until joining the Protein X-ray Crystallography group at Abbott/AbbVie in 1997. While at AbbVie he has focused on structure-based drug design on Antiviral, Immunology, Oncology and Neuroscience targets. Vincent is currently an AbbVie Community of Science Research Fellow and Heads AbbVie Structural Biology Group in Discovery Chemistry & Technology. He is an inventor on 7 issued patents and has more than 50 publications.

AbbVie Oncology, Vignettes in Small Molecule Drug Discovery

Michael Michaelides, Ph.D.
Senior Research Fellow and Head of Oncology Chemistry, AbbVie

Abstract

The tremendous advances in our understanding of the basic biology behind oncological diseases over the last 2 decades have led to the successful development of several targeted therapies. These therapies have had a significant impact on improving the lives of cancer patients. Select examples of small molecule discovery programs from Abbvie’s oncology portfolio will be discussed. The focus of the presentation will be on the crucial role that medicinal chemists play in drug discovery.

Michael earned his B.S. degree in chemistry from Stony Brook University and his doctorate in organic chemistry from the Massachusetts Institute of Technology, under the direction of Professor William Roush, in 1988. He joined Abbott immediately after completing his graduate studies.

During his 30-year tenure at Abbott and now Abbvie, Michael has carried out research in the
areas of Neuroscience, Immunoscience and Oncology. He has contributed to the invention and advancement of several clinical candidates, including adrogolide for the treatment of Parkinson’s disease and linifanib for hepatocellular carcinoma. He has over 40 issued or pending patents and 55 published articles to his name. Michael was awarded the Abbott Outstanding Researcher of the Year award in 2010.

Michael is currently Senior Research Fellow, Head of Oncology Chemistry and a member of the Global Abbvie Medicinal Chemistry Leadership Team.

Starting on the Right Foot: Integrating High Quality Chemistry and Biology in Early Drug Discovery

Russell Thomas, Ph.D.
Director of Strategic Alliances, Axxam SpA, Milan, Italy

Abstract

The talk will focus on the key aspects to consider when starting a small molecule drug discovery program. Looking at both peripheral and CNS indications, we'll think about what are the requirements for high quality starting hits and develop a critical evaluation of the benefits and risks of a range of approaches including:

• Using “Privileged structures” or focused sets
• Structure-based drug design
• High throughput screening

Examples will be given for each that highlights the challenges faced and the approaches taken to overcome them.

Russ, from Swansea in Wales, got his Ph.D in synthetic organic chemistry with Stan Roberts at Exeter University. He then spent 8 years at Glaxo in Verona Italy before moving to Evotec in Oxford as a lab head then department head. In 2004 he moved to Siena Biotech first as head of medicinal chemistry then director of portfolio operations and external alliances and finally General Manager. At Siena Russ focused on projects for neurodegeneration and neuro-oncology. He also spent 1 year at Proteros in Munich, Germany as VP of discovery research where he was involved in setting up Rodin Therapeutics in Boston with Atlas Venture. In 2014 Russ moved to Axxam in Milan, Italy and is currently director of strategic alliances, building and managing collaborations with a number of pharma, biotech and academic groups in Europe and North America.

In his spare time he still lives in Siena in Tuscany and looks after his chickens and bee hives.
**ABSTRACTS**

**Discovery of HCV NS5A Inhibitors**

**David DeGoey, Ph.D.**
Research Fellow, Discovery Chemistry and Technology, AbbVie

Abstract

Left untreated, chronic hepatitis C virus (HCV) infection can result in cirrhosis, an increased incidence of hepatocellular carcinoma and ultimately liver failure. In fact, complications due to chronic HCV infection have now become the predominant driver for liver transplantation. As a result of the severity of the disease and its widespread incidence (estimated at 170-200 million worldwide), HCV infection poses a major public health crisis. Once treatable only through lengthy, poorly tolerated and marginally efficacious regimens using pegylated interferon alpha (pegIFN-α) and ribavirin (RBV), HCV infection has now been cured with high rates using IFN-free combinations of direct-acting antivirals (DAA). Today, highly potent HCV NS5A inhibitors, together with HCV NS5B polymerase or HCV NS3 protease inhibitors, form the backbone of the highly efficacious and well-tolerated DAA combination therapies. The discovery of two FDA approved NS5A inhibitors ombitasvir (OMB) and pibrentasvir (PIB) will be described.

David DeGoey is a Research Fellow at AbbVie. He received a B.S. degree in Chemistry from the University of Wisconsin Madison and earned a Ph.D. in Chemistry from Harvard University, working in Professor Yoshito Kishi’s lab. He joined Abbott (now AbbVie) in 1995 where he has spent a large portion of his career in infectious diseases research working on the discovery of drugs to treat fungal, bacterial, and viral diseases, including HIV and hepatitis C. He co-led the medicinal chemistry team that discovered the HCV NS5A inhibitors ombitasvir (marketed as Viekira Pak) and pibrentasvir (marketed as Mavyret).

**Discovery and Development of Immunology Antibody Drug Conjugates (iADC)**

**Adrian Hobson, Ph.D.**
Research Fellow, Global Biologics, AbbVie

Abstract

Antibody Drug Conjugates (ADC) are a rapidly expanding area of pharma company pipelines. They combine the targeting of an antibody with the potency of a small molecule and were pioneered for oncology. There are now 4 marketed oncology antibody drug conjugates (oADC) and approaching 100 in clinical development. This talk will describe the technology behind oADCs and the challenges faced in modifying this technology for use with an immunology antibody drug conjugate (iADC).

Dr. Hobson earned his Ph.D. from the University of Sheffield, United Kingdom under the supervision of Charles Marson and worked for Boots Pharmaceuticals in the UK before transferring to BASF pharma in the US which became Abbott and now AbbVie.
contributed to multiple small molecule programs including sibutramine, upadacitinib, ABBV-155, ABT-459, Rho kinase inhibitors (ROCK), JAK3 and selective S1P5 agonists as a treatment for Alzheimer’s disease. Five years ago he transferred to Global Biologics to drive iADCs and his strategies have enabled the identification of new linkers and novel glucocorticoid receptor modulator payloads, leading to the development of ABBV-3373, under investigation for rheumatoid arthritis. He has set the stage for further discoveries, creating chemoinformatics and ADC registration systems in addition to advancing AbbVie’s conjugation and DAR purification capabilities.

**Discovery of P2Y12 Antagonists for Antithrombotic Therapy**

**Paul Leeson, Ph.D.**

Director, Leeson Consulting, and former Head of Medicinal Chemistry at AstraZeneca, Charnwood, UK

**Abstract**

The platelet P2Y12 receptor is a G-protein coupled receptor which regulates platelet aggregation and is a target for treatment of arterial thrombosis. The agonist for the P2Y12 receptor is adenosine diphosphate, while adenosine triphosphate (ATP) acts as an antagonist, but with very weak affinity (pIC50 3.5) and poor selectivity. Since high throughput screening was not available at the initiation of the project, a programme of chemical modification of ATP itself, a challenging prospect, was initiated. Conversion of the terminal phosphate bond of ATP to a phosphonate improved stability and introduction of hydrophobic 4,6-substituents in the purine ring resulted in Cangrelor, a potent, selective antagonist (pIC50 9.4) suitable for intravenous dosing. Cangrelor provided positive proof of concept studies and became an approved drug in 2015. For orally active compounds, it was essential to remove the triphosphate moiety. Changing the purine ring to a triazolopyrimidine allowed replacement of the triphosphate by carboxylic acids, and ultimately neutral groups, which provided oral bioavailability. Parallel synthesis at the 4,6-positions led to a key potency improvement, and then optimisation of metabolic clearance led to Brilinta (pKi 8.7), which was approved as an oral drug in 2010. Brilinta has superior efficacy in cardiovascular disease in comparison with Clopidogrel, an irreversible covalent modifier of the P2Y12 receptor.

Paul Leeson is a medicinal chemistry consultant with >35 years’ experience in major pharmaceutical companies: Smith Kline and French, Merck Sharp and Dohme, Wyeth (USA), AstraZeneca, and GlaxoSmithKline. Since 2014 he has advised pharmaceutical companies, start-ups, and academia. At AstraZeneca (1997-2011) Paul was head of medicinal chemistry at the Charnwood site and he led AstraZeneca’s Global Chemistry Forum. Paul’s drug discovery contributions have been in the cardiovascular, neuroscience, respiratory and inflammation therapy areas. He has a special interest in compound quality and in 2014 he received the Nauta Award from the European Federation of Medicinal Chemistry. Paul has a PhD from the University of Cambridge and holds an honorary professorship at the University of Nottingham.
Professor Matteson earned a bachelor's degree in chemistry in 1954 from the University of California, Berkeley and a doctorate in organic chemistry in 1957 from the University of Illinois, at Urbana-Champaign, where he did his thesis research with Professor Harold Snyder. Professor Matteson then worked as a research chemist at Du Pont investigating hydrocarbon pyrolysis.

He joined WSU's Department of Chemistry faculty in 1958 and attained the rank of professor in 1969. In 1966, he was the first WSU faculty member to receive an Alfred P. Sloan Foundation Research Fellowship. Throughout Professor Matteson's career, he has lectured extensively throughout Europe, Russia, India, Mexico, Canada, and Asia. He has served on the editorial advisory board of the journals Organometallics and Heteroatom Chemistry.

Although Professor Matteson's research has been broadly based, he is best known for his seminal developments in the fields of boronic ester chemistry and asymmetric synthesis. He has developed reactions that provide precise and general tools for stereoselective and asymmetric syntheses. As an example of the far-reaching impact of his research, Professor Matteson's chemistry is providing the key part of “Velcade,” a new anticancer drug in clinical use for treating multiple myeloma.

He is the author of two books, co-inventor on five patents, and author or co-author of 203 technical articles. In addition, Professor Matteson has served as thesis advisor for 31 doctoral students, supervised six master's students and more than two dozen postdoctoral research associates, and sponsored numerous international visitors.

Professor Matteson and his wife Marianna are generous donors to Washington State University supporting endowed chairs, graduate research assistanceships as well as undergraduate scholarships. He and his wife Marianna live in Pullman and they travel extensively.
Thank you!
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And a special thank you to
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Department of
Chemistry
College of Arts and Sciences
Washington State University