



# Applied Pharmaceutical Chemistry

# 2026

Thursday, April 2

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## ORGANIZERS' WELCOME

### **Welcome to the 2026 Applied Pharmaceutical Chemistry Conference.**

Our organizers have gathered another excellent group of speakers for the seventeenth 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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**Conference Chair:** Catherine Jorand-Lebrun, Nexo Therapeutics

**Conference Chair Elect:** Cheng Zhong, Sai Life Sciences

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Pedro Garcia-Barrantes, Vertex Pharmaceuticals

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Shashank Kulkarni, Nuvalent

Benoit Moreau, MapleSeed

Christopher Reimann, AstraZeneca

Michael Shultz, Novartis Institutes for BioMedical Research

Andy Tsai, Simcere Pharmaceutical Group



## APC 2026 CONFERENCE AGENDA

### Thursday, April 2

- 7:45 - 8:45      **Registration & Coffee**
- 8:45 - 8:55      **Conference Opening**  
Catherine Lebrun, Nexo Therapeutics
- 8:55 - 9:00      **Speaker Introduction**  
Cheng Zhong, Sai Life Sciences
- 9:00 - 9:30      **Chemomics Applied: What Leveraging a Complete DEL Dataset Looks Like in Practice**  
Rebecca Swett, X-Chem
- 9:30 - 9:35      **Speaker Introduction**  
Christopher Reimann, AstraZeneca
- 9:35 - 10:05     **Accelerated Discovery of a Carbamate Scaffold Cbl-b Inhibitor Using Generative Models and Structure-Based Drug Design**  
Taylor Quinn, AstraZeneca
- 10:05 - 10:10    **Speaker Introduction**  
Mitchell Keylor, Merck
- 10:10 - 10:40    **Design and Synthesis of BLU-654, a Potent and Selective Mutant KIT V654A Inhibitor for the Treatment of Imatinib-resistant GIST**  
Ludivine Moine, Blueprint Medicines
- 10:40 - 11:00    Break
- 11:00 - 11:05    **Speaker Introduction**  
Rebecca Casaubon, Triana Biomedicines
- 11:05 - 11:35    **Discovery and Optimization of a Novel Covalent WRN Helicase Inhibitor Series**  
Momar Toure, Moma Therapeutics
- 11:35 - 11:40    **Speaker Introduction**  
Benoit Moreau, MapleSeed
- 11:40 - 12:10    **UM171: From Stem Cell Expansion to CoREST Degradation—A Clinical Molecular Glue Story**  
Anne Marinier, University of Montreal



- 12:10 - 12:15 **Plenary Speaker Introduction**  
Catherine Lebrun, Nexo Therapeutics
- 12:15 - 12:55 **PLENARY: The Radicalization of Drug Discovery**  
Greg Verdine, LifeMine Therapeutics
- 12:55 - 2:10 Lunch
- 2:10 - 2:15 **Speaker Introduction**  
David Ebner, Pfizer
- 2:15 - 2:40 **VENDOR PRESENTATION**  
**From Computer Aided to Computer Accelerated Drug Discovery**  
Abba Leffler, Schrödinger
- 2:40 - 2:45 **Speaker Introduction**  
Michael Schultz, Novartis
- 2:45 - 3:15 **IL4i1 Inhibitors from Target Validation Through to First-In-Human Studies in Cancer Patients**  
Elsie Yu, Merck
- 3:15 - 3:20 **Speaker Introduction**  
Susan Ashwell, Sashchem Consulting
- 3:20 - 3:50 **Discovery of a DLL3-targeting Macrocyclic Peptide Radioligand Therapy for the Treatment of SCLC**  
Murray Wan, Mariana Oncology
- 3:50 - 4:10 Break
- 4:10 - 4:15 **Plenary Speaker Introduction**  
Shashank Kulkarni, Nuvalent
- 4:15 - 4:55 **PLENARY: Structure Prediction of Cyclic Peptides via Molecular Dynamics and Machine Learning**  
Yu-Shan Lin, Tufts University
- 4:55 - 5:00 **Closing Remarks**  
Cheng Zhong, Sai Life Sciences
- 5:00 - 6:00 **Reception**





## ABSTRACTS

### **Chemomics Applied: What Leveraging a Complete DEL Dataset Looks Like in Practice**

Rebecca Swett, X-Chem

X-Chem has recently launched Chemomics, an integrated approach to creating, analyzing and applying omics-scale chemistry data. This allows the full use of DEL screening data in the selection, optimization and downstream design of DEL-generated compounds. By leveraging novel computational methods designed to expand access to both positive and negative data, as well as methods to summarize DEL-scale data into pharmacophores, X-Chem is transforming DEL screening from Hit Finding to Data Generation. In this talk we will discuss recent experiences analyzing and using DEL-scale data in the context of retrospectives and prospective design.

### **Accelerated Discovery of a Carbamate Scaffold Cbl-b Inhibitor using Generative Models and Structure-Based Drug Design**

Taylor Quinn, AstraZeneca

An AI-generative design engine, REINVENT, and physics-based affinity predictions were combined with machine learning and traditional medicinal chemistry to discover a novel inhibitor for the Cbl-b enzyme. This augmented drug design approach facilitated the efficient hit to lead optimization in only three Design-Make-Test-Analyze (DMTA) cycles, comprising of four design sets and only 23 compounds made, including inactive enantiomers and diastereomers. During optimization of the Augmented-AI imide hit to the final cyclopropyl carbamate, there was approximately a 600-fold boost in potency achieved. Utilizing these new ways of designing enabled the team to discover novel chemistry which provided equivalent potency and properties to a privileged scaffold that had been challenging to replace using traditional methods. The iterative augmented design cycles prior to synthesis were key to discovering and optimizing this scaffold.

### **Design and Synthesis of BLU-654, a Potent and Selective Mutant KIT V654A Inhibitor for the Treatment of Imatinib-resistant GIST**

Ludivine Moine, Blueprint Medicines

Gastrointestinal stromal tumor (GIST) is the most common type

of sarcoma of the gastrointestinal tract, with approximately 5000 patients diagnosed per year in the USA. Approximately 80% of GIST cases are driven by activating mutations in KIT in exon 9 or 11. Patients who progress on therapies such as the front line therapy imatinib or other tyrosine kinase inhibitors (TKIs) often present with on-target resistance mutations within exons 13, 14, 17, or 18. In particular, the KIT V654A mutation (exon 13, adenosine triphosphate-binding region) is the most common single resistance mutation observed with these therapies, underscoring its clinical importance. Additionally, existing TKIs can produce a number of dose-limiting side effects as a result of off-target inhibition of kinases including wild-type KIT, platelet-derived growth factor receptor  $\alpha$  and  $\beta$  (PDGFRs), FMS-like tyrosine kinase 3 (FLT3), and vascular endothelial growth factor receptor (VEGFR). Herein, we report the discovery of BLU-654 (compound 18), a highly potent and kinome-sparing KIT V654A inhibitor. Preclinical efficacy studies demonstrated its prolonged antitumor activity in a KIT V654A cell-derived xenograft mouse model. BLU-654 offers a potent and selective profile suitable for combination therapy for KIT-mutant GIST patients.

### **Discovery and Optimization of a Novel Covalent WRN Helicase Inhibitor Series**

Momar Toure, Moma Therapeutics

Inhibition of WRN helicase activity has emerged as a very promising therapeutic approach for targeting cancer cells with specific DNA repair deficiencies, especially those with microsatellite instability (MSI). In this presentation, we will discuss the discovery and optimization of a novel covalent WRN helicase inhibitor series by leveraging internal insight from a covalent fragment investigation as part of our ATPase platform development.

### **UM171: From Stem Cell Expansion to CoREST Degradation—A Clinical Molecular Glue Story**

Anne Marinier, University of Montreal

UM171 was discovered through phenotypic screening and subsequent structure-activity relationship (SAR) optimization as a potent small molecule enabling robust ex vivo expansion of human hematopoietic stem cells. Continued SAR studies refined its activity and ultimately revealed an unexpected mechanism



of action: UM171 functions as a molecular glue that induces selective degradation of the transcriptional corepressor CoREST, resulting in reprogramming of stem cell transcriptional and epigenetic states that promotes self-renewal while restraining differentiation. Beyond stem cell expansion, UM171 establishes a clinically relevant framework for the development of CoREST molecular glue degraders with applications in regenerative medicine, aging-related diseases, and oncology.

## PLENARY TALK

### The Radicalization of Drug Discovery

Greg Verdine, LifeMine Therapeutics

The field of drug discovery stands at a watershed moment of scientific, medical, and commercial opportunity. Realization of this opportunity will require radical innovations that fundamentally expand the functional capabilities of therapeutic interventions and management of the attendant risks. This talk will focus on the discovery, development, and deployment of radically new therapeutic modalities, inspired by nature, that thrust the field forward in non-obvious, impactful, and exciting new directions.

## VENDOR PRESENTATION

### From Computer Aided to Computer Accelerated Drug Discovery

Abba Leffler, Schrödinger

Cryogenic electron microscopy (cryo-EM) has revolutionized the study of ion channels and transporters by facilitating determination of their structures, states, and ligand-bound conformations. However, it remains unclear how best to utilize these structures effectively for drug discovery. In this talk, I will describe the results of a large-scale effort to benchmark gold-standard potency prediction methods such as free-energy perturbation for an array of clinically relevant ion channels and transporters using publicly available structures and structure-activity relationship data. I will discuss the effectiveness of these calculations for prioritizing potent compounds, the role that an explicit membrane representation plays in their accuracy, and the extent to which so-called "activity cliffs" can be rationalized by displacement of high-energy waters. I will also give an overview of our germane experiences on early discovery programs and in the context of our predictive toxicology efforts.

### IL4I1 Inhibitors from Target Validation Through to First-In-Human Studies in Cancer Patients

Elsie Yu, Merck

As part of an effort to identify novel targets to enhance PD-1 inhibitor treatment efficacy in cancer, a genome-wide association analysis using RNA-Seq data from tumor tissues of patients treated with pembrolizumab was conducted, revealing a correlation between high expression of IL4I1 and response to pembrolizumab. IL4I1 encodes IL4I1 protein, an L-amino acid oxidase produced by myeloid cells and overexpressed in tumor cells that generates hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and other metabolites upon deamination of amino acid substrates, primarily L-phenylalanine to phenylpyruvate. We found that the levels of H<sub>2</sub>O<sub>2</sub> produced by IL4I1 at tumor relevant concentrations drives selective killing of T-cells, potentially driving immunosuppression in the tumor microenvironment and limiting effectiveness of PD-1 inhibitors. Unfortunately, no inhibitors of IL4I1 were known to permit testing of this hypothesis. This presentation will describe how homology based QSAR models in conjunction with iterative focused screening enabled accelerated identification of more than twenty lead series which were triaged, prioritized and optimized to afford advanced selective IL4I1 inhibitors across multiple chemotypes. The impact of structural data and binding kinetics to lead progression will be highlighted. Further, use of leads to demonstrate preclinical proof of biology will be described, as well as selection of a clinical development candidate. Finally, PK/PD and clinical efficacy data will be presented for our development candidate MK-6598.

### Discovery of a DLL3-Targeting Macrocylic Peptide Radioligand Therapy for the Treatment of SCLC

Murray Wan, Mariana Oncology

Neuroendocrine neoplasms (NENs), including small cell lung cancer (SCLC) and treatment-emergent neuroendocrine prostate cancer (NEPC), commonly exhibit upregulated surface expression of the atypical notch Delta-like ligand 3 (DLL3), a protein expressed almost exclusively by tumor cells. Bearing this in mind, we aimed to engineer a novel macrocylic peptide with high affinity to DLL3. Initial screening and optimization led to a tool compound that exhibited limited tumor uptake. Further optimization using structure-activity relationships resulted in substantially increased tumor uptake and improved tumor-to-kidney ratios. The co-crystal structure enabled structure-based



drug designs, which guided additional refinements, ultimately leading to development candidate ETN029. ETN029 binds human DLL3 with picomolar affinity and specificity, showing high cell binding and internalization in both SHP-77 and transgenic CT26. DLL3 cell lines, with minimal binding to DLL3-negative CT26.WT controls. Biodistribution studies of [<sup>177</sup>Lu]Lu-ETN029 in a SHP-77 cell-derived xenograft (CDX) mouse model showed high, rapid uptake, and retention into tumor tissue and fast clearance of the unbound compound. In CDX models (NCI-H69, SHP-77), a single dose of [<sup>225</sup>Ac]Ac-ETN029 (0.35-1.4 μCi) resulted in robust tumor regression and prolonged survival. The findings from our studies suggest further investigation of ETN029 as a treatment for patients with SCLC and other DLL3-expressing solid tumors.

## PLENARY TALK

### Structure Prediction of Cyclic Peptides via Molecular Dynamics and Machine Learning

Yu-Shan Lin, Tufts University

A major challenge in cyclic peptide development is the limited availability of structural information, which hinders structure-

based design and makes it difficult to understand why different cyclic peptide sequences exhibit varying binding affinities, membrane permeabilities, and other properties. This lack of structural insight arises because most cyclic peptides exist as ensembles of multiple conformations in solution, making them extremely challenging to characterize experimentally using techniques such as solution NMR spectroscopy. In this talk, I will describe how molecular dynamics simulations with enhanced sampling methods can be used to obtain this critical structural information. I will also introduce StrEAMM (Structural Ensembles Achieved by Molecular dynamics and Machine learning), a framework that integrates simulation data with machine learning to rapidly generate high-quality structural predictions for cyclic peptides. This capability to efficiently predict structural ensembles will help researchers uncover the structural origins of cyclic peptide behavior and significantly accelerate the development of this promising class of molecules.



## BIOGRAPHIES

**Abba Leffler, PhD, Schrödinger:** Dr. Abba Leffler is a senior principal scientist in the therapeutics 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 also an inventor on multiple patents.

**Yu-Shan Lin, PhD, Tufts University:** Dr. Yu-Shan Lin is a computational peptide chemist and currently a Professor of Chemistry and Dean of Academic Affairs at Tufts University. She received her Ph.D. in Chemistry from the University of Wisconsin, Madison, in 2009, and she was a postdoctoral fellow at Stanford from 2009 to 2012. In 2012, Dr. Lin established her research group at Tufts University, where she received tenure in 2018. Her current research endeavors focus on using molecular dynamics simulation and machine learning to understand and design the structures and properties of peptides, in particular, cyclic and other restrained peptides. Dr. Lin recently received the Machine Learning in the Chemical Sciences & Engineering Award from the Camille and Henry Dreyfus Foundation (2020) and the Rising Innovator Award from Tufts University (2023).

**Anne Marinier, PhD, University of Montreal:** Dr. Marinier is a Full Professor in the Department of Pharmacology and Physiology at the Université de Montréal and Director of Medicinal Chemistry at the Institute for Research in Immunology and Cancer (IRIC). As Head of IRIC's Drug Discovery Unit (DDU), she leads a multidisciplinary team of approximately 50 medicinal and computational chemists and biologists, supporting drug discovery programs from IRIC scientists as well as academic and pharmaceutical collaborators. She brings over 30 years of experience in medicinal chemistry, with strong industrial expertise spanning all aspects of drug discovery, including structure–activity relationship (SAR) development and compound optimization. During her 15-year tenure at Bristol-Myers Squibb, she and her team contributed to the identification of multiple preclinical candidates and to the advancement of numerous programs in oncology, infectious diseases, and inflammation. More recently, her team at IRIC's DDU has supported the progression of five small-molecule programs into clinical studies, including UM171 for hematopoietic stem cell expansion, which formed the basis of the company ExCellThera and has recently received approval in Europe. In addition to ExCellThera, Anne Marinier is also the co-founder and CEO of RejuvenRx, whose mission is to develop systemic analogs of UM171 for cancer and aging-related indications.

**Ludivine Moine, MSc, Blueprint Medicines:** Ludivine Moine is a Principal Scientist at Blueprint Medicines with over 15 years of experience in medicinal chemistry. She holds an M.S. in Organic Chemistry from the University of Montréal, in Professor Hanessian's group, and a Chemical Engineer degree from CPE Lyon, France. Ludivine began her career at Pfizer, contributing to oncology programs and advancing antibody drug conjugate technologies. She played a key role in the discovery of second-generation EZH2 inhibitors CPI-0209 (Tulmimetostat), CPI-1328 and KIT V654A inhibitor BLU-654. She currently is the chemistry lead of Blueprint's first non-kinase heterobifunctional degrader program. While being a co-inventor on multiple patents and co-author on several peer-reviewed publications, she is also known for championing cross-functional knowledge-sharing initiatives both at Blueprint Medicines and Pfizer (QuickChem).

**Taylor Quinn, PhD, AstraZeneca:** Dr. Taylor Quinn is an Associate Principal Scientist at AstraZeneca at the Waltham, MA site. Her work includes analyzing protein-ligand interactions to inform drug design, applying generative methods to design compounds, and data analysis. Prior to joining AstraZeneca in 2020, she received her PhD at the University of Notre Dame under Prof. Olaf Wiest studying the parameterization and application of transition state force fields to study enzyme catalysis using molecular dynamics.



**Rebecca Swett, PhD, X-Chem:** Dr. R.J. Swett is a computational chemist with over a decade of experience in pharma. She received her PhD from Wayne State University and completed a Presidential Postdoctoral Fellowship at Novartis in collaboration with Stanford. After working on rare disease and oncology programs at Vertex and Relay Therapeutics, she now leads Computational Chemistry Innovation at X-Chem, advancing drug discovery through DNA-encoded libraries, machine learning, and automation.

**Momar Toure, PhD, Moma Therapeutics:** Dr. Momar Toure studied chemistry at ENSCM, France, where he earned his M.Sc. degree. He then moved on to complete his Ph.D. degree in Organic Chemistry in the research group of Drs. Jean-Luc Parrain and Olivier Chuzel at Aix Marseille University, France. Momar then went on to conduct postdoctoral work in the research group of Professor Craig Crews at Yale University, where he worked in the TPD field (PROTAC). After Yale, Momar began his professional career in the medicinal chemistry group at EMD Serono, Inc. (Merck KGaA), where he held various positions from Scientist to Principal Scientist. Momar is currently a Director of Medicinal Chemistry at MOMA Therapeutics.

**Gregory Verdine, PhD, Merck:** Dr. Gregory Verdine is a pioneering scientist, educator, investor, and entrepreneur widely regarded as a founder of the field of chemical biology and one of the world's leading innovators in new drug discovery. He is Founder, President, and CEO of LifeMine Therapeutics, Executive Chairman of VidaVinci, Erving Professor of Chemistry and Harvard College Professor, Emeritus, at Harvard University and Harvard Medical School, Managing General Partner of LoLa Capital, Executive Chairman of DoveTree Medicines, and a Venture Partner at Andreessen Horowitz.

Over a distinguished career spanning more than three decades, Dr. Verdine has conducted seminal work on the mechanisms of enzymatic DNA methylation and repair, and has invented multiple new drug modalities, including stapled peptides, stereodefined oligonucleotides, and rationally designed molecular glues. He has co-founded more than a dozen biotechnology companies—including Parabalis Medicines (formerly FogPharma), WaVe Life Sciences, Warp Drive Bio (Now Revolution Medicines), and Gloucester Pharmaceuticals (acquired by Celgene) which collectively have brought multiple FDA-approved medicines to patients and advanced numerous new drug modalities into clinical development. He is credited with coining the phrase “drugging the undruggable” to describe his life's mission: transforming previously intractable disease targets into treatable ones through bold scientific innovation.

Dr. Verdine earned his Ph.D. in chemistry from Columbia University, his B.S. in chemistry from St. Joseph's University, and trained as an NIH postdoctoral fellow at MIT and Harvard Medical School. He is a Fellow of the Royal Society of Chemistry and the American Association for the Advancement of Science, and has received numerous awards and honorary degrees recognizing his groundbreaking contributions to science and medicine.

**Murray Wan, PhD, Mariana Oncology:** Dr. Murray Wan is a Principal Scientist at Mariana Oncology, a Novartis Company, where he has been since 2022 and currently is a chemistry project team leader. He has contributed to multiple drug discovery projects at Mariana Oncology, where he has gained comprehensive knowledge in the use of peptides as radioligand therapies (RLTs). He earned his B.S. in Chemistry from the University of Rochester, conducting his research with Dr. Alison Frontier, working on a novel route towards the total synthesis of ( $\pm$ )-Rocaglamide. He then obtained his M.S. in Organic Chemistry from Baylor University, working with Dr. John Wood on the total synthesis of Hippolachnin A and analogues. After his graduate studies, he then joined the discovery chemistry group at Merck in Boston. While at Merck, he initially worked on small molecule drug discovery programs, but quickly made the transition to peptide drug discovery, which has been his focus over the past 8 years.



**Elsie Yu, PhD, Merck:** Dr. Yu is an Associate Principal Scientist in Discovery Chemistry at the Merck Boston site with extensive experience in small-molecule medicinal chemistry. During her tenure at Merck, she has focused on drug discovery with an emphasis on lead optimization, advancing molecules toward preclinical candidate status. Elsie has played a key role in applying multi-parameter optimization across discovery programs spanning neuroscience, immunology, and immunoncology, integrating potency, selectivity, ADME, and safety into compound design. Her work has resulted in numerous patents and first-author publications, including impactful contributions on HPK1 and LRRK2. She has recently broadened her skillset through a cheminformatics rotation, collaborating cross-functionally to develop a potency prediction model for a pipeline program and further strengthening data-driven design in her projects. Beyond her scientific contributions, Elsie is actively engaged in mentoring diverse talent and has served as an ACS/WCC and S.H.I.N.E. mentor to multiple graduate students. Elsie received her PhD in chemistry from Boston College in Amir Hoveyda's group, where she studied olefin cross-metathesis and its application to complex natural product synthesis, providing a strong foundation in synthetic methodology and complex molecule construction that underpins her current work in medicinal chemistry.



## POSTER ABSTRACTS

### Practical, Efficient, and Accessible Binding-Affinity Prediction Through Rowan FEP

Corin Wagen, Rowan Scientific

#### Purpose:

Accurate prospective prediction of protein–ligand binding affinity remains one of the central challenges in small-molecule drug discovery. Relative binding free-energy perturbation (RBFE) methods can provide useful predictive accuracy, but in practice their broader adoption has been limited by computational cost, workflow complexity, and the expertise required to prepare, execute, and analyze calculations. This work presents Rowan FEP, an end-to-end RBFE workflow designed to make physics-based binding-affinity prediction more practical, efficient, and accessible for applied pharmaceutical chemistry.

#### Methods:

Rowan FEP integrates pose preparation, perturbation-graph construction, and free-energy calculation into a unified workflow. For pose preparation, analogue docking is used to generate MCS-aligned protein–ligand structures from a protein, a template pose, and a set of analogues. The resulting compounds are organized into an alchemical graph using either standard greedy graph construction or high-speed star-map approaches. Free-energy calculations are then executed using TMD, a high-performance FEP engine incorporating algorithmic features like local resampling, adaptive lambda scheduling, and Monte Carlo water sampling. Rowan provides configurable simulation settings together with default presets and cloud-based GPU execution within a graphical user interface.

#### Results:

In public Rowan benchmarking, Rowan FEP is reported to deliver binding-affinity prediction accuracy comparable to established methods, as evaluated by both energy-based metrics (including MAE and RMSE) and ranking metrics (including Pearson and Spearman correlation). The principal practical advantage is speed: depending on system and settings, typical runtimes are reported to be approximately 10–20 minutes per alchemical leg, enabling substantially higher throughput than conventional RBFE workflows. The platform also exposes downstream analytical outputs including ligand rankings, lambda-overlap diagnostics, cycle-closure analysis, and trajectory snapshots, supporting transparent interpretation of results by non-specialist users.

#### Conclusions:

Rowan FEP illustrates how modern RBFE methods can be packaged into an applied workflow that lowers both the computational and operational barriers to routine use. By combining competitive predictive performance with materially faster execution and a more accessible user experience, this approach has the potential to expand the use of physics-based affinity prediction in medicinal chemistry, support faster design–make–test cycles, and increase the number of compounds that can be prioritized in silico before synthesis.



## Dephosphorylation Chimeras Prevent Paradoxical Activation Induced by JAK2 Inhibitors

Kien Tran<sup>1,2,3</sup>, Varsha Venkatarangan<sup>1,2,3</sup>, Endri Kaja<sup>1</sup>, Karishma Kailass<sup>1,2,3</sup>, Surached Siriwongsup<sup>1,2,3</sup>, Shaimaa Sindi<sup>1</sup>, Amit Choudhary<sup>1,2,3</sup>

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<sup>2</sup> Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

<sup>3</sup> Divisions of Renal Medicine and Engineering, Brigham and Women's Hospital, Boston, MA 02115, USA

### Purpose:

JAK2 inhibitors are widely used in hematological malignancies, dermatology, and immunological disorders, with more than 10 approved indications, e.g., myelofibrosis, atopic dermatitis, vitiligo, and rheumatoid arthritis. However, the majority of JAK2 drugs are type I inhibitors that target the active conformation, leading to hyperphosphorylation of the kinase activation loop and priming JAK2 for hyperactivation upon discontinuation of the inhibitor. This is known as the cytokine rebound signaling and is associated with severe side effects, such as acute relapses of disease symptoms, septic shock-like syndrome, or cardiotoxicity. To address this issue, our group has developed an innovative approach to inhibit JAK-STAT pathway without rebound activation via dephosphorylation chimeras.

### Methods:

We used the established GRIPs technology from our lab to make bifunctional molecules that recruit phosphatase SHP2 to JAK2 and remove the hyperphosphorylation. GRIPs (Group Transfer for Induced Proximity) is a bifunctional molecule that uses ligand-directed labeling to covalently attach the effector enzyme with a binder of the protein target, thereby inducing their proximity. In this case, GRIPs labelled SHP2 with a JAK2 inhibitor (baricitinib), allowing the recruitment of SHP2 into the proximity of JAK2 and exerting dephosphorylation activity. Using HEL 92.1.7 erythroleukemia cells expressing mutant JAK2V617F, we measured the effect of GRIPs treatment on JAK2 phosphorylation, the downstream STAT5 phosphorylation, and the rebound effect after inhibitor washout.

### Results:

When the control compound baricitinib induced dose-dependent JAK2 phosphorylation, the GRIP reduced baricitinib-induced phosphorylation in the competition assay. GRIP alone inhibits downstream signaling, i.e., STAT5 phosphorylation, at concentrations as low as 50 nM. In the killing assay using SET2 cell lines, the bifunctional GRIP displays killing potency comparable to that of baricitinib, with an IC<sub>50</sub> of 14 nM. In the inhibitor washout experiment, baricitinib leads to massive STAT5 activation, whereas GRIP did not alter the basal level of downstream signaling. Together, the results show that GRIPs can exert a similar inhibitory effect on the JAK-STAT signaling pathway as baricitinib, without the rebound effect, potentially leading to fewer side effects.

### Conclusions:

JAK2 dephosphorylation chimeras GRIPs represent a promising avenue to inhibit the JAK-STAT pathway without the cytokine signaling rebound, potentially leading to fewer side effects.

Reference: *A Scalable Design for Proximity-Inducing Molecules*. BioRxiv 2026.02.20.706349



## mRNA display: Revolutionizing Drug Discovery

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mRNA display is a powerful in vitro selection and directed evolution technique. Compared to other display technologies, such as phage display, mRNA display offers distinct advantages, including ultra-high-diversity libraries, in vitro selection, and the ability to incorporate noncanonical amino acids. As a result, mRNA display has become the leading display technique for discovering novel (macrocylic) peptide binders with antibody-like affinities.

**PeptiFinder Biotech** is the pioneering company specializing in mRNA display technology. Our mRNA display platform features diverse libraries (linear, monocyclic, and bicyclic peptides) with ultra-high-diversity (up to  $10^{15}$ ), enabling rapid screening against nearly any biological target within 7–8 weeks and achieving a remarkable success rate (>95%). Our poster highlights the broad applicability of the platform across diverse therapeutic modalities. We will showcase how the platform can be effectively utilized for different target classes, including transcription factor proteins, extracellular domains of membrane proteins, and extracellular proteins. Several case studies that demonstrate the platform's robust performance, yielding peptide binders with affinities ranging from high nanomolar (three-digit nM) to picomolar (pM) levels.



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