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

Cohort 2, Appointed November 1, 2018

Nathan Berg
Biochemistry and Cell Biology, University of Texas Health Science Center - Houston
Primary Mentor: Dr. Holger Eltzschig, Anesthesiology (UTH)
Secondary Mentor: Dr. Diana 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.

Darius Devlin
Translational Biology and Molecular Medicine, Baylor College of Medicine
Primary Mentor: Dr. Martin Matzuk, Pathology & Immunology (BCM)
Secondary Mentor: Dr. William Gibbons, Obstetrics and Gynecology (BCM)
Investigation of sperm acrosome proteins in male fertility and targeting for male contraception
Though there are a plethora of contraceptive options available to women to aid in family planning, the extremely limited options for men have disproportionately burdened women with this responsibility for more than 50 years. My project addresses this issue by harnessing the sperm acrosome, an organelle critical for sperm-egg interaction and male fertility, as a pharmacological target. Our mouse knockout models and human studies have identified that loss of acrosome proteins ZPBP1 or SPAR1 causes infertility. Using DNA-encoded Chemistry Technology (DEC-Tec), we aim to establish lead compounds that can inhibit these target proteins for contraception. To learn more about ZPBP1 and SPAR1 functions and improve hit confirmation assay design, we will characterize their protein interaction profiles using IP-MS. Lastly, we are characterizing mouse models for two new acrosome proteins, FAM170A and FAM170B, and are revealing an important role in male fertility for FAM170A. My thesis project is focused on creating the first acrosome-targeted male contraceptive drug and uncovering new genes and protein interactions required for male fertility.

Brittany Jewell
Integrative Biology and Pharmacology, University of Texas Health Science Center - Houston
Primary Mentor: Dr. Dung-Fang Lee, Integrative Biology and Pharmacology (UTH)
Secondary Mentor: Dr. John Hancock, Integrative Biology and Pharmacology (UTH)
The potential of PARP inhibitors to treat osteosarcoma in Type II Rothmund-Thomson Syndrome patients
We have established an RTS disease model of induced Pluripotent Stem Cells and using these cells to derive osteoblasts, the precursors of osteosarcoma. We propose using the osteoblasts to test if Olaparib, a PARP inhibitor, will makes use of synthetic lethality by taking advantage of faulty DNA repair mechanisms in RTS patients with osteosarcoma that possess mutant RECQL4. We hypothesize Olaparib will kill the RTS osteoblasts but not the healthy cells, resulting in a potential treatment for osteosarcoma.

Wilhelm (Wil) Salmen
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.

Jamie Wright
Medical Scientist Training Program, Neurosciences Graduate Program, University of Texas Health Science Center - Houston
Primary Mentor: Dr. Diana Milewicz, Internal Medicine (UTH)
Secondary Mentor: Dr. Yang Xia, Biochemistry and Molecular Biology (UTH)
Role of ATR cell cycle regulation in occlusive vascular disease pathogenesis in MOPDII
Majewski Osteodysplastic Primordial Dwarfism Type II (MOPDII) is a rare autosomal recessive disorder caused by biallelic loss of function mutations in the gene encoding the centrosome protein pericentrin, PCNT. These individuals have a striking phenotype from severe pre- and post-natal growth restriction, but the main cause of morbidity and mortality is due to early-onset vascular occlusive disease. Among its many roles, pericentrin is involved in the ataxia telangiectasia and rad3 related (ATR)-dependent DNA damage checkpoint signaling pathway. I am using an inducible, smooth muscle cell-specific pericentrin knock-out mouse line to evaluate the hypothesis that the occlusive vascular disease seen in MOPDII patients is due to alterations in vascular smooth muscle cell (vSMC) proliferation resulting from dysregulation of the ATR-Chk1 pathway in response to cell stress, and that this pathway may in turn be targeted to prevent hyperproliferation of vSMCs in these patients. The goal of these studies is to identify pharmacologic inhibitors to target the ATR-Chk1 pathway in order to rescue the hyperproliferative vSMC phenotype and prevent vascular occlusive disease development in these patients.

Cohort 1, Appointed December 1, 2016 – November 30, 2018

Cameron Brown
Pharmacology, Baylor College of Medicine
Primary Mentor: Timothy Palzkill, Pharmacology (BCM)
Secondary Mentor: Martin Matzuk, Pathology & Immunology (BCM)
Characterizing mutations of CTX-M-14 found in clinical isolates and designing small molecules to inhibit antibiotic resistance.
β-lactam are the most prescribed class of antibiotics, and the most common mechanism of resistance is through the production of β-lactamase enzymes. One class of β-lactamases, CTX-M, confers high levels of resistance to cephalosporins, and there are more than 140 variants isolated in the clinics. My project aims to characterize many of the naturally occurring mutation found in these variants, as well as use DNA-encoded libraries and fragment based drug discovery to identify inhibitors.

Elizabeth Campbell
Biochemistry and Molecular Biology, Baylor College of Medicine
Primary Mentor: Trey Westbrook, Molecular & Human Genetics (BCM)
Secondary Mentor: Damian Young, Pharmacology (BCM); Adjunct in Chemistry (Rice Univ)
Developing Spliceosome Inhibitors as a New Therapeutic Class for Myc-Driven Cancers
Our lab has discovered that Myc-driven TNBCs are sensitive to partial inhibition of RNAprocessing machinery including the spliceosome while normal cells are not. Small molecules targetingthe spliceosome have entered clinical trials, opening this avenue of therapy to further development. Myproject is aimed at furthering the utilization of spliceosome inhibition as a targeted therapy for TNBCs. I will identify genes that control the response of cancers to spliceosome inhibition in order to nominate predictors of patient response and delineate pathways of resistance. I will also identify additional molecules that inhibit the activity of the spliceosome that can be developed into therapeutics. Successful completion of this work will further spliceosome inhibition as a therapeutic strategy against TNBCs and other cancers.

Nicholas Hummell
BioSciences, Rice University
Primary Mentor: Natasha Kirienko, BioSciences (Rice Univ)
Secondary Mentor: Damian Young, Pharmacology (BCM); Adjunct in Chemistry (Rice Univ)
Tertiary Mentor: Laura Segatori, Chemical & Biomolecular Engineering, BioSciences (Rice Univ)
Characterization of Protein Aggregate Inhibitor LK16
Neurodegenerative diseases pose a huge problem upon aging populations in developed countries. Many of these diseases share a common characteristic of abnormal protein aggregation which is hypothesized to be linked to their pathogenesis. We have discovered an uncharacterized small molecule, LK16, which aids in the prevention of heat induced protein aggregates. My project is focused on finding a mechanism of action for this aggregate prevention as well as determining its efficacy in preventing neurodegenerative related phenotypes using C. elegans as a model.

Daniel Konecki
Structural & Computational Biology & Molec Biophysics (SCBMB), Baylor College of Medicine
Primary Mentor: Olivier Lichtarge, Molecular & Human Genetics (BCM)
Secondary Mentor: Devika Subramanian, Computer Science; Electrical Engineering (Rice U)
Drug Repurposing Based On Multi-modal Biological Networks: Whole Exome Sequencing for Prediction of Personalized Chemotherapy
A major barrier to the development of precision medicine for the treatment of cancer, and many other diseases, is the slow process for developing drugs and bringing them to market. This project seeks to address this issue by automating the process of drug repurposing, treating a disease using drugs which are already approved to treat another disease, which could drastically increase the number of drugs available to treat diseases in a much shorter time frame. In pursuit of this goal we are constructing multimodal networks of associations

between proteins, drugs, and diseases, to which we can apply reasoning algorithms to predict drugs based on a patients diagnosis and available genetic data. To develop this method we will use the mutations present in cell lines stored in the Cancer Cell Line Encyclopedia and evaluate the drugs predicted to treat them using screening data stored in the Genomics of Drug Sensitivity in Cancer database. Using standard of care drugs and successful drug predictions, we will generate multi-drug combinations to target as many affected cellular functions as possible, in an effort to treat cancer cell lines most effectively.

Doris Taylor
Biochemistry and Molecular Biology, Baylor College of Medicine
Primary Mentor: Timothy Palzkill, Pharmacology (BCM)
Secondary Mentor: BVV Prasad, Biochemistry & Molecular Biology (BCM)
Mechanistic Characterization of OXA-48 β-lactamase Mediated Hydrolysis of Antibiotics and Discovery of Inhibitors

β-lactam antibiotics are the most prescribed worldwide and have revolutionized treatment of bacterial infection, but they are susceptible to hydrolysis by bacterial enzymes called β-lactamases. OXA-48 is a β-lactamase that confers resistance to carbapenems, the last resort β-lactam antibiotics, and has dispersed globally.

To better characterize the mechanism by which OXA-48 hydrolyzes different β-lactam antibiotics, I will create individual alanine mutants of residues implicated in catalysis, study their ability to hydrolyze various antibiotics and their structure to understand how substitution of a given residue affects the enzyme's function and structure. This will help elucidate the role of each of these residues in catalysis. To potentially find an inhibitor for OXA-48, I will be performing drug discovery using DNA-encoded library technology to screen for potential inhibitors that could block the action of OXA-48 and thus restore effectiveness to antibiotics that OXA-48 would typically hydrolyze.

Elia Lopez *(Appointed June 1, 2017 – May 31, 2019)*
Integrated Biology and Pharmacology, University of Texas Health Science Center - Houston
Primary Mentor: Carmen Dessauer, Integrated Biology and Pharmacology (UT Health)
Secondary Mentor: Edgar T. Walters, Integrated Biology and Pharmacology (UT Health)
Targeting cooperative cAMP-ERK signaling in nociceptors to reduce persistent pain

Chronic neuropathic pain is caused by damage to the nervous system, lasts long after the initial insult, and is particularly resistant to treatment. Neuropathic pain after spinal cord injury (SCI) depends upon persistent inflammatory responses. Two cell signaling pathways that are important for promoting electrical activity in nociceptive sensory neurons (nociceptors) are the extracellular signal-regulated kinase (ERK, activated by many cytokines) and cyclic adenosine monophosphate (cAMP, stimulated by important prostaglandins) pathways. The goal of this project is to determine whether combining inhibition of ERK signaling with inhibition of cAMP signaling provides a more effective treatment for chronic pain after SCI than either treatment alone. To identify potential drug targets for better treatment of chronic pain, I will test specific hypotheses about cooperative interactions between cAMP pathways and ERK pathways driven by prostaglandins and cytokines, respectively, that maintain persistent nociceptor hyperactivity after SCI and thereby drive chronic pain.