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/*

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## Meet the Trainees

**C. Ulises Gonzalez**
(Appointed November 1, 2020 – October 31, 2021)
Biochemistry and Cell Biology, University of Texas Health Science Center – Houston (UTH)
**Primary Mentor:** Dr. Vasanthi Jayaraman, Biochemistry & Molecular Biology, UTH
**Secondary Mentor:** Dr. Seung-Hee Yoo, Biochemistry & Molecular Biology, UTH
***How is the NMDA receptor involved in triple negative breast cancer***
Brain localized N-methyl D- Aspartate receptor (NMDAR) is a tetrametric ionotropic glutamate receptor able to obtain different biophysical properties based on subunit composition. Recently, NMDAR mRNA expression has been identified outside the central nervous system (CNS) and in triple negative breast cancer (TNB). I propose to find subunit composition differences in TNB using molecular techniques as well as verify their functionality using electrophysiology. Furthermore, I will use subunit specific inhibitors to measure decrease in proliferation of TNB. This will allow us to use NMDAR as a handle to pharmacologically target TNB.

**Allison Judge**
(Appointed November 1, 2019 – October 31, 2021)
Biochemistry and Molecular Biology, Baylor College of Medicine (BCM)
**Primary Mentor:** Dr. Timothy Palzkill, Pharmacology, BCM
**Secondary Mentor:** Dr. BVV Prasad, Biochemistry & Molecular Biology, BCM
***Structure, Function, and Inhibition of CTX-M Antibiotic Resistance Enzymes***
My project addresses the most commonly found antibiotic resistance genes, CTX-M family β-lactamases. The first aim employs a novel, high-throughput method for finding amino acid interactions (cooperativity) within an enzyme. This method can be used to gather basic information about structural and functional requirements in CTX-Ms. The second aim will use a DNA-encoded library (DEL) of small molecules to develop inhibitors against a clinically relevant CTX-M enzyme.

**Kaveeta Kaw**
(Appointed November 1, 2019 – October 31, 2021)
Biochemistry and Cell Biology, University of Texas Health Science Center – Houston (UTH)
**Primary Mentor:** Dr. Dianna Milewicz, Internal Medicine, UTH
**Secondary Mentor:** Dr. Hyun-Eui Kim, Integrative Biology and Pharmacology, UTH
***How do missense mutations in ACTA2 cause early-onset coronary artery disease?***
My project focuses on a heterozygous missense mutation in smooth muscle-specific alpha-actin (ACTA2 R149C), which predisposes patients to early-onset coronary artery disease (CAD). We generated a R149C mouse model that has increased atherosclerotic plaque burden and increased phenotypic switching of smooth muscle cells to macrophage-like cells, a transition which is mediated by PERK-ATF4-KLF4 signaling and promotes atherosclerosis. We hypothesize that the early-onset CAD observed in patients with the ACTA2 R149C mutation is due to disrupted folding of mutant actin that activates stress response pathways via cytosolic-to-ER stress crosstalk activation and causes increased SMC phenotypic switching to macrophage-like cells. Our goal is to assess crosstalk between stress pathways and inhibit this crosstalk to block downstream phenotypic switching of SMCs to macrophage-like cells. Ultimately, these studies will define a novel role for smooth muscle cell alpha-actin in atherosclerosis and will identify new targets for treatment or prevention of atherosclerosis.

**Miranda Lewis**
(Appointed November 1, 2020 – October 31, 2021)
Molecular Virology and Microbiology, Baylor College of Medicien (BCM)
**Primary Mentor:** Dr. Mary Estes, Molecular Virology and Microbiology, BCM
**Secondary Mentor:** Dr. Timothy Palzkill, Pharmacology and Chemical Biology, BCM
***Combating chronic human norovirus by evaluating nitazoxanide in ex vivo stem cell-derived human intestinal organoids and a clinical trial***
Human norovirus is the predominant cause of vomiting and diarrhea and can establish a chronic infection in immunocompromised people, leading to years of diarrhea which can be life threatening. Currently, there are no licensed therapeutics to treat norovirus. My goal is to determine if nitazoxanide is an effective antiviral for human norovirus, discover its mechanism of action, and determine if norovirus can become resistant to nitazoxanide. These studies will be done utilizing human intestinal organoid cultures as well as samples from an ongoing clinical trial evaluating nitazoxanide treatment in chronically infected patients. This work will support nitazoxanide as the potentially first licensed therapeutic for norovirus infection.

**Joe Tolar**
(Appointed November 1, 2019 – October 31, 2021)
BioSciences, Rice University (RiceU)
**Primary Mentor:** Dr. Natasha Kirienko, BioSciences, RiceU
**Secondary Mentor:** Dr. Bonnie Bartel, BioSciences, Rice U
**Tertiary Mentor:** Dr. Damian Young, Pharmacology (BCM); Adjunct in Chemistry (Rice U)
***Identification of Novel Mitochondria-Targeting Small Molecules for Treatment of Cancer***
The similarities between normal and cancer cells make it difficult to selectively kill cancer cells without also damaging healthy tissue. Many cancers have dysregulated metabolic processes, particularly with regard to mitochondria, a vulnerability that can be targeted in cancer therapy development. We have identified novel compounds that activate autophagic degradation of mitochondria and show increased toxicity in acute myeloid leukemia cancer cells compared to healthy blood cells. My work will focus on determining how these chemicals mediate this effect and how we can improve them to more effectively kill cancer cells while retaining, or even reducing, their impact on non-cancerous cells.

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