Applied Pharmaceutical Chemistry

WEBINAR

2020

Tuesday, October 6

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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.

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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 2020 Applied Pharmaceutical Chemistry Conference.

Our organizers have gathered another excellent group of speakers for the eleventh 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

Presiding Officers

Conference Chair: Simon Giroux, Vertex

Conference Chair Elect: Benoit Moreau, Syros Pharmaceuticals

Committee Members

Susan Ashwell, UCB
Louis Chupak, Bristol-Myers Squibb
Siva Dandapani, Skyhawk Therapeutics
Matt Hayward, Pfizer
Catherine Jorand Lebrun, EMD Serono
Jingqiang Wei, Silicon Therapeutics

APC 2020 WEBINAR AGENDA

Tuesday, October 6

10:00 - 10:05	**Conference Introduction** Simon Giroux, Vertex
10:05 - 10:10	**Speaker Introduction** Susan Ashwell, UCB & Siva Dandapani, Skyhawk Therapeutics
10:10 - 10:30	**Discovery of Orally Active Inhibitors of BRM ATPase Activity for the Treatment of BRG1-Mutant Cancers** Julien Papillon, Novartis
10:30 - 10:35	Q & A
10:35 - 10:55	**Artificial Intelligence in Drug Discovery – Revolution, Evolution, or Complete Nonsense** Pat Walters, Relay Therapeutics
10:55 - 11:00	Q & A
11:00 - 11:20	**Structure-Based Design of Novel Inhibitors of the MCL-1's Protein-Protein Interaction** Xin Huang, Amgen
11:20 - 11:25	Q & A
11:25 - 11:45	**VENDOR PRESENTATION: Advion Interchim** **Simplifying The Flash Purification Process: A Guide to Leveraging Thin Layer Chromatography and Mass Spectrometry** Daniel Eikel, Advion
11:45 - 11:50	Q & A
11:50 - 12:50	Lunch
12:50 - 12:55	**Plenary Speaker Introduction** Matt Hayward, Pfizer
12:55 - 1:30	**PLENARY: Translating RNA Sequence into Lead Small Molecule Medicines** Matt Disney, The Scripps Research Institute
1:30 - 1:40	Q & A

1:40 - 1:45	**Speaker Introduction** Benoit Moreau, Syros
1:45 - 2:05	**Discovery of the Selective, Covalent CDK7 Inhibitor SY-1365** Jason Marineau, Syros Pharmaceuticals
2:05 - 2:10	Q & A
2:10 - 2:30	**Discovery of Brain-Penetrant ASK1 Inhibitors for the Treatment of Neurological Diseases** Felix Gonzalez Lopez de Turiso, Biogen
2:30 - 2:35	Q & A
2:35 - 2:55	**Discovery of an IRAK4 Clinical Candidate by Fragment-Based Drug Design** Katherine Lee, Pfizer
2:55 - 3:00	Q & A
3:00 - 3:20	BREAK
3:20 - 3:40	**Discovering Drug Leads by Practical NMR Fragment Screening Strategies** Steven R. LaPlante, University Quebec/NMX Research and Solutions
3:40 - 3:45	Q & A
3:45 - 3:50	**Speaker Introduction** Louis Chupak, BMS
3:50 - 4:10	**Tapping into Plants' Natural Chemical Arsenals without Taxing Nature** Jing-Ke Weng, Whitehead Institute for Biomedical Research/MIT
4:10 - 4:15	Q & A
4:15 - 4:35	**Discovery of a Candidate Quality BET Inhibitor through Synergistic Use of DNA Encoded Library Technology and Fragment Screening** Gang Yao, GSK
4:35 - 4:40	Q & A
4:40 - 4:45	**Closing Remarks** Benoit Moreau, Syros

ABSTRACTS

Discovery of Orally Active Inhibitors of BRM ATPase Activity for the Treatment of BRG1-Mutant Cancers

Julien Papillon, Novartis

SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin subfamily A member 2 (SMARCA2), also known as Brahma homologue (BRM), is a Snf2-family DNA-dependent ATPase. BRM and its close homologue Brahma-related gene 1 (BRG1), also known as SMARCA4, are mutually exclusive ATPases of the large ATP-dependent SWI/SNF chromatin-remodeling complexes involved in transcriptional regulation of gene expression. No small molecules have been reported that modulate SWI/SNF chromatin-remodeling activity via inhibition of its ATPase activity, an important goal given the well-established dependence of BRG1-deficient cancers on BRM. This lecture describes allosteric dual BRM and BRG1 inhibitors that downregulate BRM-dependent gene expression and show anti-proliferative activity in a BRG1- mutant-lung-tumor xenograft model upon oral administration. These compounds represent useful tools for understanding the functions of BRM in BRG1-loss-of-function settings and should enable probing the role of SWI/SNF functions more broadly in different cancer contexts and those of other diseases.

Artificial Intelligence in Drug Discovery – Revolution, Evolution, or Complete Nonsenses

Pat Walters, Relay Therapeutics

Many have claimed that Artificial Intelligence (AI) will bring about a revolution in drug discovery and development, while others have argued that we are reaching the zenith of a hype cycle that will lead to a period of disillusionment. As is often the case, the truth lies somewhere between these extremes. This presentation will focus on areas where AI is having a real impact on drug discovery and highlight factors that are necessary to increase its utility.

Structure-Based Design of Novel Inhibitors of the MCL-1's Protein-Protein Interaction

Xin Huang, Amgen

Mcl-1, a member of the Bcl-2 family, inhibits pro-death components of the intrinsic apoptosis pathway and thus is a key survival factor in multiple myeloma and other malignancies. Although compelling, targeting disruption of Mcl-1's protein–protein interaction to induce tumor cell death was previously thought to be "un-druggable" due to the high affinities of Mcl-1 to the pro-apoptotic Bcl-2 proteins and lack of a small molecule binding pocket. We report here our structure-based drug design of novel inhibitors of the Mcl-1 that led to AMG 176, a potent, selective, and bioavailable Mcl1 inhibitor in clinical development.

VENDOR PRESENTATION

Simplifying the Flash Purification Process: A Guide to Leveraging Thin Layer Chromatography and Mass Spectrometry

Daniel Eikel, Advion

The compound synthesis, purification and confirmation processes often present challenges. From ensuring successful synthesis of your product, setting up a flash purification method, and finally confirming ID of fractions, the lengthy work flow can be time consuming and repetitive.

This presentation will provide a foundation for flash purification processes, and will showcase a novel new work flow concept that breaks down the process in to easy steps for optimal success. We will offer tips to optimize each essential segment of the workflow, and share seamless steps to quickly and easily drive the process from reaction monitoring to flash purification and fraction ID.

PLENARY TALK

Translating RNA Sequence into Lead Small Molecule Medicines

Matthew D. Disney, The Scripps Research Institute

About 80% of our genome is transcribed into RNA and only about 2% is translated into protein. Yet, drug discovery focuses almost exclusively on targeting protein. A major challenge in Medical Science has been exploiting new targets for drug development. Our programmatic focus over the past 15 years has been on developing technologies to decipher which cellular RNAs are "druggable" targets for small molecules and which small molecules can target them. Here, we will describe advances in the area of Small Molecules Interacting with RNA (SMIRNAs), including a sequence-based small molecule rational design tool dubbed Inforna. It has enabled the design of SMIRNAs against RNAs that cause hard to treat cancers and incurable genetically defined diseases that have no known treatment by scanning for druggable pockets across human RNA sequence. We will describe these compounds and their implications advancing lead medicines and also as chemical probes to understand previously unknown RNA biology. We will also describe the development of approaches that allow for targeted degradation of RNAs in cells and animals by using SMIRNAs. For example, we can recruit endogenous cellular nucleases to cleave RNAs selectively and sub-stoichiometrically in cells and animals. There is great opportunity to capture the decades of discovery of RNA biology to deliver small molecule chemical probes and lead medicines targeting RNA. Although RNA has been thought to not be broadly targetable with organic ligands, these advances suggest that this needs reassessment and as such we believe the future for SMIRNAs to deliver precision medicines is bright.

Discovery of the Selective, Covalent CDK7 Inhibitor SY-1365

Jason Marineau, Syros Pharmaceuticals

CDK7 is the catalytic subunit of the CDK-activating kinase (CAK) complex and the transcription factor TFIIH. In these roles, it regulates both the cell cycle and transcriptional control of gene expression. This functional duality makes CDK7 an attractive oncology target, particularly in cancers which are dependent on high and constant expression of certain transcription factors or have alterations in the cell cycle pathway. Our medicinal chemistry efforts began from the published tool compound THZ1. Optimization of the potency, selectivity and pharmacokinetic profile provided covalent CDK7 inhibitors capable of sustained target inhibition in vivo and significant tumor growth inhibition in xenograft models. This led to the identification of SY-1365 , the first selective CDK7 inhibitor to enter clinical trials (NCT03134638).

Discovery of Brain-Penetrant ASK1 Inhibitors for the Treatment of Neurological Diseases

Felix Gonzalez Lopez de Turiso, Biogen

ASK1 is one of the key mediators of the cellular stress response and modulation of this pathway with the ATP-competitive inhibitor Selonsertib is being tested in the clinic for the treatment of liver fibrosis. To test the therapeutic value of inhibiting ASK1 in neurological disease we have identified novel ASK1 brain-penetrant inhibitors using a structure-based drug design approach. The results from this effort will be presented.

Discovery of an IRAK4 Clinical Candidate by Fragment-Based Drug Design

Katherine Lee, Pfizer

Interleukin-1 Receptor Associated Kinase 4 (IRAK4), a serine/threonine kinase first reported in 2002, is a proximal kinase in the IL-1 receptor and toll-like receptor pathways and is recognized as an important node in innate immunity. Inhibition of IRAK4 is predicted to be beneficial in the treatment of a number of inflammatory diseases; this has led to intense effort across the pharmaceutical industry to identify potent and selective inhibitors of IRAK4.

Pfizer's IRAK4 clinical candidate PF-06650833 arose from hits from an NMR-based fragment screen of the Pfizer Global Fragment library versus IRAK4. Lead optimization of weakly active fragment hits, by applying structure- and property-based medicinal chemistry design strategies, led to a significant increase in IRAK4 potency and the discovery of an exquisitely potent, efficient series of IRAK4 inhibitors with excellent kinome selectivity and good pharmacokinetic properties. This work culminated in the discovery of PF-06650833 as a first-in-class IRAK4 inhibitor for the treatment of inflammatory disease.

Tapping into Plants' Natural Chemical Arsenals without Taxing Nature

Jing-Ke Weng, Whitehead Institute for Biomedical Research, MIT

Plants produce a repository of functionally diverse chemicals as a means to adapt to challenging environments. Many plant-derived specialized metabolites also possess unique pharmacological properties that directly impact human health. Research in my laboratory focuses on understanding how various classes of plant specialized metabolites are biosynthesized in plants, and how certain plant specialized metabolites interact with the proteome of other organisms, such as humans and microbial pathogens. Furthermore, we actively investigate well-documented medicinal plants in traditional medicines around the world, and seek to identify bioactive molecules that are responsible for the observed bioactivities. Many plant natural products have turned out to serve as valuable chemical probes to query human disease mechanisms as well as lead compounds for new pharmaceutical development. We employ a synthetic biology to produce medicinal plant natural products and their new-to-nature analogs, therefore circumventing the need of consuming valuable natural plant resources.

BIOGRAPHIES

Matthew Disney, PhD, Scripps Research: Dr. Disney is a Professor in the Chemistry Department at Scripps Research with laboratories on the Florida campus. He is also the founder of Expansion Therapeutics, a biotechnology company devoted to delivering medicines to patients affected by repeat expansion disorders such as Huntington's Disease, ALS, and Muscular Dystrophy. Matt is a native of Baltimore, his early schooling was in the Baltimore Catholic School system, and he earned his B.S. in Chemistry from the University of Maryland and his PhD in Physical Chemistry from the University of Rochester. As a graduate student, he worked with Doug Turner, Michael Zuker, and Dave Mathews to develop experimental and computational approaches to decipher the RNA structures that form in cells. Matt's research program since 2005 has been centrally focused on developing potent and selective small molecules that target folded RNA structures across indications. His and his research group's efforts have garnered several awards. These include: the NIH Director's Pioneer Award, the Tetrahedron Young Investigator Award, the Beverly and Raymond Sackler International Prize in the Physical Sciences, the Eli Lilly Award in Chemical Biology and the Robertson Award in Medicinal Chemistry from the American Chemical Society, amongst several others.

Daniel Eikel, PhD, Advion: Dr. Eikel holds a Master's Degree in Chemistry from the University of Marburg and a PhD in Analytical Chemistry and Toxicology from the University of Hanover, both in Germany. Prior to joining Advion 13 years ago, Dr. Eikel was a visiting fellow at the National Institutes of Health in Bethesda, Maryland. At Advion, he has worked on projects in R&D, application development and product management and he is currently the Director of Customer Service and Product Application.

Felix Gonzalez, PhD, Biogen: Dr. Gonzalez has been a team leader in the medicinal chemistry department at Biogen for the past 4 years where his group has been involved in the discovery of new therapies for the treatment of neurological disease. Prior to his role at Biogen, Felix worked at Amgen for 10 years where he held positions of increased responsibility and was ultimately promoted to the role of principal scientist and team leader. During his research career, Felix has led and worked in teams that have delivered six clinical candidates within three different therapeutic areas and he is a co-author in 18 publications, and a co-inventor in 17 patent applications. Felix did his postdoctoral studies with Dennis Curran working in the development of novel radical chemistry methodology and he holds a Ph.D. in chemistry from the University of Nottingham (UK) where he synthesized the furanocembrane bis-deoxylophotoxin in the group of Gerry Pattenden.

Xin Huang, PhD, Amgen: Dr. Huang is Senior Director of Structural Biology at IFM discovering and developing developing small molecule drugs that precisely target the innate immune system for inflammatory disorders and cancer. Formerly, he was Scientific Director and Head of Structural Biology at Amgen working on structure based drug discovery and development for various therapeutic areas such as oncology, inflammation, neuroscience, and metabolic disorders. Dr. Huang joined Kinetix Pharmaceutical in July 2000 and Amgen in December 2012 as a result of Amgen's acquisition of Kinetix. Prior to pharmaceutical/biotech industry, Dr. Huang was a postdoc with Prof. Michael Eck at Dana Farber Cancer Institute and Harvard Medical School. Dr. Huang holds a Ph.D. in Chemistry from Columbia University.

Steven LaPlante, University Quebec/NMX Research and Solutions: Steven LaPlante is a biophysical chemist who worked 23 years in the pharmaceutical industry (Boehringer Ingelheim) in Laval, Quebec where he helped identify drug candidates

to treat individuals infected with hepatitis C and HIV. In 2014, he founded the contract research company NMX Research and Solutions Inc. which discovers leads for many drug discovery programs. He is also a professor at the University of Quebec (INRS), visiting professor at Institut Pasteur and the Broad Institute of Harvard and MIT, consultant and member of the scientific advisory board the NMR Core of Harvard Medical School.

Katherine L. Lee, PhD, Pfizer: Dr. Lee obtained her B.S., summa cum laude, with Distinction in Chemistry from Yale University and her Ph.D. in Organic Chemistry from MIT with Professor Rick Danheiser. Katherine then did postdoctoral studies at the University of Texas at Austin with Professor Stephen Martin before joining Mitotix, Inc. (now Agennix) as a medicinal chemist. Katherine moved to Wyeth Research (now Pfizer) in 2000 and in 2009 joined Pfizer. Katherine is an expert in medicinal chemistry, with research interests including fragment-based drug design, structure-based drug design, and optimization of ADME and safety properties. Katherine is a co-inventor of several clinical compounds, including a first-in-class IRAK4 inhibitor in Phase 2 and two cPLA2α inhibitors that achieved Phase 2 Proof of Concept. In 2019, Katherine joined Pfizer's Inflammation and Immunology Research Unit as Senior Director and Head of Project Planning and Operations.

Katherine was the 2015 Chair of the Northeastern Section of the American Chemical Society (NESACS) and the 2018 Chair of the ACS Division of Organic Chemistry (ORGN). In 2019, she joined the ACS Board of Directors as the District I Director.

Jason Marineau, PhD, Syros Pharmaceuticals: Dr. Marineau is an Associate Director of Medicinal Chemistry at Syros Pharmaceuticals, Inc. Prior to joining Syros as one of the first employees, he completed a postdoctoral fellowship in the laboratory of Dr. James Bradner at Dana Farber Cancer Institute. Dr. Marineau received his BS in chemistry from Worcester Polytechnic Institute and Ph.D. in chemistry in the laboratory of Dr. Marc Snapper at Boston College.

Julien Papillon, PhD, Novartis: Dr. Papillon is a Senior Principal Scientist at the Novartis Institutes for Biomedical Research in Cambridge, MA, where he has been conducting research since 2004. As a medicinal chemist and project team leader, he has been designing and advancing small molecule modulators of numerous target classes, such as oxidases, lipases, kinases, phosphatases, methyl transferases, ATPases and ion channels for cardiovascular, oncology and ophthalmology indications. Prior to Novartis, he was a post-doctoral fellow at Stanford University in the group of Professor Barry Trost where he completed the total syntheses of amphidinolide P and fostriecin. Dr. Papillon obtained his Ph.D. from the University Of York, United Kingdom.

Pat Walters, PhD, Relay Therapeutics: Dr. Walters heads the Computation & Informatics group at Relay Therapeutics in Cambridge, MA. His group focuses on novel applications of computational methods that integrate computer simulations and experimental data to provide insights that drive drug discovery programs. Pat is coauthor of the book "Deep Learning for the Life Sciences", published by O'Reilly and Associates. His work in AI began with expert systems in the late 1980s, moved to machine learning in the 1990s, and has continued through 25 years in the pharmaceutical industry. Prior to joining Relay, Pat spent more than 20 years at Vertex Pharmaceuticals where he was Global Head of Modeling & Informatics. He is a member of the editorial advisory board for the Journal of Medicinal Chemistry, and has been a guest editor for multiple scientific journals. Pat received 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. Pat received his B.S. in Chemistry from the University of California, Santa Barbara.

Jing-Ke Weng, PhD, MIT: Dr. Weng received his B.S. (2003) in Biotechnology from Zhejiang University, China. He received his Ph.D. (2009) in Biochemistry from Purdue University, and was a pioneer postdoctoral fellow at the Salk Institute for Biological Studies and Howard Hughs Medical Institute between 2009 and 2013. Currently he is a member of the Whitehead Institute for Biomedical Research, and an Associate Professor of Biology at Massachusetts Institute of Technology.

Dr. Weng's research focuses on understanding the origin and evolution of plant specialized metabolism at enzyme, pathway, and systems levels, as well as how plants exploit discrete small molecules to interact with their surrounding biotic and abiotic environments. In addition, he utilizes plant as a unique model system to study human diseases, including metabolic syndromes and protein-misfolding diseases. He is also interested in elucidating the molecular mechanisms underlying the "matrix effect" known from many traditional herbal remedies used for thousands of years.

Dr. Weng has won numerous awards in his career, including Beckman Young Investigator Award (2016), Alfred P. Sloan Research Fellow (2016), Searle Scholar (2015), Pew Scholar in the Biomedical Sciences (2014), American Society of Plant Biologists Early Career Award (2014), and Tansley Medal for Excellence in Plant Science (2013).

Gang Yao, PhD, GSK: Dr. Gang Yao was born in China. He completed his B.S. in Chemistry at University of Science and Technology at Hefei in China and came to the USA in 1993 and earned his Ph.D. at Boston University in 1998 in the group of Professor Kosta Steliou (Endo peroxide nature product total synthesis). After gradating from BU, Gang Joined ArQule, working on the design and synthesis of small molecules arrays for the discovery of novel lead molecules. In 1992, Gang moved to Biogen at Cambridge, MA and established a parallel synthesis group in the medicinal chemistry department. During his stay at Biogen, Gang worked on adenosine A2A receptor antagonists for the treatment of Parkinson's disease and fragment based drug discovery for inhibiting protein–protein interactions with small molecules. In 1995, Gang Joined Preacis at Waltham, which was acquired by GSK in 1998. During his work at GSK, Gang has been working in the post selection chemistry group to confirm and optimize small molecule hits derived from DNA-Encoded libraries.

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