



National Institute of  
General Medical Sciences



# Houston Area Molecular Biophysics Program (HAMBP) Training Grant

Grant No. T32 GM008280

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

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

## Meet the Trainees

Currently appointed: Fall 2018 – Fall 2019



### J. Michael Bell

Quantitative and Computational Biosciences, Baylor College of Medicine

**Primary Mentor**: Dr. Steven Ludtke, Biochemistry (BCM)

***Examining the structural variability and formation of nanodiscs via electron cryomicroscopy***

My research combines biophysical studies of protein-lipid interactions with computational image processing of electron cryomicroscopy (cryoEM) data. In the wet lab, I am exploring the formation and structural variability of reconstituted nanodiscs, which are modeled after high-density lipoprotein (HDL) and used to study membrane proteins in their native environment. In the dry lab, I am developing new approaches to correct for specimen motion by aligning sequential images acquired at high speed by direct detection devices (DDD). Additionally, I am exploring the influence of thickness-related electron absorption on three-dimensional electron cryotomography (cryoET) data and designing strategies to correct it.



### David Boragine

Biochemistry and Molecular Biology, Baylor College of Medicine

**Primary Mentor**: Dr. Timothy Palzkill, Pharmacology (BCM)

***Optimization of the BLIP-II Interaction with PBP2a as a Protein Based Therapeutic Option for MRSA***

Methicillin-resistant *Staphylococcus aureus* (MRSA) confers resistance to the commonly prescribed  $\beta$ -lactam antibiotics through acquiring the novel penicillin-binding-protein (PBP2a), thus causing a rapidly growing global health crisis. Previously, our lab has discovered that  $\beta$ -lactamase inhibitory protein II (BLIP-II) can bind and inhibit PBP2a, albeit weakly. However, the binding affinity between BLIP-II/PBP2a can be enhanced through a directed evolution approach to find a tighter binding BLIP-II variant in efforts to solve the first BLIP-II/PBP2a co-crystal structure. My project will focus on optimizing the BLIP-II/PBP2a binding interaction in order to further elucidate the binding mechanism via X-ray crystallography and to determine the effect of BLIP-II on  $\beta$ -lactam efficacy versus MRSA bacteria. Overall, this work has the potential to aid drug discovery by serving as a promising foundation for developing a potential protein based therapeutic option, or a diagnostic tool, for clinical use.



**Miriam Gavriliuc**

Biology and Biochemistry, [University of Houston](#)

**Primary Mentor:** Dr. Yuhong Wang, Biology and Biochemistry (Univ of Houston)

***Measuring the Mechanical Forces During Ribosome Translocation via Elongation Factor G Crosslinking***

Elongation factor G (EF-G) is a bacterial protein that catalyzes the movement of the ribosome down the mRNA, however, this mechanism is not well understood. My project will focus on determining the role of EF-G in keeping the ribosome on the correct position of the mRNA by studying the force EF-G produces. Using internally crosslinked EF-G, I will be able to trap the protein in different stages of the translocation reaction and measure the force. To measure the force, I will use Force Induced Remnant Magnetization Spectroscopy (FIRMS), a technique developed by our lab.



**Andrei Gasic**

Physics, [University of Houston](#)

**Primary Mentor:** Dr. Margaret Cheung, Physics (Univ of Houston)

***Critical Phenomena in the Temperature-pressure-crowding Phase Diagram of a Large Protein***

My research aims to answer an important question at the interface of physics and biology: how does the crowded cellular environment influence the dynamics of a protein? Proteins are susceptible to small environmental agitations, yet stable enough to maintain structural integrity. These apparently competing behaviors are commonly exhibited by physical systems near a critical point, where distinct phases merge.

By varying temperature, pressure, and the amount of crowding from surrounding macromolecules, we are able to characterize the structural phases of a large protein, phosphoglycerate kinase (PGK), in a cellular environment. Using a combination of theory and computer simulation, I demonstrate a critical transition where several phases of PGK coexist. At the critical regime, we observe fluctuations that produce large conformational changes without a costly barrier, which would be necessary for enzymatic function.



**Douglas Litwin**

Biochemistry and Molecular Biology, [University of Texas Health Science Center - Houston](#)

**Primary Mentor:** Dr. Vasanthi Jayaraman, Biochemistry and Molecular Biology (UT Health)

***Modulation of glutamate receptors by auxiliary proteins and ions: a structural investigation***

The glutamate receptor family is responsible for the majority of excitatory neurotransmission in the central nervous system and comprises the AMPA, kainate and NMDA receptor subtypes. The kainate receptor subtype is of particular interest due to its function in both postsynaptic neurotransmitter reception and the presynaptic regulation of neurotransmitter release.

Additionally, kainate receptors have been shown to be functionally modulated by sodium ions (Na<sup>+</sup>) and auxiliary proteins (NETOs). These modulators contribute to the functional specificity of individual glutamatergic synaptic events; however, no data is available regarding the structural dynamics and conformational states involved in their modulation. The aim of this project is, therefore, to characterize the structural dynamics and conformational states involved in the modulation of kainate receptors by Na<sup>+</sup> and NETO proteins.



**Jonathan Mercado**

Molecular and Cellular Biology, [Baylor College of Medicine](#)

**Primary Mentor:** Dr. Francis T.F. Tsai, Biochemistry and Molecular Biology (BCM)

***Targeting Leishmania Hsp100 to abolish infective parasite stage differentiation***

*Leishmania* is the causative parasite of the vector-borne neglected tropical disease, Leishmaniasis. The activity of the *Leishmania* Hsp100 chaperone protein allows for the parasite to differentiate into its infective stage in humans. My project will provide insight into the potential use of small molecules for manipulating chaperone function. Identifying small molecules that interact with *L.mexicana* Hsp100 could then be used as chemical probes for future studies to understand Hsp100 activity (or lack thereof) during mammalian infections. The results of my work will be used to combat Leishmaniasis and other human infections caused by pathogenic microbes.



**Nabina Paudyal**

Biochemistry and Molecular Biology, University of Texas Health Science Center - Houston

**Primary Mentor:** Dr. Vasanthi Jayaraman, Biochemistry and Molecular Biology (UT Health)

***Understanding the allosteric mechanism in Kainate receptors by probing single molecule FRET and molecular dynamics simulation.***

Kainate receptors are ionotropic glutamate receptors involved in both pre-synaptic and post-synaptic neurotransmission. Very limited structural data is available for the full-length structure of kainate receptors and no structures are available for its auxiliary protein NETO that alters the biophysical property of the receptor. This resulted in the limited understanding of the mechanism underlying the extent of agonism on kainate receptor and also acquired gap of knowledge regarding modulation of kainate receptor by auxiliary subunits. We propose to address this using single molecule FRET and molecular dynamics simulation with the goal of gaining a comprehensive understanding of the modulation of the receptor gating mechanism and allosteric communication between the extracellular domains, transmembrane segments and intracellular domains due to agonists of varying efficacy and auxiliary proteins.



**Joshua Rosario-Sepulveda**

Quantitative and Computational Biosciences, Baylor College of Medicine

**Primary Mentor:** Dr. Theodore Wensel, Biochemistry and Molecular Biology (BCM)

**Secondary Mentor:** Dr. Zhao Wang, Biochemistry and Molecular Biology (BCM)

***Decoding the structural mechanisms behind metabotropic glutamate receptor functional selectivity***

Metabotropic glutamate receptors (mGluR) are GPCRs with a multitude of functions across the nervous system, key players in regulating neuronal excitability by modulating other ion channels in pre- and post-synaptic neurons. A key feature to understand how mGluRs regulate the activity of the receptor and direct disease phenotype lies in the concept of biased agonism. Modelling conformational plasticity is indispensable to comprehend the functional selectivity of agonists in activating a diversity of downstream pathways. I will attempt to reach near-atomic resolution of nanodisc-reconstituted mGluRs using cryo-electron microscopy. I will also aim to resolve the structure of several ligand-bound mGluRs along with pharmacological characterization, in order to discern the communication across domains.



**Matthew Ykema**

BioSciences, Rice University

**Primary Mentor:** Dr. Yizhi (Jane) Tao, BioSciences (Rice Univ)

***Characterizing Astrovirus Particles To Investigate The Mechanism Of Proteolytically-Mediated Viral Maturation***

Understanding the structure of viral capsid proteins allows for the determination of key infectious domains and targets for vaccines and anti-viral compounds. One target for structural studies is the human Astrovirus, a single-stranded RNA virus that causes gastroenteritis in children and immunocompromised individuals. The virus has a unique maturation process, in which the capsid must be proteolytically cleaved in order to induced host cell entry and exit. I aim to identify the structural changes of the capsid that occur during the proteolytically-mediated maturation using X-ray crystallography and cryo-electron microscopy.

The HAMBP program is Administered by the:



[www.gulfcoastconsortia.org](http://www.gulfcoastconsortia.org)

Questions: Contact Vanessa Herrera

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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*