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ORGANIZERS' WELCOME

Welcome to the 2025 Applied Pharmaceutical Chemistry Conference.

Our organizers have gathered another excellent group of speakers for the sixteenth 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.

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Andy Tsai, Treeline Biosciences
Cheng Zhong, Pharmaron

Applied Pharmaceutical Chemistry

APC 2025 CONFERENCE AGENDA

Thursday, April 10

7:45 - 8:45	**Registration & Breakfast**
8:45 - 8:50	**Conference Opening** David Ebner, Pfizer
8:50 - 8:55	**Speaker Introduction** Cheng Zhong, Pharmaron
8:55 - 9:25	**PROTAb Platform: An Innovative Universal Linker for DACs with CRBN-Based Degraders** Teresa Mako, Orum Therapeutics
9:25 - 9:30	**Speaker Introduction** Kenneth Boy, BMS
9:30 - 10:00	**Drugging MYC mRNA with Small Molecules** Karthik Iyer, Arrakis Therapeutics
10:00 - 10:05	**Speaker Introduction** Michael Shultz, Novartis
10:05 - 10:35	**Discovery and Optimization of a Series of MALT1 Inhibitors Using Structure-Based Drug Design and Parallel Medicinal Chemistry** Daniel Smaltz, Pfizer
10:35 - 10:55	Break
10:55 - 11:00	**Speaker Introduction** Rebecca Casaubon, Triana Bio
11:00 - 11:30	**Discovery of BIIB129, a Covalent, Selective, and Brain-Penetrant BTK-Inhibitor for the Treatment of MS** Martin Himmelbauer, Biogen
11:30 - 11:35	**Speaker Introduction** Benoit Moreau, Remix Therapeutics
11:35 - 12:05	**The First BDK Inhibitor/Degrader Clinical Candidate, PF-07328948, as a Treatment for Heart Failure** Kevin Filipski, Pfizer

12:02 - 12:10 **Plenary Speaker Introduction**
Andy Tsai, Treeline Biosciences

12:10 - 12:50 **PLENARY: Chemical Tools for Regulating Reactive Sulfur Species in Redox Biology**
Ming Xian, Brown University

12:50 - 1:50 Lunch

1:50 - 1:55 **Speaker Introduction**
Susan Ashwell, Civetta

1:55 - 2:20 **VENDOR PRESENTATION**
Exploiting Solvent Exposed Salt-Bridge Interactions for the Discovery of Potent Inhibitors of SOS1 Using Free-Energy Perturbation Simulations
Abba Leffler, Schrödinger

2:20 - 2:25 **Speaker Introduction**
Christopher Reimann, AstraZeneca

2:25 - 2:55 **DNA Encoded Libraries – Drug Discovery through DEL Screening and the Application of On-DNA Binder Confirmation**
Mark Mantell, GSK

2:55 - 3:00 **Speaker Introduction**
Pedro Garcia Barrantes, Vertex

3:00 - 3:30 **Discovery of MK-4424: an Exquisitely Selective, Potent, & CNS-Penetrant RIPK1 Type-III Inhibitor**
Brandon Vara, Merck

3:30 - 3:45 Break

3:45 - 3:50 **Speaker Introduction**
Michael Shultz, Novartis

3:50 - 4:20 **Development of a Commercial-Ready Process for TNG908, a Potent, Selective and Brain Penetrant MTA-Cooperative PRMT5 Inhibitor**
Colin Liang, Tango Therapeutics

4:20 - 4:25 **Plenary Speaker Introduction**
Catherine Jorand-Lebrun, Nexo Therapeutics

4:25 - 5:05 **PLENARY: Chemical Biology Tools for Measuring Intracellular Drug Delivery**
Joshua Kritzer, Tufts University

5:05 - 5:10 **Closing Remarks**
Catherine Jorand-Lebrun, Nexo Therapeutics

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

ABSTRACTS

PROTAb Platform: An Innovative Universal Linker for DACs with CRBN-Based Degraders

Teresa Mako, Orum Therapeutics

Targeted Protein Degradation (TPD) has enabled the effective degradation of proteins previously considered undruggable. However, poor cell permeability, low bioavailability, and lack of target selectivity hinder the clinical development of these degraders. Orum's PROTAb platform addresses these limitations through a traceless linker approach, which incorporates a chemical functionalization that enables the stable conjugation of a degrader to a cell-binding moiety, such as a therapeutic antibody. Our innovative design features a self-immolative spacer that is strategically attached to the glutarimide nitrogen of CRBN-based degraders to the linker. The resulting entity is tethered to an antibody to form a stable Degrader-Antibody Conjugate (DAC), which, upon targeted delivery, achieves seamless and traceless payload release.

To demonstrate the versatility of the PROTAb platform across diverse targets and cellular contexts, we selected several known CRBN-based heterobifunctional degraders for proof-of-concept studies. Our findings confirm that the linker technology effectively facilitates targeted protein degradation mediated by receptor antigens, underscoring the broad applicability of PROTAb in advancing TPD therapeutics.

Drugging MYC mRNA with Small Molecules

Karthik Iyer, Arrakis Therapeutics

Our mission at Arrakis is to solve very broadly the problem of how to drug RNA with small molecules. This presentation will provide an overview of the platform we have built to achieve the goal of drugging RNA and then discuss our findings towards the development of a MYC mRNA "inhibitor".

Discovery and Optimization of a Series of MALT1 Inhibitors Using Structure-Based Drug Design and Parallel Medicinal Chemistry

Daniel Smaltz, Pfizer

Here we describe the discovery and optimization of a novel series of MALT1 inhibitors. After identification of a biochemical screening hit, a scaffold hop was accomplished by parallel medicinal chemistry through a large amidation library. Subsequent optimization using structure-based drug design furnished a potent lead molecule with low clearance. Risks related to the low aqueous solubility of this compound were mitigated by the design of a phosphate prodrug which outperformed enabled formulations of the parent compound.

Discovery of BIIB129, a Covalent, Selective, and Brain-Penetrant BTK-Inhibitor for the treatment for MS

Martin Himmelbauer, Biogen

Multiple sclerosis (MS) is a chronic disease with an underlying pathology characterized by inflammation-driven neuronal loss, axonal injury, and demyelination. Bruton's tyrosine kinase (BTK) is involved in the regulation, migration, and functional activation of B cells and myeloid cells in the periphery and the central nervous system (CNS), cell types which are deemed central to the pathology of MS. Modulating immune cells by targeting BTK on both sides of the blood brain barrier with a CNS-penetrant BTK-inhibitor presents a viable strategy to meet the medical need for an effective therapy in slowing disease progression in MS-patients. Herein we describe the structure- and property-based discovery of BIIB129, a structurally distinct and brain penetrant targeted covalent inhibitor (TCI) of BTK with an unprecedented hinge-only binding mode responsible for its high kinome selectivity. BIIB129 demonstrated efficacy in disease relevant preclinical in vivo models of B cell proliferation in the CNS, exhibits a favorable safety profile suitable for clinical development as an immunomodulating therapy for MS, and has a low projected total human daily dose.

The First BDK Inhibitor/Degrader Clinical Candidate, PF-07328948, as a Treatment for Heart Failure

Kevin J. Filipski, Pfizer

Branched-chain amino acid (BCAA; leucine, isoleucine, valine) metabolism has been shown to be dysregulated in several cardio-metabolic disease states including heart failure. These essential amino acids share a common metabolic pathway whereby they are first reversibly transamidated to branched-chain ketoacids (BCKA: ketoleucine, ketoisoleucine, ketovaline) and then irreversibly converted to their CoA derivatives by the branched-

chain ketoacid dehydrogenase (BCKDH) enzyme complex. This complex is negatively regulated by BCKDH kinase (BDK or BCKDK). A BDK inhibitor therefore should enhance BCAA catabolism and is hypothesized to be a treatment for heart failure with preserved ejection fraction. Discovery efforts led to two distinct chemical series. Even though both series inhibited BDK, one led to an increase in BDK protein levels while the other decreased BDK. Assays were developed and molecular dynamics simulations preformed to understand this unexpected pharmacology in which one series acted as a destabilizer/degrader and the other acted as a stabilizer/glue – even though both inhibitor series shared a binding site. The series with desired inhibition/degrader pharmacology was optimized using structure-based drug design and discovery of a cryptic pocket. Clinical candidate PF-07328948 was proven to act as a degrader with rodent in vivo studies and preclinical evidence for heart failure efficacy was generated.

PLENARY TALK

Chemical Tools for Regulating Reactive Sulfur Species in Redox Biology

Ming Xian, Brown University

Reactive sulfur species (RSS), such as hydrogen sulfide, hydrogen polysulfides, and persulfides, play regulatory roles in many physiological and pathophysiological processes. The field of RSS physiology and pharmacology is rapidly growing in recent years, but many fundamental issues must be addressed to advance our understanding of their biology and clinical potential in the future. It is critical to investigate their chemistry and to develop useful tools/methods for regulating and tracking these species. The research in our laboratory focuses on the development of such methods and chemical tools. In this presentation, I will give an overview of our research in this field and discuss a few recent examples of specific RSS releasing agents, sensors, as well as scavengers.

VENDOR PRESENTATION

Exploiting Solvent Exposed Salt-Bridge Interactions for the Discovery of Potent Inhibitors of SOS1 Using Free Energy Perturbation Simulations

Abba Leffler, Schrödinger

Small molecules that bind the Son of Sevenless 1 protein (SOS1), thereby preventing activation of RAS, have been widely pursued as a means for cell proliferation inhibition and anti-tumor activity. Guided by free energy perturbation simulations, we discovered that two acidic residues on the perimeter of a known small molecule binding site on SOS1, E906 and 909, constitute a potency handle that can improve inhibitor affinity by as much as 750-fold when targeted with basic groups to form salt bridges, despite being solvent exposed. Structure-activity relationship (SAR) and X-ray crystallographic studies demonstrate that this effect is attributable to the electrostatic interaction between the protein and ligand. This interaction could be repurposed to create new SOS1 inhibitors, documenting its general utility for core exploration. This short talk will focus on these SAR efforts and also provide recent examples in the literature which suggest that this phenomenon may be applicable to a number of target classes.

DNA Encoded Libraries – Drug Discovery through DEL Screening and the Application of On-DNA Binder Confirmation

Mark Mantell, GSK

DNA Encoded libraries (DELs) are now an established technology in drug discovery, and are used throughout industry for the identification of new small molecule compounds against protein targets. DEL hits have traditionally been evaluated via off-DNA resynthesis and biological testing. This approach can be time- and resource-intensive, limiting the number of putative hits selected for follow-up, and hits often fail to confirm off-DNA. On-DNA hit resynthesis increases throughput and emulates the original library synthesis, enabling identification of side product binders. Here we share GSK's application of on-DNA binder confirmation to evaluate and expand hits from DEL screens.

Discovery of MK-4424: an Exquisitely Selective, Potent, & CNS-Penetrant RIPK1 Type-III Inhibitor

Brandon Vara, Merck

RIPK1, a death-domain-containing kinase, is a master mediator of TNFR1 signaling upon activation by TNF-α. Multiple proteins that directly regulate RIPK1 kinase activity are causally implicated by human genetics in amyotrophic lateral sclerosis (ALS) and Alzheimer's Disease (AD). Recently, type-III small molecule inhibitors of RIPK1 have advanced to clinical trials to treat patients with ALS, AD, and MS.

Herein, we describe the early discovery campaign and the

invention of a potential best-in-class, highly selective, CNS-penetrant type-III RIPK1 inhibitor for neurodegenerative indications. A focused lead identification effort leveraging knowledge-based approaches and in silico "Tier 0" principles, including SBDD and iterative QSAR modeling focusing on CNS penetration and PK, led to the discovery of a unique acylaminal tricycle series. Lead optimization delivered excellent potency in our human whole blood MIP1-β assays, FASSIF solubility, oral bioavailability, and half-life commensurate with once-daily dosing across pre-clinical species. The team navigated hERG challenges and expanded our CV safety window while optimizing physicochemical properties to enable conventional oral formulation. Our development candidate, MK-4424, lacks efflux transporter (e.g., P-gp, BCRP) liabilities and exhibits an excellent off-target and in vitro safety profile.

Development of a Commercial-Ready Process for TNG908, a Potent, Selective and Brain Penetrant MTA-Cooperative PRMT5 Inhibitor

Colin Liang, Tango Therapeutics

TNG908 is a potent, selective, and brain-penetrant MTA-cooperative PRMT5 inhibitor for the treatment of MTAP-deleted tumors. We describe here the chemical process development for the synthesis of TNG908 and the improvements that were achieved over the medicinal chemistry route with much higher yields and better purities. This commercial ready process is convergent, diastereoselective, safe, reproducible, and robust. A total of eight GMP batches have been successfully manufactured, resulting in high-purity API meeting all specifications.

PLENARY TALK

Chemical Biology Tools for Measuring Intracellular Drug Delivery

Joshua Kritzer, Tufts University

Large-molecule therapeutics including peptides, oligonucleotides, and proteins make up a large and growing portion of the drug development pipeline. One of the greatest barriers to developing these drugs is cell penetration. Most enter the cell through a complex pathway involving endocytosis followed by endosomal escape. This process is so poorly understood and difficult to study that it is challenging simply to measure how much compound has actually accessed the cytosol at any given point. The Kritzer Lab has developed new tools for making these and related measurements. The Chloroalkane Penetration Assay (CAPA) is a versatile assay that measures cell penetration using cellularly expressed HaloTag protein and a small chloroalkane tag on the molecule-of-interest. CAPA has been used by the Kritzer group to measure cell penetration for many classes of peptide and oligonucleotide therapeutics, to measure penetration to different subcellular compartments, and to measure relative penetration in different cell types. CAPA has also been adopted by academic and industrial groups all over the world to investigate cell penetration. The Kritzer group has also used molecular evolution to produce new HaloTag variants which work optimally with a fluorogenic benzothiadiazole dye. The resulting "BenzoTag" system allows for turn-on, no-wash cell labeling in seconds. BenzoTag is currently being applied to produce a "turn-on" version of CAPA for continued investigation of drug delivery and mechanisms of endosomal escape.

BIOGRAPHIES

Kevin J. Filipski, PhD, Pfizer: Dr. Filipski is currently an Associate Research Fellow, with 26 years of experience working as a medicinal chemist at Pfizer, Inc. He has worked in the cardiovascular and metabolic diseases therapeutic area for his entire career which has spanned sites in Ann Arbor, MI, Groton, CT, and currently Cambridge, MA. Job responsibilities have included synthetic lab work, coordination of internal and external synthesis teams, project-centered chemistry team leadership, research program leadership, and supervisory roles. Kevin has contributed to teams that have advanced 10 molecules into human clinical trials including 5 into phase 2 studies. He has 75 external publications, patents, and presentations. Kevin previously attended the University of Rochester and University of Michigan.

Martin Himmelbauer, PhD, Biogen: Dr. Martin Himmelbauer, is currently an Principal Scientist at Biogen where he started his industrial career nine years ago. At Biogen his research has been focused on the discovery of small molecules for the treatment of various CNS-indications. He has been impacting several programs in various roles from individual contributor, MedChem- to program-lead resulting in multiple stage-gate transitions and including development candidate nomination. Prior, Martin has followed his passion for synthetic organic chemistry and natural product synthesis receiving his MS and PhD working under the supervision of Prof. Johann Mulzer at the University of Vienna before conducting postdoctoral studies with Prof. John A. Porco, Jr. at Boston University. To date, Martin has co-authored 13 scientific papers and is the co-inventor on 11 patents. Additionally, his achievements have been honored by various fellowships and awards including the "ACS Early Career Investigator Award" in 2022.

Karthik Iyer, PhD, Arrakis Therapeutics: Dr. Iyer is currently the Director and Head of Medicinal Chemistry at Arrakis Therapeutics, where he leads or oversees medicinal chemistry efforts across multiple programs. Prior to Arrakis, he held positions of increasing responsibility at Cyclerion Therapeutics, and Ironwood Pharmaceuticals. He received his Ph.D. in organic chemistry from University of Utah in the field of natural product synthesis and conducted post-doctoral research at Memorial Sloan-Kettering Cancer Center with Professor Sam Danishefsky.

Joshua Kritzer, PhD, Tufts University: Dr. Joshua Kritzer is a Professor of Chemistry at Tufts University in Medford, MA, with appointments in the Molecular Microbiology Program and the Cell, Molecular and Developmental Biology Program at Tufts University's School of Graduate Biomedical Sciences in Boston, MA. The Kritzer lab combines approaches from chemistry, biology, and biotechnology to solve foundational problems in drug discovery. Current projects include discovering constrained peptides for difficult-to-target proteins in autophagy, and measuring cytosolic penetration of peptide and oligonucleotide therapeutics. Prof. Kritzer has won numerous teaching and mentoring awards, and his academic awards include the Smith Family Award for Excellence in Biomedical Research, an NIH New Innovator Award, and a Sanofi iAward for projects involving cross-disciplinary solutions to pressing problems in chemical biology and drug development.Group in

Abba Leffler, PhD, Schrodinger: Dr. Abba 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.

Colin Liang, PhD, Tango Therapeutics: Dr. Colin Liang obtained his Ph.D. in organic chemistry at the University of Hong Kong, focusing on nitrene transfer reactions to build heterocyclic molecules. He then moved to the U.S. and conducted

postdoctoral research in the lab of Prof. Doug Taber at the University of Delaware, working on the total synthesis of natural products. In 2007, he joined Vertex Pharmaceuticals, where he spent 14 years specializing in route scouting and discovery process optimization to develop scalable and cost-effective processes across multiple therapeutic areas. He joined Tango Therapeutics in 2021 and is currently the head of Process Chemistry, overseeing all drug substance (DS) delivery, from early toxicology batches for DRF/GLP studies to IND-enabling GMP delivery, clinical DS resupply, and registration/PPQ batches.

Teresa Mako, PhD, Orum Therapeutics: Dr. Teresa Mako is a Senior Scientist on the Medicinal Chemistry team at Orum Therapeutics, where she leverages her synthetic chemistry and medicinal chemistry experience to lead the design and synthesis of payloads and linkers to support ADC development. Prior to Orum, Teresa held multiple roles in small molecule chemistry, including in drug discovery at Mersana Therapeutics, and in materials discovery at Zymergen, and C2Sense. Teresa received a PhD and Masters in Organic Chemistry from The University of Rhode Island and Boston College, respectively.

Mark Mantell, PhD, GSK: Dr. Mark Mantell joined GSK in 2020 after completing a PhD at the University of Michigan Ann Arbor. He began work with GSK's DNA-Encoded Library platform, specializing in on-DNA reaction development and library production. He has aided in the development of several novel on-DNA reactions and served as the chemistry expert in the development of GSK's on-DNA binding confirmation platform

Daniel Smaltz, PhD, Pfizer: Dr. Daniel Smaltz is a medicinal chemist and project leader at Pfizer where he is currently Associate Research Fellow, supporting preclinical drug discovery efforts in the Inflammation & Immunology at the Cambridge, Massachusetts site. In ten years at Pfizer, Dan has supported projects in Neuroscience, Internal Medicine, and Anti-Infectives across medicinal chemistry Design and Synthesis. In addition to portfolio projects, Dan has contributed to efforts toward the early prediction of Drug-Induced Liver Injury risk and a platform for Late-Stage Lead Diversification. He received a Ph.D. in Organic Chemistry from Harvard University in 2014 under the direction of Prof. Andrew Myers, completing modular syntheses of trioxacarcin natural products and novel analogs and initiating their development into antibody-drug conjugates.

Brandon Vara, PhD, Merck: Dr. Brandon Vara, a native of Fairfax, Virginia, holds a B.S. degree in Chemistry from James Madison University. As an undergraduate, he completed an internship at Amgen, Thousand Oaks in medicinal chemistry, where he worked on developing diterpene libraries via enzymatic biooxidations under the tutelage of Victor Cee. Subsequently, Brandon pursued graduate studies at Vanderbilt University under the guidance of Prof. Jeffrey Johnston, leveraging enantioselective organocatalysis to synthesize novel MDM2-P53 Nutlin-3 derivatives, chiral β-fluoro amines, and uncovered a novel enantioselective CO2-fixation reaction with homoallylic alcohols.

Following his graduate studies, Brandon undertook postdoctoral research with Prof. Gary Molander at the University of Pennsylvania, exploring various Ni/photoredox reactions, including the use of alkyl xanthates as Csp3 radical coupling partners, and the selective arylation of native cysteines and biomolecules. Since then, Brandon embarked on his pharmaceutical career in Discovery Chemistry at Merck (Boston), where he has had the privilege to work across various therapeutic areas, including oncology and neuroscience, while helping build HTE and catalysis capabilities. In his leisure time, Brandon pursues interests in sports and economics alongside cherishing moments with his wife and daughter.

Ming Xian, PhD, Brown University: Dr. Ming Xian received his BS from Nankai University, China and PhD from Wayne State University, Detroit, MI. He was a DOD postdoctoral fellow at the University of Pennsylvania. His training was in organic chemistry. He started his independent academic career at the Washington State University (WSU), Pullman, WA, in 2006. He was named the inaugural Ralph G. Yount Distinguished Professor in Chemical Biology at WSU in 2017. He moved to Brown University in 2020. He is currently the Jesse H. Metcalf Professor of Chemistry at Brown.

POSTER ABSTRACTS

Virtual Screening of Vast Combinatorial Libraries using Thompson Sampling Through Roulette Wheel Selection

Melissa A. Yu[a], Symon Gathiaka[a], Eva Nittinger[b], Christian Tyrchan[b], Hongtao Zhao[b]
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Purpose:

Virtual screening of synthesis-on-demand libraries has emerged as a powerful tool for hit identification and expansion. In recent years, commercial libraries have rapidly expanded into ultra large collections, and pharmaceutical companies are augmenting these collections to access expanded drug-like chemical space. For example, we have recently described a virtual chemical space built upon more than 4100 established library synthesis protocols, estimated to be approximately 1015 compounds.1 Unfortunately, enumeration and evaluation of such vast libraries using traditional brute-force virtual screening methods is practically unfeasible.

Methods:

Klarich et al.[2] have recently proposed Thompson sampling as a solution to efficiently evaluate the reagent space, rather than enumerated space, thereby enabling the screening of vast combinatorial libraries.

Results and Conclusions:

Through enhanced sampling efficiency, we have improved the performance of the method leading to increased recovery rate of top hits from enumeration.3 Our evaluation of this new algorithm using internally curated reagent collections and chemistries and its use in internal pipeline projects will be discussed.

1. *J. Chem. Inf. Model.* 2020 60, 4274
2. *J. Chem. Inf. Model.* 2024 64, 1158
3. *Manuscript in preparation*

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