Icahn School of Medicine at Mount Sinai

Department of Pharmacological Sciences

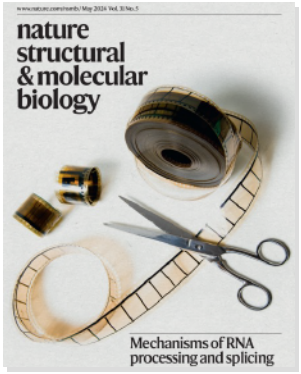
YR YEAR IN REVIEW 2024

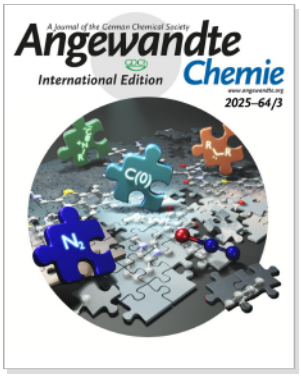
2024 YEAR IN REVIEW

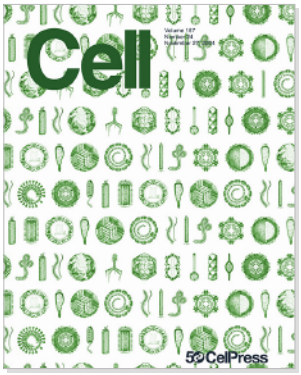
MESSAGE FROM THE CHAIR

MING-MING ZHOU, PhD
Dr. Harold and Golden Lamport Professor & Chairman

2024 has been a landmark year for the Department of Pharmacological Sciences (DPS) as we advance our vision to become an Engine for Scientific Discovery and Therapeutics Development. Our students, postdocs, scientists, and faculty have made groundbreaking discoveries, published in top-tier journals, and received significant peer recognition. With the School's support, we established the Mount Sinai Cryo-EM Center as a new Dean's Core, led by Profs. Aneel Aggarwal and Daniel Wacker. Equipped with a state-of-the-art Glacios cryo-EM microscope, funded by a $2 million NIH grant, the Center will support numerous Mount Sinai laboratories. In spring 2024, we welcomed Prof. Min Xue from UC Riverside, whose Peptide Chemistry & Drug Discovery Lab expands our research enterprise. Grant spending reached a record $35.7 million—a 21.5% increase from 2023—propelling DPS to No. 3 among U.S. Pharmacology Departments in NIH funding. We remain committed to fostering an inclusive, high-quality research and training environment. These achievements underscore the strength of our program and the exceptional support of our administrative team and Student-Postdoc Association (SPA). As we look ahead to 2025, we will continue executing our strategic plan, including faculty recruitment in Chemical Biology & Drug Discovery. Welcome to our 40+ new DPS members—we look forward to a shared journey of discovery and innovation.

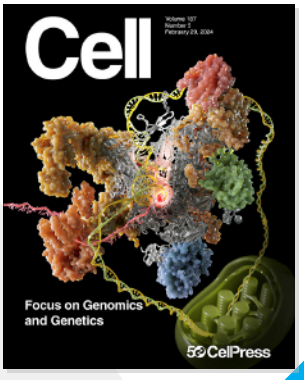






RESEARCH HIGHLIGHT

The DPS research labs—driven by students, postdocs, scientists, and faculty—continue expanding our understanding of fundamental biology and disease mechanisms. We develop chemical probes and therapeutics, translating discoveries into innovative treatments. Our studies explore protein structure-function, mechanisms, and regulation, including cell receptors, transporters, signaling, differentiation, and gene regulation. By investigating novel pharmacological modulators, we gain mechanistic insights into cancer, inflammation, and neurological disorders like Alzheimer's, paving the way for new therapeutic strategies. Supported by federal agencies, foundations, and industry partners, our research has a significant impact. Explore our 2024 **Publications** and **Grants** lists for details.



PUBLICATION HIGHLIGHTS

"Activation of CBASS Cap5 Endonuclease Immune Effector by Cyclic Nucleotides"

ANEEL AGGARWAL, PhD

The bacterial cyclic oligonucleotide-based antiphage signaling system (CBASS) mirrors the human cGAS–STING pathway, featuring an enzyme that synthesizes a cyclic nucleotide upon viral infection and an effector that detects this second messenger to trigger an antiviral response. Cap5, the most abundant CBASS effector, contains a SAVED domain linked to an HNH DNA endonuclease, but its activation mechanism remains unclear. Here, we present high-resolution structures of full-length Cap5 from Pseudomonas syringae bound to second messengers. PsCap5 activation involves a dimer-to-tetramer transition, where second messenger binding induces an open-to-closed shift in the SAVED domains, forming a tetrameric assembly surface. This conformational change aligns the HNH domains, enabling DNA cleavage. These findings highlight Cap5's role in bacterial cell suicide and suggest potential for extrinsic CBASS activation against bacterial infections.

"The First-In-Class Deubiquitinase -Targeting Chimera Stabilizes and Activates cGAS"

JIAN JIN, PhD

Deubiquitinase-targeing chimera (DUBTAC) is a promising technology for targeted protein stabilization (TPS). However, its application has been limited due to modest stabilization effects and a lack of effective deubiquitinase ligands. Here, we report MS7829 and MS8588, the first-in-class DUBTACs for cGAS, a key component of the cGAS-STING pathway. Although based on a cGAS inhibitor, these DUBTACs effectively stabilized cGAS and activated cGAS/STING/IRF3 signaling. To develop these cGAS DUBTACs, we optimized EN523, an OTUB1 covalent ligand, into MS5105, an improved version. We validated MS5105 by creating a MS5105-based CFTR DUBTAC, which was ~10-fold more effective in stabilizing the ΔF508-CFTR mutant protein than the EN523-based version. These findings advance DUBTAC technology for TPS, highlighting its potential for therapeutic applications.

"Adaptive Multi-Epitope Targeting and Avidity-Enhanced Nanobody Platform for Ultrapotent, Durble Antiviral Therapy"

YI SHI, PhD

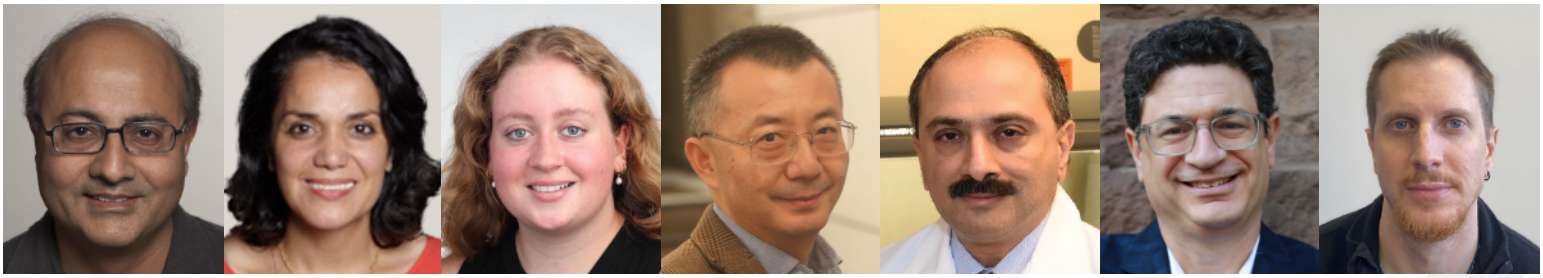
Pathogens evolve, developing mutations that evade immunity and treatment. Countering these escape mechanisms requires targeting conserved vulnerabilities, where mutations often reduce fitness. We introduce adaptive multi-epitope targeting with enhanced avidity (AMETA), a modular nanobody platform conjugating potent bispecific nanobodies to an IgM scaffold. AMETA displays over 20 nanobodies, enabling high-avidity binding to multiple conserved neutralizing epitopes. Using multi-epitope SARS-CoV-2 nanobodies and structure-guided design, AMETA enhances antiviral potency by over a million-fold compared to monomeric nanobodies. It exhibits ultrapotent, broad, and durable efficacy against sarbecoviruses, including Omicron sublineages. Cryo-EM and modeling reveal multiple antiviral mechanisms within a single construct. At picomolar to nanomolar concentrations, AMETA induces inter-spike and inter-virus cross-linking, promoting spike post-fusion and viral disarmament. Its modularity enables rapid, cost-effective adaptation to evolving pathogens.

"Structural Pharmacology and Therapeutic Potential of 5- Methoxytryptamines"

DANIEL WACKER, PhD

Psychedelics like lysergic acid diethylamide (LSD) and psilocybin show promise for treating neuropsychiatric disorders by modulating serotonin (5-HT) receptors, primarily 5-HT2A. However, the 5-HT1A receptor also plays a key role in the behavioral effects of tryptamine hallucinogens, particularly 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), a psychedelic found in the venom of the Colorado River toad. While 5-HT1A is a well-established therapeutic target, its interaction with psychedelics remains poorly understood. Here, we investigate the pharmacology of 5-MeO-DMT using five cryo-EM structures of 5-HT1A, along with medicinal chemistry, receptor mutagenesis, and mouse behavior studies. Structure–activity analyses of 5-methoxytryptamines at 5-HT1A and 5-HT2A identify key molecular determinants of 5-HT1A signaling potency, efficacy, and selectivity. Comparisons between 5-MeO-DMT, its analogues, LSD, and clinically approved 5-HT1A agonists reveal that a 5-HT1A-selective 5-MeO-DMT analogue retains anxiolytic and antidepressant effects while lacking hallucinogenic-like activity, offering a path toward more targeted neuropsychiatric therapies.

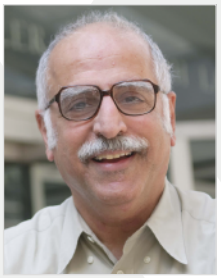
HONORS AND AWARDS



The outstanding achievements of our students, postdocs, and faculty are reflected in the prestigious honors and awards they have received from peers in their fields. In 2024, we are especially proud to celebrate Prof. Aneel Aggarwal's election as a Fellow of the American Academy for the Advancement of Science; Prof. Lahouaria Hadri's American Heart Association Transformative Award and American Lung Association Innovation Award; Kate Jankowski's MSBS Award for Scientific Excellence; Prof. Jian Jin's MSIP I3 Genesis Innovation Award; Prof. Daniel Wacker's Dr. Harold and Golden Lamport Research Award; and Prof. Mone Zaidi's election as a Foreign Member of Academia Europaea and recipient of the American College of Physicians' Hariett P. Dustan Award. Additionally, Dr. Avner Schlessinger was named the Dr. Amy and James Elster Professor of Molecular Biology. Please join us in congratulating our esteemed awardees on these well-deserved honors.

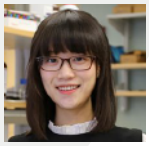
DPS ANNUAL RESEARCH RETREAT AND SCIENTIFIC LECTURES

The Department of Pharmacological Sciences continues its tradition of hosting cutting-edge scientific lectures. On March 21, 2024, Dr. Dinshaw J. Patel, Abby Rockefeller Mauzé Chair in Experimental Therapeutics at Memorial Sloan-Kettering Cancer Center, delivered the 24th Irving L. Schwartz Lecture in Structural & Chemical Biology, titled "*Structural Biology of Bacterial Antiphage Defense*", in the Davis Auditorium at Mount Sinai. The 2024 DPS Annual Research Retreat took place on September 12 at the New York Botanical Garden, where faculty, students, postdocs, and scientists presented breakthrough research through oral and poster sessions. Awards were given for Best Presentation and Best Poster. As part of the event, Dr. Robert E. Gerszten, Herman Dana Professor of Medicine at Harvard Medical School and Chief of Cardiovascular Medicine at Beth Israel Deaconess Medical Center, delivered the Jack Peter Green Lecture, *"Out for Blood: Biochemical Profiling of Human Populations for Cardiovascular Pathway Discovery."* Additionally, DPS co-hosted the Cryo-EM in Disease and Mechanism Symposium with the Dean's Core on May 7 and the 2024 Diversity Symposium with the Neuroscience Department on May 28, featuring keynote lectures by Dr. Jue Chen (The Rockefeller University) and Dr. Angeline Dukes (University of Minnesota Twin Cities), respectively.



LAB PRESENTATION WINNERS

Lauren Qiu
Assoc. Researcher
Yazawa Lab

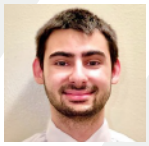


Yufei Xiang, PhD
Instructor
Shi Lab

Yue Zhong
Grad. Student
Jin Lab

Jerrel Catlett
Grad. Student
Jin Lab

POSTER PRESENTATION WINNERS



Frank Fonseca
Grad. Student
Guccione Lab

Jeffrey Kim
Grad. Student
Shi Lab

Giacomo Marino
Bio Sw. Engineer
Ma'ayan Lab

Lauren Qiu
Assoc. Researcher
Yazawa Lab

Leah Yim
Grad. Student
Jin Lab

EXTERNAL PAGES

Visit our other pages for additional notable information from our department!

PUBLICATIONS GRANTS MEMBERS
PRESENTATIONS, SERVICES, HONORS & AWARDS