THE UNIVERSITY OF ARIZONA
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Undergraduate Research Opportunities Consortium

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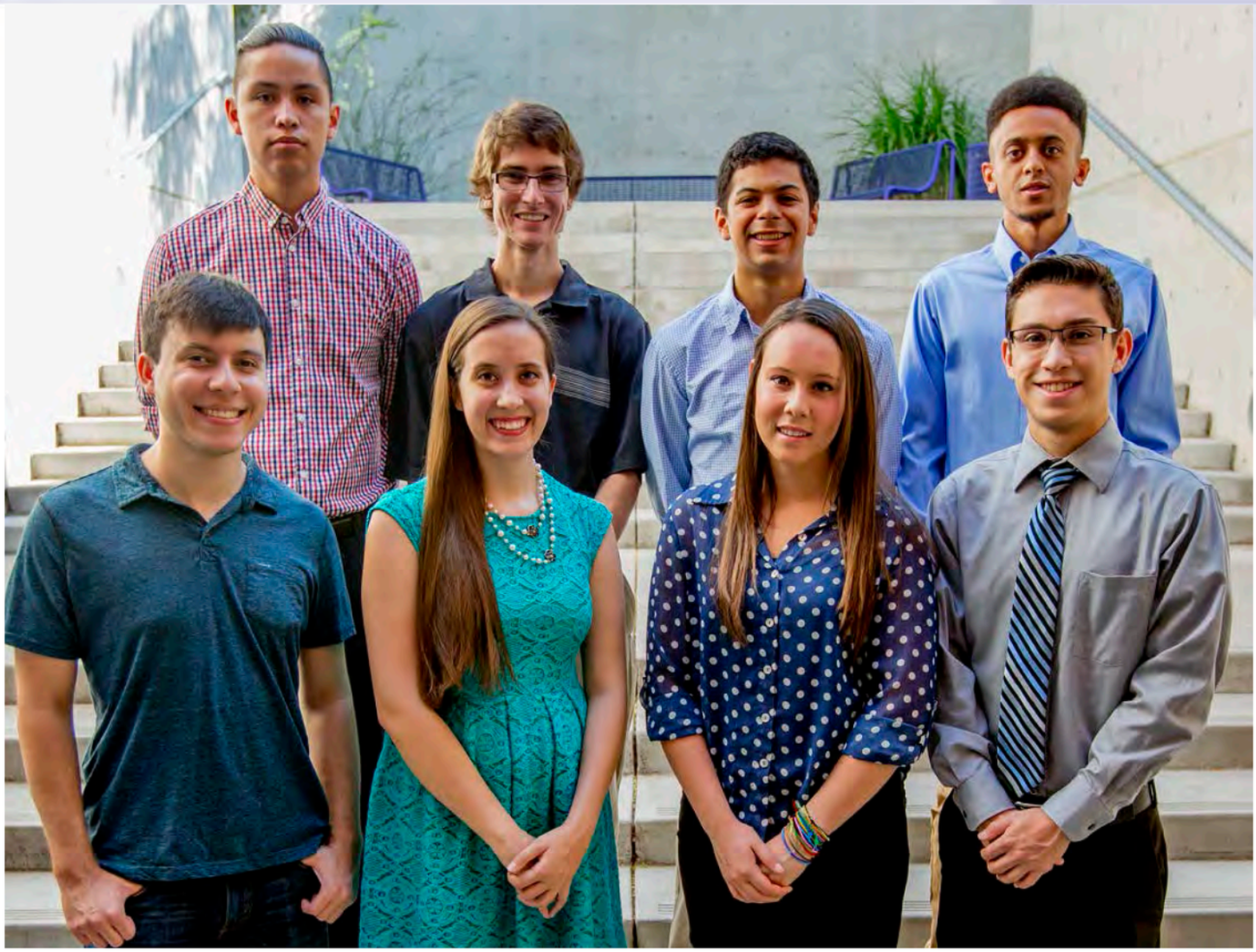
Abstract Review

August 2015



Maximizing Access to Research Careers

Primary Investigator: Megan McEvoy, PhD
Co-PI: Maria Teresa Vélez, PhD

Coordinator: Cindy Neal, MEd
Co-PI: Marc Tischler, PhD

This is a unique research, mentoring, financial, and academic opportunity for UA undergraduates belonging to a group considered underrepresented in biomedical research and who have interest and potential to pursue a career in this broad field. Benefits include training and financial support for the last two years of enrollment at UA. MARC Trainees from other schools are invited to participate in MHD, which meets jointly with the MARC program during the summer.

Katherine Marina Andersh

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PI: Dr. Carol Barnes

AGE-RELATED REVERSAL LEARNING IMPAIRMENTS IN BONNET MACAQUES

Abstract: For many years in neuroscience and psychology, non-human primates have been used as cognitive models due to the anatomical and functional similarities in memory structures with humans. It has been demonstrated that aged monkeys perform some, but not all cognitive tasks less proficiently than young monkeys. For example, young and aged monkeys are able to form object-pair associations equally well, but the ability to extinguish a learned association and acquire a new one is diminished in aged monkeys. The dynamics of learning and unlearning these associations remains unstudied since learning states are not inherently observable, but rather must be estimated through complex statistical means. In our study, bonnet macaque monkeys (Macaca radiata) were taught to associate a single object in a pair with a reward. After reaching a 90% criterion, the baited object in the pair was switched and the monkeys were required to learn this new rule. Using state-space statistical models to estimate learning curves, the differences in the ability of young and aged monkeys to form associations was studied. We hypothesized that younger monkeys would exhibit a higher level of cognitive flexibility in learning new rules. From the preliminary results, both aged and young animals require similar amounts of exposure to form the initial object-reward associations. After the rule switch, however, aged animals required more trials on any individual object pair to learn the novel association. These data indicate that aged animals are not impaired in the formation of associations, but rather are less flexible in breaking them.

Jeffry Carlos Granados

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PI: Dr. Mark Pagel

GOSSYPOL AS TREATMENT FOR IDIOPATHIC PULMONARY FIBROSIS USING ACIDOCEST MRI

Abstract: Idiopathic pulmonary fibrosis (IPF) is a disease of the lungs that affects over 200,000 people in the United States. Fibrous legions grow within the lungs as a result of myofibroblast differentiation. As of right now, the cause of the disease has yet to be determined, and thus, there is no cure for the condition. However, there has been a correlation between transforming growth factor beta (TGF-β) and lactate dehydrogenase (LDH) observed within IPF patients. Studies have yielded different results as to whether an increase in TGF-β leads to an increase in LDH or vice versa. Regardless, both of these are potential targets for therapy. Gossypol, which is known to inhibit LDH, has been shown, in vitro, to decrease myofibroblast differentiation. To determine whether Gossypol is an effective treatment, an imaging technique known as acidoCEST MRI was used. AcidoCEST MRI has the ability to measure the pH of lung lesions in an accurate and noninvasive manner, which is very important to anyone with a lung disease. It is predicted that Gossypol will decrease the size of the lesion and increase the pH of it, indicating metabolic stability. A mouse model was used for this experiment, in which all mice where intratracheally exposed to bleomycin to produce fibrous lesions in the lungs. Half were given Gossypol, and the other half were given a vehicle control. Positive results could translate to an effective treatment for those with IPF.

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PI: Dr. May Khanna

THE OPTIMIZATION OF THE EXPRESSION AND PURIFICATION OF YEAST RRP40

Abstract: Pontocerebellar hypoplasia type 1 (PCH1) is an autosomal recessive disease that affects the development of the brain. About half of all cases of PCH1 are caused by mutations in the EXOSC3 gene, resulting in the expression of a mutated EXOSC3 protein, a protein that is part of the RNA exosome complex. We hypothesize that these mutations may have a detrimental effect on the solution structure of EXOSC3. Since the solution structure of Rrp40 has been solved, mutations in the yeast homolog of EXOSC3, Rrp40 from S. cerevisiae, will be used in our study. Expression and attempted purification of Rrp40 have failed since the protein is predominantly found in inclusion bodies. Our attempts at solubilizing the protein away from inclusion bodies will be presented.

This work was funded by NIH MARC Training Grant T34 GM 08718.

Kyle Eric Lopez

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PI: Dr. William R. Montfort

DETERMINING NITRIC OXIDE-INDUCED CONFORMATIONAL CHANGES IN SOLUBLE GUANYLATE CYCLASE

Abstract: Nitric Oxide (NO) is a crucial signaling molecule involved in vasodilation and regulation of blood pressure. A key target for NO signaling is soluble guanylate cyclase (sGC), a heterodimeric protein that upon NO binding converts GTP to a secondary messenger, cGMP. NO binding at the ferrous heme of the beta subunit of the sGC dimer induces a conformational change in the protein resulting in increased production of cGMP. Attempts to regulate the enzymatic activity of sGC by various drugs treating cardiovascular disease are hindered by lack of information on the mechanism of this allosteric regulation and the structure of the protein. One of the methods that can provide a better understanding of conformational changes in sGC is lanthanide-based resonance energy transfer (LRET). This technique monitors luminescence of terbium ion (Tb3+) bound to a lanthanide-binding tag (LBT) inserted into a protein sequence. We have designed several sGC constructs with the LBT tag at different locations in the protein in addition to 6His-tag, which can bind transition metals and quench luminescence of the LBT-bound Tb3+. Rates for Tb3+ luminescence decay upon quenching by Cu2+ bound to the 6His-tag were used to calculate the distance between the metal ions using the Förster equation. Our preliminary conclusions from the LRET experiments are: (i) Tb luminescence decays with a bi-exponential time course and a rate constant for the slow phase of ~2.3 ms, (ii) significant quenching of Tb luminescence is observed in the presence of millimolar concentrations of Cu2+, (iii) a calculated distance of ~23 Å between Tb and Cu ions in construct NT19_LBT2 suggests the C and N termini lie close to one another in the protein.

Elise Noelle Munoz

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A NOVEL DROSOPHILA MODEL OF ALS BASED ON PROFILIN 1

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder, leading to death of patients usually within 2-5 years of diagnosis. Rare mutations in the profilin 1 gene PFN1 cause 1-2% of familial ALS, however the mechanism of pathology remains unknown. Profilin 1 is a well-studied actin-binding protein linked to multiple cellular processes. Efforts towards developing animal models of ALS based on profilin 1 have been made in yeast and Drosophila. Here we describe a Drosophila ALS model based on the expression of human wild-type profilin 1, ALS-linked C71G mutant profilin 1, and synthetic mutant H120E profilin 1 in motor neurons. Recently, profilin 1 was shown to associate with RNA stress granules, a hallmark of ALS pathology. Since TAR DNA-binding protein (TDP-43) is a pathological marker of ALS associated with stress granules, we hypothesize that profilin 1 and TDP-43 may function together in vivo. To test this, we have performed genetic interactions between profilin 1 variants and human TDP-43 variants. We utilized the Gal4/UAS system to express the proteins of interest specifically in photoreceptor or motor neurons. A larval turning assay showed a decrease in locomotor function in C71G mutant profilin 1 and H120E mutant profilin 1 compared to controls. Overexpression of wild-type, C71G, and H120E proflin 1 in the eye resulted in a suppression of neurodegeneration caused by overexpression of wild-type and mutant TDP-43. This novel Drosophila model affords the tools to studying the mechanisms behind ALS pathogenesis caused by profilin 1 mutations and their link to RNA stress granules.

Eric Alexander Simental

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PI: Dr. Peter Cotty

NUCLEAR ACTIVITY IN A. FLAVUS MAY ALLOW FOR AUXOTROPHIC COMPLEMENTATION AGAINST STRONG BARRIERS TO GENE FLOW

Abstract: Filamentous fungi, including A. flavus, have a self/non-self recognition system that limits gene flow among dissimilar individuals. Vegetative compatibility groups (VCGs) in A. flavus are determined with functional assays in which complementation of paired nitrate non-utilizing mutants is dependent upon identity at multiple polyallelic het loci. Mat loci are known to function as het loci and to independently serve as barriers to gene flow. Certain VCGs of A. flavus defined by laboratory assays contain both mat loci. Population analyses suggest gene flow does not occur in nature between members of the same laboratory defined VCG. The current study seeks to characterize nuclear behavior during complementation of auxotrophic mutants to test mechanisms through which mat loci differences prevent gene flow in populations, but allow auxotroph complementation in culture. We developed methodologies for random mutagenesis to generate 5-flouro-orotic acid resistant pyrG mutants of both wild-type and nitrate non-utilizing A. flavus strains within the YV150 VCG. A DNA construct is being designed that replaces the pyrG gene, thus restoring 5-flouro-orotic acid sensitivity, and fluorescent tags that localize to the nuclear membrane. Nuclear behavior during complementation, visualized using fluorescence, will be observed during complementation of isolates of different mating type. In doing so, we hope to find undescribed nuclear behavior that allows for auxotrophic complementation against strong barriers to gene flow. Understanding gene flow among closely related Aspergilli may allow for the design of superior atoxigenic strain biocontrol agents for long-term stable reductions in the aflatoxin content of foods.

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MODIFYING PLASMON RESONANT LIPOSOMES TO BE TARGET SPECIFIC TO MOLECULAR MARKERS LOCATED IN CELL MEMBRANES

Abstract: Gold-coated liposomes uniquely combine liposome's ability to encapsulate and deliver contents with sensitivity to near-infrared wavelengths, characteristic of plasmon resonance observed in nanoparticles of gold. Resulting near-infrared induced content release, optical trapping, photothermal laser ablation may find many biomedical applications. However, these gold-coated liposomes do not have ability to target biological markers present in cells, important in diagnostic and treatment modalities.

Here we examine whether gold coated liposomes are amenable to certain covalent modifications so targeting molecules, such as antibodies, can be attached. We hypothesize that the liposomes can be modified to support formation of gold coating and formation of covalent bonds without loss of plasmon resonance properties. In this project, lipid composition is first modified to include a fraction of lipid carrying a functional group, distearyl phosphatidylethanolamine -polyethylene glycol 2000-carboxylic acid. Then, formation of a covalent attachment is tested using fluorescein-5-thiosemicarbazide and carbodiimide chemistry. Finally, using same synthetic method, we test attachment of an antibody to these modified gold-coated liposomes.

Fully developed, this technology will allow for targeted delivery of therapies such as laser ablation or delivery and release of pharmaceutical contents. Therapies targeted to specific cells of interest will improve the overall efficacy of treatment and reduce side effects.

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Sponsors: University of Arizona; Graduate College; The Partnership for Native American Cancer Prevention (NACP) training program, a collaboration between Northern Arizona University and the University of Arizona Cancer Center, funded by the National Cancer Institute; College of Medicine – Office of Diversity and Inclusion, Health Resources and Services Administration (HRSA) Centers of Excellence; Western Alliance to Expand Student Opportunities (WAESO); Department of Physics.

MINORITY HEALTH DISPARITIES SUMMER RESEARCH PROGRAM (MHD)
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Sponsor: NIGMS/TWD Division GM 08718

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Sponsors: University of Washington/National Science Foundation (NSF). Funding for this research was provided by NSF Grant No. CHE-1156598.

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Sponsors: National Science Foundation (NSF) Engineering Research Center for Integrated Access Networks (ERC CIAN). Funding for this research was provided by the NSF Engineering Research Center No. EEC-0812072.

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