Applied Pharmaceutical Chemistry

2024

Thursday, April 4

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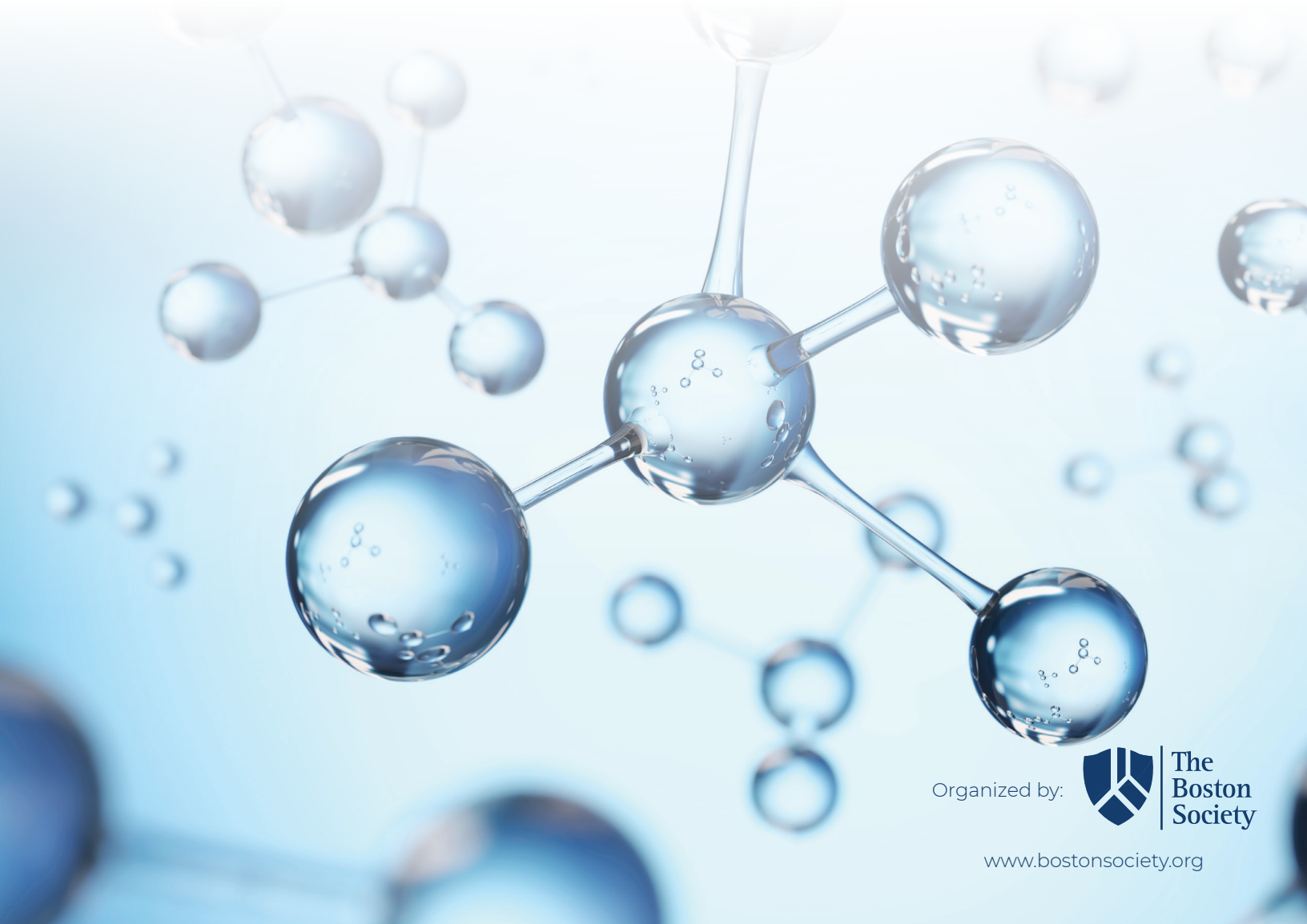

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We're focused on discovering, developing and bringing innovative medicines to people with serious diseases so they can lead better lives. In pursuit of this mission, we are advancing a robust research pipeline that includes potentially transformative treatments for cystic fibrosis, pain, sickle cell disease, beta thalassemia, alpha-1 antitrypsin deficiency, APOL1-mediated kidney disease, Duchenne muscular dystrophy, type 1 diabetes and more.

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We are proud of the advancements we have made in oncology, hematology, immunology and cardiovascular disease, and we are dedicated to helping patients prevail over serious diseases through our diverse and promising pipeline and new scientific platforms.

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Applied Pharmaceutical Chemistry

ORGANIZERS' WELCOME

Welcome to the 2024 Applied Pharmaceutical Chemistry Conference.

Our organizers have gathered another excellent group of speakers for the fifteenth 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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Kenneth Boy, BMS
Rebecca Casaubon, Exscientia
Eamon Comer, Kymera Therapeutics
Baudouin Gerard, Nuvalent Inc.
Catherine Jorand Lebrun, Nexo Therapeutics
Benoit Moreau, Remix Therapeutics
Andy Tsai, Treeline Biosciences

APC 2024 CONFERENCE AGENDA

Thursday, April 4

8:00 - 9:00	**Registration & Coffee**
9:00 - 9:05	**Conference Opening** Pedro Garcia Barrantes, Vertex
9:05 - 9:10	**Speaker Introduction**
9:10 - 9:40	**MTA-Cooperative PRMT5 Inhibitors for the Treatment of MTAP-Deleted Cancers** Kevin Cottrell, Tango Therapeutics
9:40 - 9:45	**Speaker Introduction** Eamon Comer, Kymera Therapeutics
9:45 - 10:15	**Discovery of Potent, Orally Bioavailable IRAK4 Degraders for the Treatment of Oncology and Immuno-Inflammatory Diseases** Matt Weiss, Kymera Therapeutics
10:15 - 10:20	**Speaker Introduction** Kenneth Boy, BMS
10:20 - 10:50	**Sustainability-Driven Science: How Process Chemistry at Sanofi Integrates Eco-Design with Process Development** Eileen Hoang, Sanofi
10:50 - 11:10	Break
11:10 - 11:15	**Speaker Introduction** Andy Tsai, Treeline Bio
11:15 - 11:45	**Discovery and Characterization of a First-in-Class Selective IKZF2 Glue Degrader for Immuno-Oncology Applications** Michael Visser, Novartis
11:45 - 11:50	**Plenary Speaker Introduction** Catherine Lebrun, Ananke Therapeutics
11:50 - 12:35	**PLENARY: Next-Generation Covalent Drug Discovery – Targeting Residues Beyond Cysteine** Lyn Jones, Dana-Farber Cancer Institute
12:35 - 1:50	Lunch

1:50 - 1:55 **Speaker Introduction**
David Ebner, Pfizer

1:55 - 2:20 **VENDOR PRESENTATION**
Exploiting High-Energy Hydration Sites for the Discovery of Potent Peptide Aldehyde Inhibitors of the SARS-CoV-2 Main Protease with Cellular Antiviral Activity
Abba Leffler, Schrödinger

2:20 - 2:50 **Small Molecule GLP-1 Receptor Agonists Suitable for Once-Daily Oral Administration**
David Griffith, Pfizer

2:50 - 2:55 **Speaker Introduction**
Benoit Moreau, Remix Therapeutics

2:55 - 3:25 **Rational Discovery and Design of Molecular Glue Degraders**
Bernhard Fasching, Monte Rosa Therapeutics

3:25 - 3:40 Break

3:40 - 3:45 **Speaker Introduction**
Andy Tsai, Treeline Bio

3:45 - 4:15 **Identification of a Novel Linker Enabling Bioconjugation of a Cyclic Dinucleotide for the STING Antibody Drug Conjugate TAK-500**
Hong Myung Lee, Takeda

4:15 - 4:20 **Plenary Speaker Introduction**
Rebecca Casaubon, Exscientia

4:20 - 5:05 **PLENARY: Chemical Synthesis of Complex Molecules for Translational Science**
John A. Porco, Jr., Boston University

5:05 - 5:10 **Closing Remarks**
David Ebner, Pfizer

5:10 - 6:10 **Reception**

ABSTRACTS

Discovery and Characterization of a First-in-Class Selective IKZF2 Glue Degrader for Immuno-Oncology Applications

Mike Visser, Novartis Biomedical Research

Growing malignant tumors must evade destruction by the immune system, a hurdle some malignancies overcome by attracting immune-suppressive regulatory T-cells (Tregs). The IKZF2 (Helios) transcription factor plays a crucial role in maintaining function and stability of Tregs, and IKZF2 deficiency enhances immune responses to tumors in mice, suggesting IKZF2 may be an attractive target for cancer immunotherapy. Here we describe the discovery and characterization of DKY709, the first molecular glue degrader of IKZF2/4 which spares IKZF1/3. DKY709 was identified through a recruitment-guided medicinal chemistry campaign that redirected the degradation selectivity of CRBN binders towards IKZF2.

PLENARY TALK

Next-Generation Covalent Drug Discovery – Targeting Residues Beyond Cysteine

Lyn Jones, Dana-Farber Cancer Institute

The recent resurgence in covalent drug discovery has been driven by the prospect of addressing proteins previously deemed 'undruggable' through the delivery of rationally designed electrophilic small molecules with enhanced pharmacodynamics compared to reversible binding ligands. Additionally, covalent modalities aid the discovery of allosteric and cryptic sites, assist selectivity profiling, and enable the development of translational target occupancy biomarkers. Covalent drug design has historically focused on targeting protein cysteine residues due to the high intrinsic nucleophilicity of the side chain, and several drugs have been approved that operate via this mechanism of inhibition.

However, cysteine has a low occurrence in protein binding sites, and the high nucleophilicity of the thiol/thiolate can hamper the development of highly selective probes and drugs. Additionally, Cys-to-Ser resistance mutations rapidly emerge in the clinic for covalent kinase inhibitors used to treat cancer, resulting in relapse.

This talk will describe the development of a next-generation covalent drug discovery platform at DFCI that targets amino acid residues beyond cysteine to expand the druggable proteome and to yield chemical probes that unearth fundamental insights into biology and disease. Sulfonyl exchange chemistry will be presented that illustrates new opportunities to synthetically re-engineer protein surfaces and to chemically target cancer vulnerabilities.

VENDOR PRESENTATION

Exploiting High-Energy Hydration Sites for the Discovery of Potent Peptide Aldehyde Inhibitors of the SARS-CoV-2 Main Protease with Cellular Antiviral Activity

Abba Leffler, Schrödinger

Small molecule antivirals that prevent the replication of the SARS-CoV-2 virus by blocking the enzymatic activity of its Main Protease (Mpro) are and will be a tenet of pandemic preparedness. However, the peptidic nature of such compounds often precludes the design of compounds within favorable physical property ranges, limiting cellular activity. Here we describe the discovery of peptide aldehyde Mpro inhibitors with potent enzymatic and cellular antiviral activity. This structure-activity relationship (SAR) exploration was guided by the use of calculated hydration site thermodynamic maps (WaterMap) to drive potency via displacement of waters from high-energy sites. Thousands of diverse compounds were designed to target these high-energy hydration sites and then prioritized for synthesis by physics- and structure-based Free Energy Perturbation (FEP+) simulations, which accurately predict biochemical potencies. This approach ultimately led to the rapid discovery of lead compounds with unique SAR that exhibited potent enzymatic and cellular activity with excellent pan-coronavirus coverage.

Small Molecule GLP-1 Receptor Agonists Suitable for Once-Daily Oral Administration

David Griffith, Pfizer

Glucagon-like peptide-1 (GLP-1) is a neuroendocrine hormone that is released from the small intestine in response to food intake. Activation of the GLP-1 receptor (GLP-1R) by GLP-1 stimulates insulin release in a glucose-dependent manner, delays gastric emptying, and suppresses food intake. To date, all approved agents are large peptides that are generally administered by injection, limiting the uptake of these highly effective medicines, though an oral formulation of semaglutide utilizing permeation enhancers was recently approved. We recently disclosed the oral small molecule agonist danuglipron, which has a half-life suitable for twice-daily administration. In seeking a 2nd generation compound with increased half-life, we developed constrained analogues with improved potency and preclinical ADME characteristics. This presentation will describe the design of these series, including clinical candidate lotiglipron.

Identification of a Novel Linker Enabling Bioconjugation of a Cyclic Dinucleotide for the STING Antibody Drug Conjugate TAK-500

Hong Myung Lee, Takeda

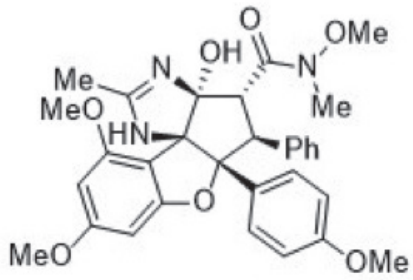
The role of Stimulator of Interferon Genes (STING) in activation of innate immune system by inducing type 1 interferon (IFN) production has been well documented. Targeted delivery of STING agonist to CCR2 expressing myeloid cell population could induce the activation of the immune cells within tumor microenvironment (TME) and antitumor activity. The chemistry strategy was established to enable targeted delivery of a cyclic dinucleotide STING agonist TAK-676 to CCR2+ myeloid cells through an antibody-drug conjugate (ADC) approach. A self-immolative spacer between the adenine of TAK-676 and the Cathepsin-B cleavable Val-Ala dipeptide linker rendered a linker-payload with enhanced chemical and plasma stability that is rapidly cleaved upon internalization into endosome. Stochastic Cysteine conjugation of the TAK-676 containing these linkers provided immune cell stimulating ADC (iADC) TAK-500 and its mouse surrogate mTAK-500. In mouse models mTAK-500 showed antitumor activity as well as the induction of cytokines with IFN activation and the increase of CD8+ T cells.

PLENARY TALK

Chemical Synthesis of Complex Molecules for Translational Science

John A. Porco, Jr., Boston University

The plant genus *Aglaia* produces a number of secondary metabolites including the cyclopenta[b]benzofuran rocaglamide A. Cyclopenta[b]benzofuran natural products possess potent anticancer properties due to modulation of DEAD-box RNA helicases including eukaryotic initiation factor 4A (eIF4A), which is involved in loading ribosomes onto mRNA templates during translation initiation, a step frequently deregulated in cancer. In this presentation, we will describe our efforts to synthesize rocaglate natural products and designed congeners rocaglate analogues such as the amidino rocaglate (ADR) **CMLD012824** using photocycloaddition of 3-hydroxyflavones with various dipolarophiles and evaluation of the rocaglates produced in targeted applications.



CMLD012824

BIOGRAPHIES

Kevin Cottrell, Tango Therapeutics: Kevin Cottrell, is the Executive Director of Medicinal Chemistry at Tango Therapeutics. He received his education at the University of Delaware and has an extensive background in pharmaceuticals, with 3 years at Zeneca Pharmaceuticals and 18 years at Vertex Pharmaceuticals. During his time at Vertex, he was a member of the teams that discovered the HCV protease inhibitor Incivek and the DNA-PK inhibitor VX-984. For the past 7 years, he has been at Tango Therapeutics, where he serves as the Executive Director of Chemistry. He is credited with discovering TNG908 and TNG462, Tango's clinical MTA-cooperative PRMT5 inhibitors. Additionally, he was the chemistry lead on the TNG908 program and project and chemistry lead on the TNG462 program.

Bernhard Fasching, PhD, Monte Rosa Therapeutics: Dr. Fasching graduated from the University of Dortmund and the Max Planck Institute for Kohlenforschung in 2007 in Total Synthesis with Prof. Fuerstner followed by a Post-Doc experience at Memorial Sloan Kettering working on glycopeptide synthesis with Prof. Danishefsky. Ever since, he has been working on the discovery and development of novel pharmacologically active molecules and principles for Hoffmann-La Roche and for a number of biotech companies in the areas of neuroscience, oncology and rare diseases. He has successfully lead drug discovery programs, using medicinal chemistry to advance molecules to patients. More recently, he has put a focus on the creation of biotech platforms centered around novel modes of action such as molecular glue degraders. Currently he is the head of chemistry at Monte Rosa Therapeutics leading the medicinal chemistry teams in drug discovery as well as the platform group with the aim to understand and employ the molecular mechanisms of ternary complex induction by small molecule drugs.

David Griffith, PhD, Pfizer: Dr. Griffith received his undergraduate degree from Harvey Mudd College and his PhD in Chemistry from Yale University in the laboratory of Professor Sam Danishefsky. Following postdoctoral studies at the University of California, Berkeley, with Professor Clayton Heathcock, he joined Pfizer in 1995. There he has led Medicinal Chemistry efforts and broader Project Teams against targets for Obesity, Osteoporosis, Diabetes and Infectious Disease resulting in multiple candidates advanced for clinical testing including the Ph3 CB-1 antagonist otenabant and the Ph2 GLP-1R agonists danuglipron and lotiglipron. He is an author on 53 publications and is an inventor on 51 patents.

Eileen Mai-Huong Hoang, PhD, Sanofi: Dr. Hoang received her B.A. in biochemistry from Swarthmore college and her Ph.D. in chemistry from Harvard University working in the lab of Professor Brian Liau where she synthesized natural product derivatives for functional genomics. Following the completion of her doctoral studies, Eileen started her industrial career at Sanofi in mid-2021 as a process scientist. As part of Sanofi's process chemistry team, Eileen has supported small molecule programs at various stages of development from commercial route ideation and evaluation to final API synthesis and crystallization. She serves as a company representative at various external organizations such as the ACS GCIPR and the Boston chapter of EWOC. Outside of the lab, Eileen enjoys exploring new cafes and coffeeshops, going to art museums, and reading.

Lyn Jones, PhD, Dana-Farber Cancer Institute: Dr. Jones completed PhD studies in synthetic organic chemistry at the University of Nottingham, before starting his postdoctoral research at The Scripps Research Institute (La Jolla, California) in chemical biology. He joined Pfizer (Sandwich, UK) as a medicinal chemistry team leader, eventually becoming Head of Chemical Biology and Lead Discovery Technologies. He transferred to Pfizer Cambridge, MA to become Head of Rare Disease Chemistry and Head of Chemical Biology. He then joined Jnana Therapeutics as Head of Chemistry and Chemical Biology, before moving to the Dana-Farber Cancer Institute in Boston as Director of the Center for Protein Degradation.

His research interests include the creation and application of chemistry-based technologies to advance therapeutic target discovery and to accelerate drug development. He is an elected Fellow of the American Association for the Advancement of Science, the Royal Society of Chemistry, the Royal Society of Biology, and the Linnean Society, and serves on the editorial board of the journal RSC Medicinal Chemistry and the board of the Medicinal and Bioorganic Chemistry Foundation.

Hong Myung Lee, PhD, Takeda: Dr. Lee grew up in South Korea and obtained B.S. in chemistry at Seoul National University. He came to US for an advanced degree and received Ph.D. in chemistry at Harvard University in 2009 under the supervision of Professor Matthew D. Shair, with the research on the development of enantioselective aldol reactions and the total synthesis of a natural product Cortistatin A. He started his industrial research career as a medicinal chemist by joining Takeda Pharmaceuticals at Cambridge, MA in 2009 where he is currently a Principal Scientist. His research focus has been the development of small molecule drugs and antibody-drug conjugates on oncology.

Abba E. Leffler, PhD, Schrödinger: Dr. Leffler is a Senior Principal Scientist in the Drug Discovery group at Schrödinger, where he currently focuses on small-molecule drug discovery. He received his AB in Chemistry with a Certificate in Applied Mathematics from Princeton University, after which he worked at D. E. Shaw Research before going on to obtain his PhD in Neuroscience from NYU School of Medicine. His research has been published in Science, The Journal of Neuroscience, The Journal of Chemical Information and Modeling, and Proceedings of the National Academy of Sciences among others. He is an inventor on multiple patents as well.

John A. Porco Jr., PhD, Boston University: Dr. Porco received his B.A. in chemistry in 1985 from the College of the Holy Cross and a Ph.D. in organic chemistry from Harvard University with Professor Stuart Schreiber in 1992. From 1992-1993, he was an NSF postdoctoral fellow with Professor Chi Huey Wong at the Scripps Research Institute. John then spent six years in industry, first working in venture capital at Avalon Ventures, and then at Argonaut Technologies where he became Director of Parallel Medicinal Chemistry. He joined the Department of Chemistry at Boston University in 1999 as Assistant Professor and was promoted to Professor in September 2004. In 2002, he successfully led an effort to establish the Center for Chemical Methodology and Library Development at Boston University (CMLD-BU). Funded by the National Institutes of Health (NIH) as a Center of Excellence, the focus of the CMLD-BU was the discovery of new methodologies to produce novel chemical libraries of unprecedented complexity for biological screening. In 2014, the CMLD-BU was transitioned to the Center for Molecular Discovery (BU-CMD), an integrated infrastructure for the discovery of small molecule chemical probes. Professor Porco is Director of the BU-CMD. In terms of academic honors, Prof. Porco received the A.C. Cope Scholar Award in 2009 and was appointed Samour Family Professor of Chemistry at Boston University in 2018.

Recent research themes in the Porco Laboratory include:

- **Dearomatization Strategies in Complex Synthesis** aim to utilize aromatic scaffolds as starting materials as precursors to complex natural products.
- **Biomimetic Synthesis Approaches** involve development of methodologies to test plausible biosyntheses of complex natural products and derivatives.
- **New Reaction Discovery** is done in conjunction with the BU-CMD and aims to discover transformations leading to novel chemotypes.
- **Medicinal Chemistry and Target Identification** involves elaboration of complex natural product scaffolds into drug molecules and probes for target identification

Mike Visser, PhD, Novartis: Dr. Visser is a group leader at Novartis Biomedical Research in Cambridge, MA. In this role, he applies his skills as a medicinal chemist in multi-disciplinary team settings in the search for new therapeutics to treat human disease. He received his undergraduate chemistry degree from Syracuse University in 1992 working in the lab of Professor Donald Dittmer. In 1997, he received a PhD from Boston College, working in the lab of Professor Amir Hoveyda in the areas of asymmetric catalysis, metathesis, and organic synthesis. He then was a post-doctoral fellow in Professor Samuel Danishefsky's lab at Memorial Sloan Kettering Cancer Center contributing to the synthesis of the core of the N-linked glycopeptide High Mannose. In 1999 Mike began his industrial career at Pfizer and later moved to Novartis in 2007. Mike has conducted research toward new therapeutics for treating cancer, diabetes, cardiovascular disease, and infectious diseases. He has worked on range of targets and modalities on projects for the treatment of cancer, including efforts which identified the Protein Kinase C inhibitor, LXS196, and Helios degrader, DKY709, which are currently being evaluated in patients. Mike's current research is focused on small molecule approaches to harness the body's immune system to fight cancer.

Matt Weiss, Kymera Therapeutics: Matt joined Kymera Therapeutics in 2018 and now serves as VP, head of chemistry and early drug discovery. In his time at Kymera, he has delivered numerous development candidates across both oncology and immunology. Prior to joining Kymera, he spent 13 years at Amgen in Cambridge, MA where he focused primarily in the areas of Oncology and Neuroscience, delivering development candidates within both.

POSTER ABSTRACTS

Exploiting high-energy hydration sites for the discovery of potent peptide aldehyde inhibitors of the SARS-CoV-2 main protease with cellular antiviral activity

Daniel W. Carney [a 1], Abba E. Leffler [b 1], Jeffrey A. Bell [b], Asela S. Chandrasinghe [c], Cecilia Cheng [d], Edcon Chang [a], Adam Dornford [e], Douglas R. Dougan [a], Leah L. Frye [c], Mary E. Grimes [c], Tim Knehans [f], Jennifer L. Knight [b], Mallareddy Komandla [a], Weston Lane [g], Hubert Li [d], Sophia R. Newman [c], Katalin Phimister [h], Kumar S. Saikatendu [a], Hercules Silverstein [c], Shaghayegh Vafaei [b]

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Small-molecule antivirals that prevent the replication of the SARS-CoV-2 virus by blocking the enzymatic activity of its Main Protease (Mpro) are and will be a tenet of pandemic preparedness. However, the peptidic nature of such compounds often precludes the design of compounds within favorable physical property ranges, limiting cellular activity. Here we describe the discovery of peptide aldehyde Mpro inhibitors with potent enzymatic and cellular antiviral activity. This structure-activity relationship (SAR) exploration was guided by the use of calculated hydration site thermodynamic maps (WaterMap) to drive potency via displacement of waters from high-energy sites. Thousands of diverse compounds were designed to target these high-energy hydration sites and then prioritized for synthesis by physics- and structure-based Free-Energy Perturbation (FEP+) simulations, which accurately predict biochemical potencies. This approach ultimately led to the rapid discovery of lead compounds with unique SAR that exhibited potent enzymatic and cellular activity with excellent pan-coronavirus coverage.

Alternative to antibiotics – Approaches to design glycomimetics and peptidomimetics as anti-adhesives for the prevention of bacterial pili-adherence in the treatment of infectious diseases

Priyanka Samanta*,[1] and Robert J. Doerksen*,[1,2]

[1] Department of BioMolecular Sciences, University of Mississippi, University, MS, USA
[2] Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, University, MS, USA

Purpose:
Infectious diseases are the leading cause of disability-adjusted life years worldwide, leading on average to the loss of 1 year of healthy life per capita. Bacterial infections are the second leading cause of death worldwide. Traditional antibiotic treatment has led to the rise of antibiotic-resistant strains of pathogenic bacteria. Therefore, there is a need to pursue a better understanding of alternate effective therapeutic strategies. One such alternate therapeutic approach is anti-adhesive therapy, in which the first step of bacterial contact with the human cell epithelial layer is inhibited.

Methods:
In this work, we have used advanced and novel molecular modeling techniques, such as fragment-based pharmacophore modeling, virtual mutagenesis, molecular dynamics simulations, binding free energy calculations and machine-learning based pharmacokinetic property predictions to design glycomimetics and peptidomimetics as anti-adhesives for the treatment of *E. coli*-induced urinary tract infections and *Salmonella*-induced abdominal disorders, as case studies.

Results:
E. coli and *Salmonella* express fibers known as pili tipped with adhesins that bind to specific receptor proteins present on host cell surfaces which enable them to colonize host tissues. For the first case study, we have used computer-aided drug design techniques to identify novel competitive pili-binding glycomimetics that are predicted to inhibit *E. coli* adhesion. We have designed a novel fragment-based virtual screening workflow and utilized structure-based rational design using scaffold hopping to predict *E. coli* pili inhibitor fragments. We have generated a database containing ~190K small molecules which could be utilized to identify new glycomimetics for the prevention of *E. coli* adherence. For the second case study, we have designed peptides and peptidomimetics using virtual mutagenesis techniques to prevent the biogenesis of *Salmonella* pili. It is known that *Salmonella* pili undergo a chaperone-usher pathway assembly mechanism to generate the host-recognizing functional form of the pilus. Preventing the pilus biogenesis by targeting the pilus subunit polymerization could prevent host recognition. We have used virtual alanine mutagenesis and protein–protein interaction studies to identify hotspot residues. Using binding affinity maturation studies, we have prepared a library of 110 peptides and 400 peptidomimetics that are predicted to bind strongly to *Salmonella* pili. For both the case studies, molecular dynamics simulations and implicit-solvent-based binding free energy calculations identified key pairwise interactions between the proteins and the glycomimetics/peptidomimetics. Machine-learning-based ADMET predictor models were used to investigate the toxicity and metabolism profiles of the designed glycomimetics and peptidomimetics.

Conclusions:
Our work provided new insights into the design of novel anti-virulence therapies targeting bacterial infections.

Thank you to all of our Organizers, Speakers, Sponsors and Delegates! Without your dedication, support and participation APC 2024 would not be possible. We greatly value your comments regarding APC 2024 as well as thoughts or suggestions for improving future conferences. Please take the time to fill out our survey when we send it to you next week.

Sincerely,

The Boston Society