Maximizing Access to Research Careers (MARC)

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	**Lillian Delacruz** Starving the malaria parasite: Physiological effects of PANK in mosquitoes with altered midgut insulin signaling University of Arizona, Molecular & Cellular Biology Mentor: Dr. Michael Riehle – Entomology **Abstract** Coenzyme A (CoA) is an essential cofactor in a variety of eukaryotic metabolic processes such as the tricarboxylic acid cycle and fatty acid oxidation. Pantothenate kinase (PANK) is a key regulatory enzyme in the five-step CoA biosynthetic pathway, catalyzing the initial rate-limiting step of CoA synthesis by phosphorylating pantothenate to 4'-phosphopantothenate. This step traps pantothenate within the cell's cytosol, consigning it fully to CoA synthesis. To carry out de novo CoA biosynthesis, *Plasmodium falciparum*, the most dangerous human malaria parasite, requires exogenous uptake of pantothenate from its *Anopheles stephensi* host. This parasite-vector relationship suggests *P. falciparum* must compete for and utilize host metabolites for CoA synthesis to facilitate its own development. Thus, an increase in PANK expression within the mosquito midgut may restrict the pantothenate available to the parasite and limit its development. To assess the role of PANK in mosquitoes, we measured its transcript and protein expression as well as its downstream effects with CoA assays in *P. falciparum* resistant transgenic *A. stephensi* lines in comparison to wildtype (WT) populations. We investigated expression levels in our MKP4, Akt and PTEN transgenic lines, which have midgut-specific manipulation of the insulin/insulin-like growth factor 1 signaling (IIS) that confers variable resistance against parasite development by targeting the cascade's role in innate immunity and lifespan.
	**Naya Ibrahim** Effects of Alpha-synuclein overexpression on song timing in a zebra finch model of Parkinson's disease University of Arizona, Neuroscience and Molecular & Cellular Biology Mentor: Dr. Julie Miller – Neuroscience **Abstract** Parkinson's disease (PD) is a neurodegenerative disease without a cure. Researchers have identified voice and speech problems during the early stages of the disease. During the later stages, limb motor symptoms are due to degeneration of dopaminergic neurons in the Substantia Nigra, which are accompanied by the appearance of aggregated alpha-synuclein protein (A-syn) within the basal ganglia. Whether aggregation of A-syn in the basal ganglia leads to vocal motor problems is not known. To model PD vocal symptoms, we use the zebra finch system because its song control circuit is similar to human

	speech circuits. I hypothesize that the aggregation of A-syn within basal ganglia regions is a neuropathological contributor to Parkinsonian speech symptoms, such as a slower speech rate. To test this hypothesis, a viral vector containing the human wildtype A-syn gene is injected into Area X, a song-dedicated basal ganglia region. Our preliminary data indicate that between one to two months post-injection, parkinsonian-like changes occur in song. To test for A-syn related neuropathology, levels of aggregated and soluble A-syn protein will be analyzed via immunoblotting. I will also quantify the amount of time the birds spend singing relative to levels of aggregated protein in Area X. The prediction is that increased A-syn aggregation leads to profound song deficits. Results will contribute to our understanding of the neuropathology of PD in regards to vocal deficits.
	**Christa Imrich** Biophysical Nature of Interactions between NS1 and Sp1 University of Arizona, Molecular and Cellular Biology Mentor: Dr. Nancy Horton – Molecular & Cellular Biology **Abstract** Human parvovirus B19 is a member of the family *Parvoviridae* and is pathogenic in humans. Common manifestations of B19V infection include hydrops fetalis, erythema infectiosum and rheumatoid arthritis with some cases of B19V infection leading to life-threatening conditions. Nonstructural protein 1 (NS1) of B19V plays a variety of roles throughout viral replication and has been shown to upregulate the function of the P6 promoter- the functional promoter in the viral genome. Human specificity protein 1 (Sp1) has been implicated in viral replication and has been shown to bind the P6 promoter, though its role has not been fully characterized in literature to date. The goal of this study is to elucidate information about potential biomolecular interactions between NS1 and Sp1. A series of affinity-based purification techniques were employed to obtain pure samples of glutathione s-transferase (GST)-tagged Sp1 and histidine and maltose binding protein (hMBP)-tagged NS1. To date, the purification of NS1 and Sp1 is ongoing, and the future direction will be to perform pull-down assays to detect the potential binding of these proteins. Determining the biophysical nature of interactions between these proteins, if any, could have implications in control of the viral P6 promoter and would further our understanding of viral infection.

Ryan Ochoa

Quantification of pulmonary vascular structure in the Sugen/Hypoxia mouse model of pulmonary hypertension

University of Arizona, Physiology
Mentor: Dr. Rebecca Vanderpool - Medicine

Abstract

Pulmonary arterial hypertension (PAH) is defined by an increase in mean pulmonary artery pressure, a low pulmonary capillary wedge pressure and increased pulmonary vascular resistance. Right ventricular (RV) function is the main determinant of mortality in patients with PAH. Available treatments slow the progression but not the reversal of pulmonary vascular remodeling. Mice exposed to a combination of Sugen and chronic hypoxia develop pulmonary hypertension. The aim of the study is to quantify the structural changes in the pulmonary vasculature in relation to right ventricular function in the Sugen/Hypoxia mouse model of pulmonary hypertension. Eight to 12 week old Mice were exposed to 4 weeks of Sugen/Hypoxia (n = xx) or normoxia (n = xx). Pulmonary and RV hemodynamics were measured using closed chest cardiac catheterization (Millar, Houston, TX). The lungs were then perfused with MicroFil (Flowtech, city) and imaged in the MicroCT (Siemens Inveon). Measurements of vascular volume, surface area and diameter were made from segmentations of the pulmonary vasculature (Slicer 3D and SimVascular). Differences between groups will be tested using Student T-tests and a $p < 0.05$ is considered significant. Results showed that in the pulmonary vasculature, a mouse with PAH has a volume of 21.92 mm^3 and surface area of 293.13 mm^2. Continuing the investigation of normoxia and hypoxia mice lungs will result in quantifiable differences between the arteries that could be of significance.

Daniela Ortiz

Nuclear EGFR Drives Epigenetic Dysregulation

University of Arizona, Biochemistry and Molecular & Cellular Biology
Mentor: Dr. Joyce Schroeder – Molecular & Cellular Biology

Abstract

The Epidermal Growth Factor Receptor (EGFR) is a receptor tyrosine kinase located at the basolateral membrane and is responsible for cell-signaling events. In cancer, however, it is often amplified throughout the whole membrane of a transformed cell. Intracellularly, EGFR takes a retrograde trafficking route that localizes it into the nucleus rather than being recycled or degraded. The glycoprotein Mucin 1 (MUC1) protects EGFR from lysosomal degradation and promotes its internalization to the nucleus. Nuclear EGFR is correlated with high levels of acetylated histones in the DNA. As previously

	established, MUC1 alters the interaction between EGFR and promoter regions that are transcriptionally active. The information leads us to **hypothesize that nuclear EGFR deregulates the transcription of Cyclin D1 (CCND1) epigenetically through direct contact with the CCND1 promoter.** Here, we tested the interaction between EGFR and the Cyclin D1 promoter under the influence of MUC1 and also tested by blocking retrograde trafficking. This experiment offers more comprehension on retrograde trafficking and further directions to studying nuclear EGFR's effects as a co-transcriptional factor.
	**Nicolai "Nic" Pena** Aberrant cap-dependent translation in TDP-43 model of ALS University of Arizona, Neuroscience and Biochemistry Mentor: Dr. Daniela Zarnescu – Molecular & Cellular Biology **Abstract** Amyotrophic lateral sclerosis (ALS), a progressive and fatal neurodegenerative disorder, primarily targets motor neurons. An overwhelming majority of brain and spinal tissue samples from ALS patients contain TAR DNA-binding protein-43 (TDP-43) aggregates. Many cellular processes have been studied in the context of TDP-43 pathology, including RNA metabolism. In particular, dysregulation of mRNA translation appears in several models of ALS. How TDP-43 could exert toxic effects on protein synthesis is not well understood. We investigated genetic interactions of TDP-43 with eukaryotic initiation factors (eIFs) in *Drosophila melanogaster*. Our experiments provide evidence of TDP-43 disrupting the initiation step of translation, possibly through interactions with eIFs. In-vivo locomotor assays highlight the relationship between translation initiation and TDP-43 toxicity. We show enhanced activity of eukaryotic initiation factor 4E binding protein (4EBP) worsened locomotor phenotypes in larvae expressing TDP-43. Furthermore, we directly tested translational activity through puromycin incorporation into nascent peptide chains. Preliminary data from Drosophila ventral nerve cord (VNC) and neuromuscular junction (NMJ) samples, as well as human lymphoblastoid cells, suggest reduced translation in our ALS models of TDP-43 proteinopathy. Finally, we are using non-canonical amino acid tagging (BONCAT/FUNCAT) to measure translation in-vivo. This approach will allow for identification of newly synthesized proteins with tandem MS, or in situ visualization of global translation.

Jocelyne Rivera
Red Blood-Cell Artificial Protein Hydrogels: Translating Protein Nanomechanics to Macroscale Materials
University of Arizona, Biomedical Engineering
Mentor: Dr. Minkyu Kim – Biomedical Engineering

Abstract

Researchers have been working to develop new strategies for treating cardiovascular diseases, the cause of death nationally and worldwide according to the National Institute of Health. Targeted drug delivery has been an important biomedical goal for several decades to avoid debilitating side effects. Herein, we offer new mechanisms for targeting cardiovascular disease by designing mechanosensitive artificial protein hydrogels that mimic the spring-like nanomechanics of ankyrin, a red blood cell cytoskeletal protein. Translating protein nanomechanics to macroscopic materials has been limited to date due to topological defects in polymer networks. In this study we developed triblock self-associating proteins that utilize the rigidity of NI6C, an ankyrin-repeat protein, to reduce topological defects, as well as improve crosslinking homogeneity and strengthen gelation kinetics. This design to control effective crosslinking in the polymer network is being investigated as a mean to improve the translation of NI6C nanomechanics to artificial protein hydrogels in order to develop mechanosensitive micro-gels that reversibly deform under high fluid shear stress. Responding to high fluid shear stress environments, indicative of atherosclerotic regions, the proposed micro-gel will deform for targeted drug delivery for patients suffering from cardiovascular diseases.