Houston Area Molecular Biophysics Program (HAMBP) Training Program

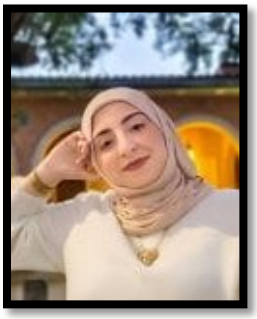
Grant No. T32 GM008280

Program Director: **Theodore Wensel**, PhD
Professor and Chair, Department of Biochemistry and Molecular Biology
Baylor College of Medicine

http://www.gulfcoastconsortia.org/home/training/molecular-biophysics-hambp/

Meet the Trainees

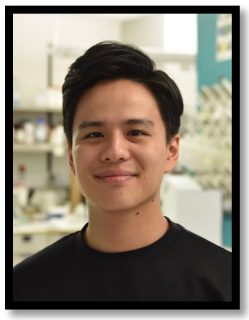
2023-2024



Sara Abouelniaj
Appointed August 1, 2022 – July 31, 2024
Department of Materials Science and NanoEngineering, Rice University
Primary Mentor: Dr. Yimo Han, Materials Science and NanoEngineering (RU)
Investigation of the Structural Dynamics of Voltage-Responsive Membrane Proteins
Biological membranes and their embedded proteins are of tremendous significance in modern biology and medicine, as they are encoded in approximately 30% of genes in most genomes and are the target of over 50% of FDA-approved drugs. Among them, transmembrane proteins are essential for the transport of ions and molecules in and out of the cells, making them of significant interest in cellular pathways and drug discovery. Voltage-gated ion channels (VGICs) are transmembrane proteins that activate in response to changes in the voltage (membrane potential), allowing specific ions to travel across these channels. Better study of the structure of these channels will be crucial in understanding the functionality and properties, which can be the target for developing drugs for mechanical pains, seizures, or cardiac arrhythmias. Though studies have been made, usual techniques disrupt the membrane potential by studying the VGIC only under its active state. Here, I propose to develop a voltage-gated nanodevice for cryogenic electron microscopy by using techniques from materials science, which will allow us to investigate the protein in its native electrical potential environment. This would enable us to gain new insights into the molecular mechanisms of these channels, allowing better understanding and utilization of the pore-opening, and ion-inductance mechanisms, which would potentially lead to new drug delivery methods by targeting the voltage sensors on these proteins. Not only that, but this will have a long-lasting impact on the research of all types of membrane proteins by providing protein structure in their native voltage potential.

Paula Bender
Appointed August 1, 2023 – July 31, 2024
Department of Biochemistry and Molecular Biology, University of Texas Health Science Center - Houston
Primary Mentor: Dr. Vasanthi Jayaraman, Biochemistry and Molecular Biology (UTH)
Subtype-Specific NMDA Receptor Function
The N-methyl-D-aspartate (NMDA) receptor is a calcium-permeable ionotropic glutamate receptor. NMDA receptors play an important role in excitatory neurotransmission in the central nervous system. The proper functioning of these receptors is critical for synaptic plasticity, learning, and memory formation. Their dysfunction has been implicated in various neurological diseases, such as Alzheimer's disease, epilepsy, and ischemic stroke. Thus, it is important to understand the mechanisms underlying NMDA receptor channel gating and activation to aid in developing novel pharmaceuticals targeting dysfunctional receptors. The NMDA receptor has several subtypes, each displaying different biophysical properties. My project will reveal the conformational and dynamic differences between these NMDA receptor subtypes to explain their variations in activation and desensitization. Additionally, I will investigate the mechanism of partial agonism, which activates NMDA receptors to a sub-maximal degree, and explore how this mechanism differs between NMDA receptor subtypes. Lastly, I aim to develop a novel multi-color fluorescence resonance energy transfer (smFRET) technique to investigate allosteric crosstalk between domains of the NMDA receptor and how this regulates receptor function.

Mandi Feinberg
Appointed July 1, 2021 – June 30, 2024
Department of Biochemistry, Cellular, and Molecular Biology - Molecular Biophysics Educational Track, University of Texas Medical Branch at Galveston
Primary Mentor: Dr. Kyung Choi, Biochemistry and Molecular Biology (UTMB)
Structure of West Nile virus RNA promoter, stem-loop A, and its interaction with viral polymerase NS5
West Nile virus (WNV) is the causative agent of West Nile fever in humans, an emerging infectious disease, and the most common mosquito-borne disease in the United States. WNV replication is dependent upon the presence of the stem loop A (SLA) structure in the 5' untranslated region (UTR) of the viral genomic RNA. The viral polymerase, non-structural protein 5 (NS5), interacts with the 5' SLA and initiates synthesis of the negative strand. My project aims to identify and understand how WNV NS5 interacts with SLA to initiate RNA synthesis by determining the structure of the SLA in its native state and bound to the viral polymerase.



Hanwen Feng
Appointed August 1, 2023 – July 31, 2024
Department of Chemical, Physical, and Structural Biology, Baylor College of Medicine
Primary Mentor: Dr. Zhao Wang, Biochemistry and Molecular Biology (BCM)
Structural Characterization of Fibrinogen-Bound Integrin αIIbβ3
Platelets are blood cells responsible for clotting and blood homeostasis. In platelets, integrin receptors are the central regulators for platelet activation, thus it is an important therapeutic target for anti-clotting drugs. When platelets flow through a vascular wound, their primary integrin, αIIbβ3, can become activated by binding with the extracellular ligand fibrinogen. This activation leads to platelets forming a plug to stop bleeding. However, the precise mechanisms of the interaction between αIIbβ3 and fibrinogen, as well as the cellular consequences of platelet activation upon binding, are currently not well understood. I will utilize single particle cryo-EM to solve the αIIbβ3-fibrinogen protein complex. Additionally, I will use cryo-electron tomography to determine platelet morphological changes.

Jordan Johnson
Appointed September 1, 2021 – August 31, 2024
Department of Biology and Biochemistry, University of Houston
Primary Mentor: Dr. Yuhong Wang, Biology and Biochemistry (UH)
Force Generation and Mechanism Elucidation of EF-Tu
Elongation factor thermal unstable (EF-Tu) is a bacterial enzyme that delivers aminoacyl-tRNAs to the ribosome during translation, however its mechanism is not well understood. My project will be observing the conformational changes of EF-Tu using FRET and determining if a power stroke is generated, similarly to other elongation factors, using Force Induced Remnant Magnetization Spectroscopy (FIRMS). I will also observe how mutations in the GTP binding pocket will affect EF-Tu's mechanism and function as mutations in EF-Tu have been linked to a variety of health issues and it is unknown how mutations contribute to the occurrence of these health issues.

Rebekah Rothacher
Appointed August 1, 2023 – July 31, 2024
Department of Chemical, Physical, and Structural Biology, Baylor College of Medicine
Primary Mentor: Dr. Anthony Mustoe, Biochemistry (BCM)
Investigating the role of mRNA structural dynamics in RNA binding protein recognition and subsequent regulation"
RNA binding proteins (RBP) play vital roles in myriad processes including stem cell differentiation, cell growth, and neurological functioning. RBPs can modulate the expression of target mRNAs via binding consensus motifs. The mechanism by which some RBPs differentially bind and induce various fates on their targets remains poorly characterized. RNAs typically fold into structural ensembles, existing in dynamic equilibrium between competing structures. The equilibrium of these ensembles can be perturbed by RBPs, shifting to favor a particular structural state. In addition, RBP recruitment is mediated by RNA structure within the 3´UTR. We hypothesize that both basal structure and structural remodeling play a role in RBP-mediated mRNA regulation. The goal of my project is to characterize the role of 3´UTR structure and structural remodeling in the differential effects that specific RBPs induce on their targets.

Savannah Seely
Appointed August 1, 2021 – July 31, 2024
Department of Biochemistry and Molecular Biology, The University of Texas Medical Branch
Primary Mentor: Dr. Matthieu Gagnon, Microbiology and Immunology (UTMB)
Investigating the Molecular Mechanism of Ribosome Recycling
In all organisms, the ribosome decodes mRNA and synthesizes proteins through four essential steps: initiation, elongation, termination, and recycling. Currently, more than 50% of clinically relevant antibiotics target the ribosome. Remarkably, the final step, recycling, is the least characterized and has not been exploited for structure-based drug design. Recycling is the necessary bridge between termination and initiation, and a better understanding of the molecular aspects of this step could lead to development of new therapeutics. I propose to determine the molecular mechanism of recycling in the human pathogen *Pseudomonas aeruginosa*, which employs a specialized Elongation Factor-G that functions exclusively in recycling. I will also investigate features within the ribosome that are involved in its disassembly by determining the structure of amikacin bound to the ribosome; an antibiotic that has been reported to cause recycling deficits. Taken together, I will determine at high resolution the mechanism of ribosome recycling by elucidating what ribosome features are altered as well as what molecular interactions occur between the ribosome and recycling factors. The anticipated results of these studies will improve our knowledge of this step-in translation and may open new doors for the development of antibiotics.

Justin Van Riper
Appointed August 1, 2022 – July 31, 2024
Department of Biochemistry and Cellular Biology, Baylor College of Medicine
Primary Mentor: Dr. Monica Pillon, Biochemistry and Cellular Biology (BCM)
Characterization of the FASTKD4 mitochondrial RNA binding protein
Mitochondrial homeostasis is critical for vital biological processes such as energy production. Mitochondrial plasticity is largely orchestrated by nucleic acid binding proteins tasked with regulating the mitochondrial genome, transcriptome, and proteome. While strict mitochondrial gene regulation is imperative to maintain ATP pools, little is known about the molecular mechanisms that govern mitochondrial gene regulation. FASTKD4 is a poorly characterized post-transcriptional regulator linked to precursor mitochondrial RNA maturation. I am mounting a biophysical and biochemical program aimed at elucidating FASTKD4 function and regulation in mitochondrial RNA processing.

The HAMBP program is Administered by the:

Gulf Coast Consortia
QUANTITATIVE BIOMEDICAL SCIENCES

www.gulfcoastconsortia.org
Questions: Contact Elizabeth Lawrence
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The GCC is a collaboration of:
Rice University
Baylor College of Medicine
University of Houston
University of Texas Health Science Center at Houston
University of Texas Medical Branch at Galveston
University of Texas MD Anderson Cancer Center
Institute of Biosciences & Technology at Texas A&M Health Science Center
Houston Methodist Research Institute