National Institute of General Medical Sciences

# Training Interdisciplinary Pharmacology Scientists (TIPS)

Program Director: **Carmen Dessauer,** PhD, Professor, Integrative Biology and Pharmacology, The University of Texas Health Science Center at Houston
Program Co-Director: **Timothy Palzkill**, PhD, Professor and Chair, Pharmacology and Chemical Biology, Baylor College of Medicine
http://www.gulfcoastconsortia.org/home/training/pharmacological-science-tps/

## Meet the Trainees

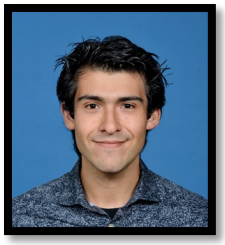
**Megan Daneman**
Appointed January 1, 2025 – December 31, 2025
Biochemistry and Cellular Biology Graduate Program, Rice University
**Primary Mentor:** Dr. Natasha Kirienko, BioSciences, Rice University
**Secondary Mentor:** Dr. Scott Gilbertson, Chemistry, University of Houston
***Investigating novel compounds for selective acute myeloid leukemia cytotoxicity***
Acute myeloid leukemia (AML) is an aggressive hematological malignancy with poor prognosis. AML undergoes metabolic reprogramming (increased oxidative phosphorylation and glutaminolysis) which makes them sensitive to mitochondrial damage. Substantial mitochondrial damage often leads to mitophagy, which is compromised and potentially lethal in AML cells. Our lab identified drugs that increase levels of the mitophagy-inducing protein, (PINK1-stabilizing (PS) compounds) and selectively kill AML cells. We conducted a structure-blind, in silico screen of >4M molecules based on cheminformatic-predicted activities of active PS compounds. Preliminary data indicate prioritized molecules are selectively cytotoxic against AML and synergistic with commercial chemotherapeutics. My project will further investigate the molecular mechanisms of our best candidates by evaluating the cheminformatic-predicted activities, mitochondrial bioenergetic changes, and the relationship between mitophagy and reactive oxygen species in selective cytotoxicity.

**Megan Fisher**
Appointed November 1, 2024 – October 31, 2025
Cancer Biology Graduate Program, University of Texas Health Science Center at Houston (UTH)
**Primary Mentor:** Dr. Dung-Fang Lee, Integrative Biology and Pharmacology, UTH
**Secondary Mentor:** Dr. Xiaoqin Wu, Integrative Biology and Pharmacology, UTH
***Decoding p53(R249S)-mutated liver cancer: from developmental origins to targeted therapies***
Liver cancer is the sixth most prevalent cancer worldwide and the second leading cause of cancer-related mortality. Conventional treatments for early-stage disease have limited effectiveness, highlighting the need for more effective therapies. Recent advancements unveiled the p53(R249S) mutation as critical in hepatocellular carcinoma (HCC) development. However, most research was conducted in cancer cell lines with

secondary genomic mutations, clouding our understanding of the cellular malfunctions directly triggered by mutant p53. Additionally, there exists a clinical imperative to explore whether the HCC-relevant p53(R249S) mutation can be leveraged as a therapeutic vulnerability for the treatment of HCC. Hence, our human pluripotent stem cell (hPSC) platform featuring the p53(R249S) mutation, free of secondary mutations, is an ideal model for investigating the oncogenic role of mutant p53 in HCC. Preliminary findings suggest a link between p53(R249S) and FOXM1, associated with poorer patient outcomes in HCC. Further investigation into FOXM1's role in HCC and potential inhibitors is crucial.

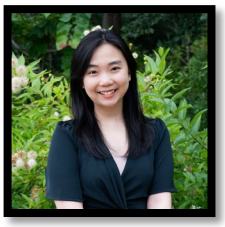
**Peyton High**
Appointed January 1, 2024 – December 31, 2025
Biochemistry & Cell Biology Graduate Program, University of Texas Health Science Center at Houston (UTH)
**Primary Mentor:** Dr. Kendra Carmon, Institute of Molecular Medicine, UTH
**Secondary Mentor:** Dr. Jin Wang, Biochemistry & Molecular Pharmacology, BCM
***EGFR-mediated regulation of LGR5 expression and strategies to enhance the efficacy of antibody-drug conjugates targeting colorectal cancer stem cells***

Antibody-drug conjugates (ADCs) are an emerging class of anti-cancer therapeutics that specifically hone cytotoxic payloads to tumor cells while sparing normal tissue. Our lab has generated ADCs targeting leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5), a positive definer of colorectal cancer stem cells (CSCs). Upon treatment, LGR5-directed ADCs promote tumor regression, yet relapse following ADC withdrawal is a major obstacle to sustained tumor elimination. Notably, therapies targeting epidermal growth factor receptor (EGFR), an oncoprotein overexpressed in colorectal cancers (CRCs), have been shown to increase LGR5 *mRNA* and protein levels. Additionally, LGR5 genetic ablation sensitized CRC cells to EGFR-targeted therapy. The goals of my project are two-fold: (1) determine the mechanism underpinning EGFR-mediated regulation of LGR5 expression; and (2) assess the effect of EGFR-LGR5 dual-targeted therapeutic approaches versus monospecific LGR5 ADC treatment on anti-tumor efficacy and tumor relapse.



**Michael Lopez**
Appointed November 1, 2024 – October 31, 2025
Chemical, Physical, and Structural Biology Graduate Program, Baylor College of Medicine (BCM)
**Primary Mentor:** Dr. Timothy Palzkill, Biochemistry and Molecular Pharmacology, BCM
**Secondary Mentor:** Dr. Mingxing Teng, Pathology and Immunology, BCM
***Discovery of Novel Covalent β-lactamase Inhibitors***

Antibiotic resistance, particularly due to $\beta$-lactamase enzymes like KPC-2 and CTX-M-15, present an ongoing threat to global health by neutralizing key antibiotics such as carbapenems and penicillins. My work focuses on developing novel covalent inhibitors that increase ligand-target binding, preventing the deactivation of antibiotics. By screening covalent warhead-linked compounds and conducting dose-dependence studies, I aim to identify inhibitors that effectively target these $\beta$-lactamases. Kinetic analysis will help refine inhibitor efficacy, while structural studies will provide insights into enzyme-inhibitor interactions. These are crucial steps to developing effective drugs to overcome enzyme-mediated resistance. The primary objectives of this project are to identify covalent inhibitors that can block KPC-2 and CTX-M-15 $\beta$-lactamase hydrolysis of antibiotics and optimizing these inhibitors based on structure-activity relationship studies to improve their potency. The ultimate goal of this work is to make forward-thinking contributions in developing new therapeutic strategies to combat the increasing threat of antibiotic-resistant infections resulting from multi-drug-resistant bacteria.



**Thao K. Nguyen**
Appointed November 1, 2023 – October 31, 2025
Immunology, Therapeutics and Pharmacology Graduate Program, University of Texas Health Science Center at Houston (UTH)
**Primary Mentor:** Dr. Zhiqiang An, Institute of Molecular Medicine, UTH
**Secondary Mentor:** Dr. Kai Xu, Institute of Molecular Medicine, UTH

***Investigation of LILRB5 and LILRB5 as immune-checkpoint targets during Mycobacterial tuberculosis infection***

Immune checkpoint pathways aid the survival of *Mycobacterium tuberculosis* (*M.tb*) inside the host, but they are also vital in controlling *M.tb*-induced pathologies. Therefore, our therapeutic strategies for *M.tb* infection must target only the immune checkpoint factors exploited by the pathogen. Our preliminary data identified the LILRB5 receptor on human immune cells binding to *M.tb*-secreted molecules. Therefore, my goal is to investigate how the activation of LILRB5 limits the human immune response against *M.tb* and its potential as a therapeutic target. Our lab also generated monoclonal IgG antibodies targeting the LILRB5 receptor. They allow us to evaluate the immune-modulating effects of LILRB5 activation during primary *M.tb* infection by blocking the receptors and will facilitate immediate translation from biomedical research to therapeutic applications.

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The TIPS program is administered by the:

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QUANTITATIVE BIOMEDICAL SCIENCES

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The GCC is a collaboration of:
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*Baylor College of Medicine*
*University of Houston*
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*University of Texas MD Anderson Cancer Center*
*Institute of Biosciences & Technology at Texas A&M Health Science Center*
*Houston Methodist Research Institute*