Applied Pharmaceutical Chemistry

WEBINAR

2021

Thursday, June 3

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VERTEX is a global biotechnology company that invests in scientific innovation to create transformative medicines for people with serious and life-threatening diseases.

We discovered and developed the first medicines to treat the underlying cause of cystic fibrosis (CF), a rare, life-threatening genetic disease. In addition to clinical development programs in CF, Vertex has more than a dozen ongoing research programs focused on the underlying mechanisms of other serious diseases.

Founded in 1989 in Cambridge, Massachusetts, our corporate headquarters is now located in Boston's Innovation District, and our international headquarters is in London, United Kingdom. We currently employ approximately 2,500 people in the United States, Europe, Canada, Australia and Latin America with nearly two-thirds of our staff dedicated to research and development.

ORGANIZERS' WELCOME

Welcome to the 2021 Applied Pharmaceutical Chemistry Conference.

Our organizers have gathered another excellent group of speakers for the twelfth annual APC conference. The program is arranged to incorporate extensive audience participation and discussion. We encourage attendees to take full advantage of the opportunity to engage in discussion in order to receive the maximum benefit from the APC experience.

Thank you for your participation.

ORGANIZING COMMITTEE

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Siva Dandapani, Skyhawk Therapeutics
Matt Hayward, Pfizer
David Ebner, Pfizer
Baudouin Gerard, Nuvalent, Inc.
Pedro Garcia Barrantes, Vertex

APC 2021 WEBINAR AGENDA

Thursday, June 3

10:00 - 10:05	**Conference Introduction** Benoit Moreau, Syros
10:05 - 10:10	**Speaker Introduction** David Ebner, Pfizer; Siva Dandapani, Skyhawk Therapeutics and Susan Ashwell, UCB
10:10 - 10:30	**Hit-to-Lead Medicinal Chemistry Targeting Neglected Tropical Diseases** Michael Pollastri, Northeastern University
10:30 - 10:35	Q & A
10:35 - 10:55	**One Atom Makes All the Difference - The Fine Line Between Activation and Inhibition of SOS1** Juergen Ramharter, Boehringer Ingelheim, Austria
10:55 - 11:00	Q & A
11:00 - 11:20	**Discovery of PF-07059013: A Non-covalent HbS Modulator for Treatment of Sickle Cell Disease** David Piotrowski, Pfizer
11:20 - 11:25	Q & A
11:25 - 11:40	**VENDOR PRESENTATION: Interchim** **Tools for Rapid Characterization and Purification in Drug Discovery** Michelle Armstrong, Interchim
11:40 - 11:45	Q & A
11:45 - 12:45	Lunch
12:45 - 12:50	**Plenary Speaker Introduction** Matt Hayward, Pfizer
12:50 - 1:25	**PLENARY: Targeted Protein Degradation – Challenges and Opportunities** Nathanael Gray, Stanford
1:25 - 1:35	Q & A

1:35 - 1:40	**Speaker Introduction** Louis Chupak, BMS and Baudouin Gerard, Nuvalent, Inc.
1:40 - 2:00	**The Discovery of Milvexian (BMS-986177/JNJ-70033093): An Inhibitor of Factor XIa in Phase 2 Studies for Antithrombotic Therapy** James Corte, BMS
2:00 - 2:05	Q & A
2:05 - 2:25	**Discovery of Selective, Targeted Covalent FGFR4 Inhibitor** Haibo Liu, BMS
2:25 - 2:30	Q & A
2:30 - 2:50	BREAK
2:50 - 3:10	**Discovery of BIIB091, a Reversible, Selective BTK Inhibitor for the Treatment of Multiple Sclerosis** Brian Hopkins, Biogen
3:10 - 3:15	Q & A
3:15 - 3:20	**Speaker Introduction** Pedro Garcia Barrantes, Vertex
3:20 - 3:40	**From Broad Repurposing Hub Hit to a Drug Development Candidate for a Rare Chronic Kidney Disease** Florence Wagner, Broad Institute
3:40 - 3:45	Q & A
3:45 - 3:50	**Closing Remarks** Baudouin Gerard, Nuvalent

ABSTRACTS

Hit-to-lead Medicinal Chemistry Targeting Neglected Tropical Diseases

Michael P. Pollastri, Northeastern University

Current therapies for neglected tropical diseases (NTDs) are often poorly effective and highly toxic. Though over a billion people suffer from one or more of these diseases worldwide, disproportionately little drug discovery research is performed in the industrial sector to target them; this is mainly due to the lack of profitability inherent in the process of discovering new drugs for treating these diseases of poverty. In the interest of streamlining the drug discovery process, we have been applying methods for repurposing classes of established inhibitors of human enzymes and pathways as starting points for inhibitor discovery for the pathogens that cause NTDs. Specifically, we have used multiple approaches to identify promising human kinase inhibitor chemotypes that can be effectively and efficiently redirected towards new antiparasitic leads. Our Lead Repurposing efforts will be described, highlighting progress made in several kinase inhibitor chemotypes to identify potent, non-toxic, in vivo efficacious lead compounds. These advancements have been catalyzed by close collaboration with GlaxoSmithKline, AstraZeneca, and the Walter Reed Army Institute for Research. Progress towards identifying high-quality lead compounds for African sleeping sickness, Chagas disease, leishmaniases, and malaria will be reported, with a focus on optimization of physicochemical and ADME properties.

One Atom Makes All the Difference - The Fine Line between Activation and Inhibition of SOS1

Juergen Ramharter, Boehringer Ingelheim, Austria

With the emergence of KRAS G12C selective approaches, the high unmet medical need for therapies addressing other KRAS oncoproteins is increasingly coming into focus. One promising option is targeting the protein protein interaction (PPI) of KRAS with its guanine nucleotide exchange factor SOS1. Positioning of a comparably small substituent between a key amino acid pair formed by KRAS and SOS1 allows for potent and selective PPI inhibition. Variation of this substituent led to the surprising observation that a single atom determines whether our compounds activate or inhibit SOS1. These findings challenge the dogma that large molecules are required to disrupt challenging PPIs. Instead, a "foot in the door" approach, whereby single atoms or small functional groups placed between key PPI interactions, can lead to potent inhibitors even for challenging PPIs such as SOS1-KRAS.

Discovery of PF-07059013: A Non-covalent HbS Modulator for Treatment of Sickle Cell Disease

David Piotrowski, Pfizer

Sickle cell disease (SCD) is a genetic disorder caused by a single point mutation (β6 Glu→Val) on the β-chain of adult hemoglobin (HbA) that results in sickled hemoglobin (HbS). In the deoxygenated state, polymerization of HbS leads to sickling of red blood cells (RBC). Several downstream consequences of polymerization and RBC sickling include vaso-occlusion, hemolytic anemia, and stroke. The design of a non-covalent modulator of HbS, clinical candidate PF-07059013, will be described. The seminal hit molecule was discovered by virtual screening and confirmed through a series of biochemical and biophysical studies. After a significant optimization effort, we arrived at PF-07059013, a compound that specifically binds to Hb with nanomolar affinity and displays strong partitioning into RBCs. In a 2-week multiple dose study using Townes SCD mice, PF-07059013 showed a 37.8% reduction in sickling compared to vehicle treated mice. PF-07059013 has advanced to Phase 1 clinical trials.

VENDOR PRESENTATION

Tools for Rapid Characterization and Purification in Drug Discovery

Michelle Armstrong, Interchim

Flow chemistry and reaction monitoring are two techniques which benefit from the use of mass spectrometry (MS). Several rapid MS techniques are used to improve the flow chemistry and reaction monitoring workflow. In addition to the rapid techniques, the MS can also be used with a TLC plate reader and

mass triggered purification.

PLENARY TALK

Targeted Protein Degradation – Challenges and Opportunities

Nathanael Gray, Stanford

Targeted protein degradation (TPD) refers to the use of small molecules to induce ubiquitin-dependent degradation of proteins. These degrader molecules are of great interest in drug development as they can address previously inaccessible targets. However, degrader discovery and optimization remains an inefficient and empirical process due to a lack of understanding of the key molecular events required to successfully induce target degradation. In this seminar I will discuss the use chemo-proteomics to annotate the 'degradable kinome'. This work will not only fuel kinase degrader discovery, but also provides a blueprint for evaluating targeted degradation across entire gene families, to accelerate understanding of TPD beyond the kinome.

The Discovery of Milvexian (BMS-986177/JNJ-70033093): An Inhibitor of Factor XIa in Phase 2 Studies for Antithrombotic Therapys

James Corte, Bristol Myers Squibb

Thrombosis is the formation of a blood clot in the vasculature and is the common pathology of ischemic heart disease and ischemic stroke, which accounted for 11.7 million deaths worldwide in 2017. While oral anticoagulants exist to treat and prevent thrombosis such as the vitamin K antagonist warfarin, a thrombin inhibitor, and Factor Xa (FXa) inhibitors, each of these therapies has limitations. Warfarin requires dose titration to maintain target levels within a narrow therapeutic window. Thrombin and FXa inhibitors have improved bleeding risk profiles compared to warfarin, however, still carry a risk of bleeding and require reversal agent administration in emergency (or urgent) surgical situations.

Inhibition of Factor XIa (FXIa) has the potential to reduce thromboembolic events with a minimal increase in bleeding risk. Preclinically, small molecule, direct inhibitors of FXIa have demonstrated robust antithrombotic efficacy while maintaining hemostasis. Recently, clinical validation for the mechanism was provided by studies of a FXI antisense oligonucleotide (ASO) and a FXIa-targeting IgG1 antibody in knee arthroplasty. Both were well tolerated and significantly reduced the incidence of venous thrombosis post-operatively.

This presentation describes the optimization of the physical properties of our previously described macrocyclic FXIa inhibitors. These modifications led to the discovery of milvexian (BMS-986177/JNJ-70033093), a potent and orally bioavailable FXIa inhibitor, which inhibited thrombus formation in our preclinical animal models of thrombosis with no effects on bleeding. Several Phase I clinical studies have been completed, in which milvexian was well-tolerated. Currently, two Phase II studies in total knee replacement and in secondary stroke prevention are ongoing to investigate the safety and efficacy of milvexian for the prevention of thromboembolic events.

Acknowledgments: The authors wish to acknowledge the contributions of Indawati De Lucca, Qian Xiang, Zhen Lou, Joanna J. Zheng, and James K. Hennan as former employees of Bristol Myers Squibb.

Discovery of Selective, Targeted Covalent FGFR4 Inhibitors

Haibo Liu, Bristol Myers Squibb

Hepatocellular carcinoma (HCC) accounts for 85-90% of primary liver cancer and is one of the most common forms of cancer and cancer-related mortality worldwide. Aberrant signaling of the FGF19-FGFR4 pathway has been shown to cause HCC in mice and is hypothesized to be a driver in FGF19 amplified HCC in humans. Multiple small molecule inhibitors have been pursued as targeted therapies for HCC in recent years including four selective FGFR4 inhibitors that are currently being evaluated in clinical trials. We discovered a novel series of highly selective, covalent 2-amino-6, 8-dimethyl-pyrido[2,3-d]pyrimidin-7(8H)-one that potently and selectively inhibits FGFR4 signaling through covalent modification of Cys552 which was confirmed by X-ray crystallography. Correlative PK/PD and tumor regression was observed in preclinical models of orthotopic and sorafenib-resistant HCC.

Discover of BIIB091, A Reversible, Selective BTK Inhibitor for the Treatment of Multiple Sclerosis

Brian Hopkins, Biogen

BIIB091 is a structurally distinct orthosteric ATP competitive, reversible inhibitor that binds the BTK protein in a DFG-in confirmation. Biogen's proprietary chemical matter was designed to access the unique "H3" pocket, necessary to obtain exquisite kinome selectivity and translated to improved safety/tolerability in preclinical chronic toxicological studies. In addition, binding in the "H3" pocket enabled BIIB091 to sequester Tyr-551, an important phosphorylation site on BTK, into an inactive conformation with excellent affinity in whole blood assay under both stimulated and unstimulated conditions. This presentation will provide an overview of the lead optimization process focusing on strategies for improving drug-like-properties and whole-blood potency, which is necessary for delivering a best-in-class reversible BTK inhibitor into the clinic for the treatment of non-oncology indications.

From Broad Repurposing Hub Hit to a Drug Development Candidate for a Rare Chronic Kidney Disease

Florence Wagner, Broad Institute

AGN192403 (rac-3-exo-isopropylbicyclo[2.2.1]heptan-2-endo-amine), also known as BRD4780, has been shown to selectively clear frameshift Mucin 1 (MUC1), a protein that results in MUC1 Kidney Disease (MKD), in vitro and in vivo. We will retrace the discovery of BRD4780 and our strategy towards developing a development candidate to treat MKD.

BIOGRAPHIES

Michelle Armstrong, PhD, Interchim: Dr. Armstrong is local in the Boston area and has been working with Interchim Inc for the past 12 years. She has been supporting the biotech community and universities with solutions in purification. She has also been supporting Pharma with the Advion MS with the puriFlash systems for the past 8 years. You can usually find her around Cambridge having coffee and updating Scientists on the latest technologies in purification.

James R. Corte, PhD, Bristol Myers Squibb: Dr. Corte received his B.S. degree in Chemistry from Eckerd College and his Ph.D. degree in Organic Chemistry from Stanford University under the direction of Professor Barry M. Trost. Jim joined the Medicinal Chemistry Department at Bristol Myers Squibb in 1999 and is currently a Scientific Associate Director. During his career, Jim has worked on multiple medicinal chemistry programs in osteoporosis, cardiovascular and fibrosis disease therapeutic areas encompassing diverse targets (nuclear hormone receptors, serine proteases, GPCRs and kinases). He has authored and co-authored over 50 scientific publications and patents. Jim is a co-inventor of two Factor XIa clinical candidates, Milvexian (BMS-986177, Phase 2) and BMS-986209 (Phase 1), and a PET imaging agent for the assessment of LPA1 receptors in idiopathic pulmonary fibrosis (18F-BMS-986327, Phase1).

Nathanael Gray, PhD, Stanford: Nathanael Gray is a Professor of Chemical and Systems Biology at Stanford, Co-Director of Cancer Drug Discovery, Co-Leader of the Cancer Therapeutics Research Program, Member of Chem-H, and Program Leader for Small Molecule Drug Discovery for the Innovative Medicines Accelerator (IMA). His research uses the tools of synthetic chemistry, protein biochemistry, and cancer biology to discover and validate new strategies for addressing anti-cancer targets. Dr. Gray's research has had broad impact in the areas of kinase inhibitor and degrader design and in circumventing drug resistance. Dr. Gray's generalized strategy for structure-based design of inhibitors that stabilize the inactive kinase conformations (type II) has been widely adopted by the research community and has had a significant impact on the development of numerous inhibitors of tyrosine kinases that are currently undergoing clinical development.

Brian Hopkins, PhD, Biogen: Dr. Hopkins is Principal Investigator and group leader at Biogen in the department of medicinal chemistry. For the past four years, he has been the Research and Development Program Leader responsible for the clinical development of BIIB091 for the treatment of multiple sclerosis. He obtained his Ph.D. from SUNY at Buffalo in 2000 with Professor Wayne Anderson, the Dean of the pharmacy school, and completed his post Doctoral studies with Professor Tony Barrett at Imperial College London. In 2002, Dr Hopkins joined Infinity Pharmaceuticals, and he was the chemistry team leader responsible for overseeing the Novartis collaboration for the BCL-2 program. Since joining Biogen in 2007, his research interests have focused on developing small molecule drug candidates to treat various diseases in immunology, neuro-inflammation, and neuro-degeneration.

Haibo Liu, PhD, BMS: Dr. Liu is a Senior Principal Scientist at Bristol Myers Squibb in Cambridge, MA. As a medicinal chemist and project team leader, his research experience includes targeted covalent drug discovery, allosteric protein inhibitors, molecular glue degraders, phenotypic and fragment-based screening, structure based drug design and lead candidate optimization. Haibo has worked on target classes that include kinases, phosphatases, RNases, and nuclear hormone receptors, with applications in oncology, immuno-oncology, immunology and inflammation, fibrosis and cell therapy . Dr. Liu received

his B.S. in Chemistry from Peking University and his Ph.D. in Organic Chemistry from Stanford University with Professor Eric Kool. He did his postdoctoral research at Memorial Sloan-Kettering Cancer Center with Professor Samuel Danishefsky, after which he worked on Diversity-Oriented Synthesis in the Chemical Biology Platform at the Broad Institute. In 2011, Haibo moved to Avila Therapeutics and in 2012 joined Celgene, which became BMS in 2019.

David W. Piotrowski, PhD, Pfizer: Dr. Piotrowski obtained his Ph. D. from University of Wisconsin-Madison (Prof. Vedejs). At Pfizer for > 20 years, with primary focus on discovery of drugs for treatment of cardiovascular, metabolic and rare diseases. Currently, a Research Fellow in the medicinal chemistry group conducting small molecule research aimed at rare disease targets.

Michael Pollastri, PhD, Northeastern University: Dr. Michael Pollastri is serving as the Senior Vice Provost for Portland, where he leads the academic and research portfolio at the Roux Institute. Mike worked at Pfizer in hit-to-lead and lead optimization medicinal chemistry for nearly ten years. In 2007 he accepted a research faculty position in the Boston University Department of Chemistry, where he led the establishment of the Center for Molecular Discovery, a collaborative University resource that encompassed a combination of high-throughput screening and medicinal chemistry optimization capabilities. In 2009, he joined the faculty in the Department of Chemistry and Chemical Biology at Northeastern University, where he was appointed department chair in 2015 and rose to the rank of full professor in 2017. He was appointed Interim Dean of the College of Science in March 2019, and assumed the role of Senior Vice Provost for Portland at the Roux Institute at Northeastern University in June 2020. His research is focused on discovery of new therapeutics for neglected tropical diseases. Dr. Pollastri earned his bachelor's degree from the College of the Holy Cross, a master's degree from Duke University, and his doctorate from a graduate program he developed in partnership between Pfizer and the Brown University Department of Chemistry.

Juergen Ramharter, PhD, Boehringer Ingelheim: Juergen Ramharter was born and raised in Austria. He is an organic chemist by training, with a strong background in natural product synthesis. Juergen joined Boehringer Ingelheim in 2012 and is currently Principal Scientist and Project Lead with focus on SOS1 and other KRAS related projects. As a team, Juergen and his colleagues believe they can crack the most common oncogenic driver in human cancers by developing new strategies to target KRAS mutated cancers.

Florence Wagner, PhD, Broad Institute: Florence Wagner is director of medicinal chemistry in the Stanley Center for Psychiatric Research and the Center for the Development of Therapeutics (CDoT) at Broad Institute, where she is also an institute scientist. At the Stanley Center, her group focuses on designing and implementing strategies for the development of novel therapeutics for psychiatric disorders, and, at CDoT, on novel strategies to treat inflammatory and metabolic disorders. These strategies include the rational design and development of novel, potent, and highly selective small molecules suitable for drug and biomarker development. Wagner's projects span targets from epigenetic modulators and kinases to G-protein coupled receptors and ion channels. Her group's recent accomplishments include the design of a toolkit of differentially selective histone deacetylase (HDAC) inhibitors to explore the functional activity of individual isoforms and the discovery of first-in-class paralog selective inhibitors of glycogen synthase kinase 3 (GSK3). Wagner and collaborators discovered novel applications for these compounds as potential therapeutics for various diseases of unmet medical need. In addition, Wagner leads a number of academic and industrial collaborations focused on extending their therapeutic potential to new disease indications.

Wagner obtained her master's degree from the Department of Chemistry and Process Engineering at the Lyon (France) School of Chemistry and Electronics. Her keen interest in drug discovery developed out of a yearlong internship at Scynexis, a biotech company in North Carolina. From there, she went on to North Carolina State University, where her doctoral research under the supervision of Daniel L. Comins focused on developing novel methods for the synthesis of nicotine derivatives for application in neurodegenerative disorders. Prior to joining the Stanley Center, Wagner worked for Altiris (formerly Metastatix, Inc.) in Atlanta, GA, on the discovery of chemokine receptor modulators. She joined the Broad Institute in 2008.

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