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

C. Ulises Gonzalez
Appointed November 1, 2020 – October 31, 2022
Biochemistry and Cell Biology, University of Texas Health Science Center at 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.

Harmon Greenway
Appointed December 1, 2020 – November 30, 2022
Chemical, Physical, and Structural Biology, Baylor College of Medicine (BCM)
Primary Mentor: Dr. Jin Wang, Pharmacology and Chemical Biology, BCM
Secondary Mentor: Dr. Bert O'Malley, Molecular & Cellular Biology, BCM
Anti-tumor efficacy of alternative splicing inhibitors as HER2-targeted antibody-drug conjugates
The presentation of neoantigens is an important driver of antitumor immunity and a significant correlate of the clinical outcome for both checkpoint blockade and adoptive T-cell therapies. Dysregulation of pre-mRNA alternative splicing has been implicated in many cancers and produces a class of neoantigen which may yield viable immunotherapeutic targets. Small-molecule inhibitors of alternative splicing machinery have been developed to increase neoantigen burden and demonstrate a selective, cytotoxic effect on tumors. To improve the safety and efficacy of these treatments, we will develop spliceosome inhibitors as antibody-drug conjugates targeted to HER2+ and triple negative breast cancer. Utilizing cancer immunotherapies, we will evaluate the role of neoantigens produced by alternative splicing in T cell-mediated antitumor response.

Joan Jacob
Appointed December 1, 2021 – November 30, 2022
Biochemistry and Cell Biology, University of Texas Health Science Center at Houston (UTH)
Primary Mentor: Dr. Kendra Carmon, IMM-Center for Translational Cancer Research, UTH
Secondary Mentor: Dr. Mary Estes, Molecular Virology and Microbiology, Baylor College of Medicine

Targeting EREG for the Treatment of Colorectal Cancer

Epiregulin (EREG) is a ligand protein found highly expressed in treatment resistant colorectal cancers (CRC) of various mutation statuses and in both differentiated and undifferentiated cancer stem cell (CSC) populations. The goal of my project is to understand the role of EREG in tumor progression and create an EREG-targeted antibody-drug conjugate (ADC) that functions like a guided missile to deliver a cytotoxic drug to EREG-expressing tumors without harming healthy tissue. I will also generate a bispecific ADC co-targeting EREG and LGR5, to determine if it is more effective in targeting CRC cell plasticity. I will test our ADCs for safety and efficacy against a panel of CRC cell lines and patient-derived tumor and healthy organoid models.

Miranda Lewis
Appointed November 1, 2020 – October 31, 2022
Molecular Virology and Microbiology, Baylor College of Medicine (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.

Thi Thu Trang Luu
Appointed January 1, 2022 – December 31, 2022
Biochemistry and Cell Biology, University of Texas Health Science Center at Houston (UTH)
Primary Mentor: Dr. Guangwei Du, Integrative Biology and Pharmacology, UTH
Secondary Mentor: Dr. John Hancock, Integrative Biology and Pharmacology, UTH

Reprogramming of lipid metabolism by anti-nucleotide drugs creates a vulnerability in triple-negative breast cancer cells

Breast cancer is a life-threatening disease in women. However, low response rate to the drug and development of resistance have been problematic in the clinic. I propose to understand how a commonly used anti-cancer drug, 5-fluorouracil, changes the production and use of fats through altering the levels of free nucleotides in aggressive triple negative breast cancer. I will then demonstrate that combined inhibition of fat storage or utilization and 5-fluorouracil treatment improve efficacy in breast cancer therapy.