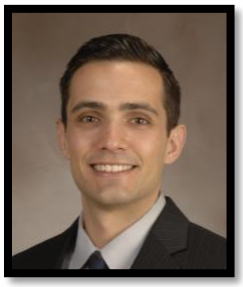
National Institute of General Medical Sciences

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, Baylor College of Medicine
http://www.gulfcoastconsortia.org/home/training/pharmacological-science-tps/

Meet the Trainees



Nathan Berg
(Appointed November 1, 2018 – October 31, 2020)
Biochemistry and Cell Biology, University of Texas Health Science Center – Houston (UTH)
Primary Mentor: Dr. Holger Eltzschig, Anesthesiology (UTH)
Secondary Mentor: Dr. Dianna Milewicz, Internal Medicine (UTH)
The Role of miR-147 in Acute Respiratory Distress Syndrome
Acute respiratory distress syndrome (ARDS) is an inflammatory, life threatening injury of the lungs that can occur in many high risk surgical patients and in critically-ill patients. Our research focuses on how microRNAs (miRNA) regulate inflammation during ARDS with an emphasis on identifying novel mechanisms that control the onset or resolution of inflammation. Recently, we have identified miR-147 as a protective regulator during ARDS based on observations in mouse models that suggest it plays a role in promoting the resolution of inflammation. Furthermore, miR-147 appears to be primarily expressed in pro-inflammatory recruited macrophages and its transcription is regulated by Hypoxia Inducible Factor 1 – alpha (Hif1a). My project aims are to better understand the expression of miR-147, define its mechanistic function in promoting the resolution of inflammation, and ultimately to target miR-147 as a pharmacologic treatment for ARDS.

Allison Judge
(Appointed November 1, 2019 – October 31, 2020)
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, 2020)
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.

Wilhelm (Wil) Salmen
(Appointed November 1, 2018 – October 31, 2020)
Molecular Virology and Microbiology, Baylor College of Medicine
Primary Mentor: Dr. BVV Prasad, Biochemistry & Molecular Biology (BCM)
Secondary Mentor: Dr. Timothy Palzkill, Pharmacology (BCM)
Mechanisms of Neutralization of Noroviruses by Human-Derived Monoclonal Antibodies
Human noroviruses cause approximately 685 million cases of acute gastroenteritis and are responsible for an estimated 50,000 deaths worldwide in children under the age of five. Currently, there are no vaccines for norovirus infections. One challenge to address the development of an effective vaccine to prevent norovirus-associated disease is the vast diversity of field strains. The goal of my project is to investigate how the human host can elicit broadly neutralizing antibodies against the rapidly evolving strains of norovirus to disrupt attachment. Utilizing structural biology approaches, we intend to characterize the complex interactions of the viral capsid protein bound to human-derived monoclonal antibodies. This study will provide insight into the precise mechanism by which the human adaptive immune system can elicit neutralization, as well as for understanding the immune correlates of protection against human norovirus for the development of prophylactic immunotherapeutic agents.

Joe Tolar
(Appointed November 1, 2019 – October 31, 2020)
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.
