Training in Precision Environmental Health Sciences (TPEHS)

Program Director:
Cheryl Walker, PhD, Director, Center for Precision Environmental Health, Professor, Molecular & Cell Biology, and Medicine, Baylor College of Medicine

Program Co-Directors:
Richard Finnell, PhD, Professor, Center for Precision Environmental Health, Baylor College of Medicine;
Daniel Gorelick, PhD, Associate Professor, Cellular & Molecular Biology, Baylor College of Medicine.
Craig Hanis, PhD, Professor, Epidemiology Human Genetics & Environmental Sciences, and Human Genetics Center, School of Public Health, UT Health Science Center at Houston: and
Rui Chen, PhD, Professor, Molecular and Human Genetics, Baylor College of Medicine

http://www.gulfcoastconsortia.org/home/training/training-in-precision-environmental-health-sciences-tpehs/

Meet the TPEHS Trainees

The following trainees are supported by T32ES01781, an NIEHS T32 program:

Rachel Keuls
Appointed: July 1, 2021 – June 30, 2023 (Grant year 05)
Department of Development, Disease Models and Therapeutics, Baylor College of Medicine
Primary Mentor: Dr. Ronald Parchem, Molecular and Cell Biology, BCM
Secondary Mentor: Dr. Richard Finnell, CPEHS, BCM
MicroRNAs regulate maternal-fetal nutrient exchange during neural tube closure
Neural tube closure is the first step in central nervous system formation that begins early during embryonic development before the placenta and embryonic vasculature are established. Many neural tube closure defects (NTDs) are lethal, but even if the fetus survives, lifelong disability results. Approximately 300-500 babies are born each day with an NTD. NTDs are of complex etiology resulting from both environmental and genetic factors. Neural tube closure requires a precise input of a variety of metabolites, such as folic acid, glucose, and lipids. How metabolic pathways are regulated to ensure neural tube closure is not well understood. During neural tube closure, the yolk sac serves as the primary site of maternal-fetal nutrient exchange. Previously it has been demonstrated that microRNA mediated gene silencing is required for neural tube closure, yolk sac formation, and proper embryonic metabolism. My research aims to understand how microRNAs promote the proper uptake and processing of nutrients within the yolk sac and the embryo to ensure neural tube closure. This work will reveal mechanisms that could be used to prevent or correct neural tube closure defects in-utero.

Gabriel Tukeman
Appointed: July 1, 2021 – June 30, 2023 (Grant year 05)
Department of Molecular and Cellular Biology, Baylor College of Medicine
Primary Mentor: Dr. Richard Finnell, CPEHS, BCM
Secondary Mentor: Dr. Daniel Gorelick, MCB, BCM
Cellular response to HIV integrase inhibitor dolutegravir with varying folate status
Dolutegravir (DTG) is a medication use in the treatment and management of Human Immunodeficiency Virus (HIV). It is the number one recommended treatment of HIV by the World Health Organization, regardless of age and sex. In 2018, DTG was flagged as a potential factor that could result in neural tube defects (NTDs) when taken at the onset of pregnancy. Post- market surveillance studies in Botswana as of 2020 have shown that mothers taking dolutegravir from the beginning of their pregnancy were twice as likely to have a pregnancy resulting in an NTD birth defect. DTG has previously been shown as a partial antagonist to folate receptor 1, and folate supplementation is a long known modifier to against NTD risk. My project aims to study cellular response to DTG in natural and synthetic folate environments and identify potential mechanisms leading to increased NTD risk. I will utilize primary mouse embryonic fibroblasts harvested from wildtype, FOLR1$^{+/-}$, and FOLR1$^{-/-}$ embryos and treat with step-wise concentrations of DTG supplemented with either natural 5-methyl-tetrahydrofolate (5-MTHF) or synthetic folic acid. I will then stain and visualize cells for structural changes as well as look at changes in the transcriptome and methylome between conditions. These experiments will reveal processes impaired with the addition of DTG and if such impairment can be rescued with additional folic acid or 5-MTHF.

Georg Otto Milan Bobkov, PhD
Appointed: July 1, 2022 – June 30, 2023 (Grant year 05)
Department of Molecular and Human Genetics, Baylor College of Medicine
Primary Mentor: Dr. Chonghui Cheng, Molecular and Human Genetics, BCM
Secondary Mentor: Dr. Zheng Sun, Molecular and Cellular Biology, BCM
The effect of arsenic exposure on clustering of circulating tumor cells in TNBC
Breast cancer (BC), if recognized early, is largely curable. This drastically changes, however, if the tumor has already spread to non-breast tissues. Spreading is most prevalent in triple-negative breast cancer (TNBC) and occurs via a process called metastasis. Metastases originate from so called circulating tumor cells (CTCs), which are cells that detach from the primary tumor to migrate to distant organs. The likelihood of CTCs to successfully establish a metastasis is greatly increased if those CTCs travel as a cluster and not as single cells. We have recently discovered a new TNBC CTC clustering mechanism, which is based on the extracellular macromolecule Hyaluronic Acid (HA). Interestingly, HA Synthase 2 (HAS2), the major producer of HA, can be upregulated via a signaling pathway that is also altered by inorganic arsenic. Inorganic arsenic is the most significant chemical contaminant in drinking-water and can context-dependent both promote and prevent cancer. I will investigate whether the inorganic arsenic compound arsenic trioxide (ATO) indeed increases HAS2 expression, thereby promoting HA-dependent CTC clustering and ultimately TNBC metastasis. I will further perform an inhibitor screen to identify compounds that reduce HA production. I will also combine both approaches to investigate whether the identified inhibitors can revert the ATO-mediated phenotype. This will pave the way for potential anti-clustering treatments in TNBC and provide crucial information whether drug delivery agents should be developed to adapt ATO, which is used for the treatment of acute promyeloitic leukemia, as a treatment option for other cancers.

Danielle Gonzales, MD
Appointed: June 1, 2021 – May 31, 2023 (Grant year 04)
Department of Clinical Fellow- Section of Neonatology, Baylor College of Medicine
Primary Mentor: Dr. Bhagavatula Moorthy, Molecular and Cell Biology, BCM
Secondary Mentor: Dr. Abiodun Oluyomi, Epidemiology and Population Sciences, Department of Medicine, BCM
Prenatal Exposure to Heavy Metals in Living Proximity to Superfund Sites and Associated Maternal and Neonatal Complications
Preterm birth has been a source of research for decades. Harris county, Texas has a preterm birth rate that is higher than the national average. Many factors contribute to

preterm birth, including maternal health complications. Certain heavy metals have been associated with an increased risk of preterm birth and pre-eclampsia but there are many others that remain to be studied. In addition, Superfund sites have been known to have many contaminants of concern, including heavy metals, but their impact on preterm birth and maternal complications have not been studied. A biospecimen suppository will be used to measure heavy metal levels in cord blood samples in two cohorts of women based on living proximity to Superfund sites. Further, using geospatial analysis, distribution of those who experience preterm birth and certain maternal complications, such as pre-eclampsia, will be analyzed in relation to the environmental hazard.

Joshua Marcus, PhD
Appointed: January 1, 2022 – December 31, 2022 (Grant year 04)
Department of Molecular and Cellular Biology, Baylor College of Medicine
Primary Mentor: Dr. Jason Lee, MCB, BCM
Secondary Mentor: Dr. Daniel Gorelick, MCB, BCM
Mechanisms of stress granule quality control by the endoplasmic reticulum in response to arsenite exposure
Exposure to environmental contaminants disrupts normal physiological processes and negatively impacts human health. Cells respond to adverse environmental changes, such as arsenic exposure, through a program called the integrated stress response (ISR). One function of the ISR is to conserve energy by inhibiting bulk protein synthesis and sequestering mRNAs into inducible membrane-less organelles called stress granules. Membrane-less organelles are a new class of cellular compartments that allow the separation of biomolecules without the need of a surrounding membrane. Stress granules form shortly after the onset of stress and disassemble after the stress has been cleared, but the quality control mechanisms that dictate the timing of these events remain unknown. Previous studies from the Lee Lab show that stress granules interact with the endoplasmic reticulum (ER). My initial experiments in the Lee Lab show that the timing of stress granule disassembly can be altered simply by changing ER morphology, suggesting that a specific domain of the ER plays a role in stress granule quality control. Understanding the mechanisms of these inducible organelles is crucial because defects in stress granule dynamics have been linked to neurodegenerative diseases such as amyotrophic lateral sclerosis, frontotemporal dementia, and Alzheimer's disease. My project will investigate inter-organelle contact sites between the ER and stress granules to elucidate the mechanisms of stress granule quality control. These studies will provide new insights into how membrane-bound organelles interact with membrane-less organelles to compartmentalize the cytoplasm in health and disease.

Kenneth Andrew Trimmer, PhD
Appointed: May 1, 2022 – April 30, 2023 (Grant year 04)
Department of Genetics, the University of Texas MD Anderson Cancer Center
Primary Mentor: Dr. Swathi Arur, Genetics, MDACC
Secondary Mentor: Dr. Cheryl Walker, Center for Precision Environmental Health, BCM
Regulation of C. elegans germline stem cells by environmental cues
While accurate development of germ cells is integral to the propagation of many species, this process requires energy and nutrients to complete successfully, leaving germ cells susceptible to environmental conditions such as starvation. To counteract inaccurate germ cell development in these situations, many organisms have developed ways to arrest germ cell development while there are insufficient nutrients, such as in C. elegans. During C. elegans oogenesis, when the animal encounters starvation, its germline stem cells will stop dividing, though the specific environmental cues which initiate this as well as the consequences of its improper regulation are still unknown. This response is due to the activation of a cell cycle checkpoint at G2 which we find is initiated by Insulin and TOR signaling. Using mutant backgrounds which increase or decrease the signaling in these pathways, we plan to modulate activation of this checkpoint to uncover the consequences of bypassing this checkpoint, the environmental cues which initiate this checkpoint, and the metabolic cues which indicate improper regulation of this checkpoint. Since many signaling pathways which control oogenesis, along with their functions, are conserved between C. elegans and mammals, this will give insight into an aspect of oogenesis which may be sensitive to nutrient availability in mammals as well.

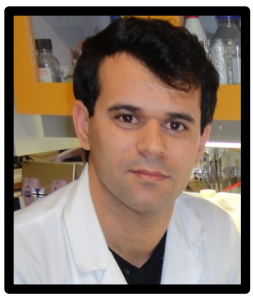
The following TPEHS trainees receive financial support from their home institutions:

Sofia Ivana Aramburu

Appointed: July 1, 2021 – June 30, 2023 (Grant year 05)
Program in Development Disease Models and Therapeutics, Baylor College of Medicine
Primary Mentor: Dr. Susan M. Rosenberg, MHG, BCM
Secondary Mentor: Dr. Cristian Coarfa, Molecular and Cellular Biology, BCM
Identifying human proteins that protect the cell from DNA damage
Cells are subject to an estimated 70000 DNA-damaging events every day, stemming from both internal and external sources. Although these events are usually repaired correctly, inefficient, or low-fidelity repair can lead to mutations. Mutation accumulation during aging causes loss of cellular function, thus increasing the risk of age-related diseases. Water bears and stress resistant organisms possess proteins that protect them from damage. We have identified human proteins with shared biochemical and structural properties and used DNA damage markers that show them to reduce DNA damage when over-produced in human cells. The goal of this project is to determine what kinds of DNA damage are reduced and how these proteins reduce damage. Moreover, because the ultimate goal of preventing DNA damage is reducing the accumulation of mutations in cells, we will measure whether mutations are decreased by the over-production of the protein candidates to identify those that can maintain a low number of mutations. This project will provide valuable insight into disease development and open the door to new potential disease prevention strategies.

Andi Liu

Appointed: November 1, 2021 – October 31, 2022 (Grant year 04)
Epidemiology, Human Genetics and Environmental Sciences (EHGES), The University of Texas Health Science Center - Houston
Primary Mentor: Dr. Zhongming Zhao, EHGES, UTHealth
Secondary Mentor: Dr. Xianglin Du, EHGES, UTHealth
Precision Subtyping of Alzheimer's Disease Mediated with Comorbidities Using Big Data and Integrative Omics Approaches
Alzheimer's disease (AD) is a common neurodegenerative disorder in the elderly, imposing a heavy burden on the healthcare system and community. However, the complicated manifestations and pathogenesis of AD are largely unknown, as they involve both genetic and environmental factors, such as comorbidities. Multiple dimensional molecular signals, multi-omics data, have been measured in post-mortem brain samples of AD and controls in large-scale cohorts. Thus, I aim to develop a novel statistical method to identify molecular subtypes and their genetic divers in AD by capturing heterogeneous molecular signals within multi-omics data. Moreover, environmental factors including common chronic conditions, such as diabetes, vascular events, hypertension, and hypercholesterolemia, have been reported to be associated with AD risk, which may act jointly with genetic factors to disrupt AD pathogenesis. I will explore the drugs that are associated with decreased risk of AD subtypes in the light of comorbidities management of AD utilizing the rich medical data.



Vahid Zadmajid, PhD

Appointed: July 1, 2021 – June 30, 2023 (Grant year 05)
Department of Molecular and Cellular Biology, Center for Precision Environmental Health (CPEH), Baylor College of Medicine
Primary Mentor: Dr. Daniel A Gorelick, Molecular and Cell Biology, CPEH, BCM
Secondary Mentor: Dr. Margot Kossmann Williams, Molecular and Cell Biology, CPEH, BCM
Endocrine disruption through membrane steroid receptors
Endocrine-disrupting chemicals (EDCs) are exogenous small molecules that mimic endogenous hormones and alter the functions of the endocrine system. EDCs alter endocrine functions by activating or inhibiting steroid hormone receptors. So far, the field has been focused on how EDCs bind to nuclear hormone receptors such as estrogen receptors alpha and beta. To date, data on EDC engagement with membrane steroid receptors, such as G protein-coupled estrogen receptor, is limited. Here, I hypothesize that EDCs act via membrane steroid receptors, in addition to previously defined nuclear steroid receptors, to

cause adverse effects on embryonic development. I will expose zebrafish embryos to multiple classes of EDCs (estrogens, progestins, androgens) and assay morphological phenotypes. I will then test whether the phenotype is rescued in zebrafish with mutations in the corresponding membrane steroid receptor versus nuclear steroid receptor. Results from this study will increase our understanding of the molecular and cellular mechanisms by which EDCs influence embryonic development.

The TPEHS program is Administered by the:

Gulf Coast Consortia
QUANTITATIVE BIOMEDICAL SCIENCES
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The GCC is a collaboration of:
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University of Texas Medical Branch at Galveston
University of Texas MD Anderson Cancer Center
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