Distinguished Postbaccalaureate Scholars Program

2024 NIDDK Distinguished Postbaccalaureate Scholars Program Investigators

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Daniel H. Appella, PhD
Synthetic Bioactive Molecules Section, Laboratory of Bioorganic Chemistry, NIDDK, NIH

Keywords: Peptide Nucleic Acid, Thyclotide, Nanoparticles, Nucleic Acid Testing, HIV

Project Description:

Diagnostic testing of individuals for viral infection is essential to provide effective treatment and to prevent spreading the infection to others. There is an ongoing need to develop new methods to rapidly detect virus-derived nucleic acid sequences in a patient at the point-of-care. My lab is developing new types of molecules that can recognize and bind to DNA or RNA sequences that are associated with viruses, and we incorporate these molecules into microfluidic-based devices to study their ability to detect their target sequences. The molecules used in our work are called Peptide Nucleic Acids (PNAs). The chemical backbone of PNA consists of a synthetic polyamide, and attached to the backbone are the nucleic acids of DNA. We chemically synthesize PNAs in my lab. While PNA molecules do not exist naturally, a PNA with a distinct sequence of nucleobases will bind to a complementary DNA or RNA sequence following the same Watson-Crick hydrogen bond pairing that occurs in nature between complementary nucleic acids. My lab has developed a new method to incorporate cyclopentane rings into the PNA backbone to enhance the binding of PNA to its target nucleic acids, and we have made several cyclopentane-PNAs designed to target nucleic acid sequences of HIV-1. Recently, we have introduced tetrahydrofuran rings into the backbone to create a new class of molecules we call thyclotides. To construct a detection device prototype, we attach the PNA to the surface of a microfluidic channel and then flow a solution of a complementary nucleic acid sequence (DNA or RNA) through the channel (Figure 1). The PNA will bind to the target nucleic acid sequence, and prevent it from flowing through the exit of the channel. Once the target is retained in the channel, its presence can be detected using a combination of gold nanoparticles and silver solution. My lab is continuing to refine and improve this detection method and extend its applications.

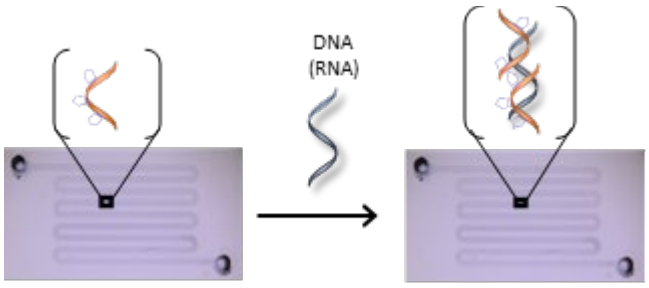


Figure 1. A cyclopentane PNA (orange strand) is attached to the surface of a microfluidic channel. When complementary DNA or RNA (blue strand) is flowed through the channel, a complex between the PNA and nucleic acid is formed which can then be detected.

Diversity Statement:

Encouraging and promoting diversity and inclusion across all genders, races, orientations, and ethnicities is critically important to promoting a healthy working environment within chemistry, biomedical research, and all scientific disciplines. Within my own lab, I strive to bring together a diverse group of individuals from different backgrounds, and I always encourage open discourse of scientific ideas as well as mutual respect between all individuals. My lab encompasses a wide range of scientific disciplines, including organic chemistry, nucleic acid biochemistry, and microfluidic engineering. We highly value the diversity of everyone's background to contribute to advancing our scientific research.

Leslie J Baier, PhD
Diabetes Molecular Genetics Section, Phoenix Epidemiology and Clinical Research Branch

Keywords: human genomes, induced pluripotent stem cells, type 2 diabetes, Indigenous populations, health disparities

Project Description:
The prevalence of type 2 diabetes and obesity varies by ethnicity. While different ethnic groups often undergo different environmental/lifestyle exposures, previous studies have shown that genetics has an important role in determining risk for these diseases. Our group has been determining which genes contribute to type 2 diabetes and obesity in an Indigenous population isolate living near Phoenix Arizona, who suffer from a particularly high prevalence of these diseases. Prior genetic studies across diverse ethnic groups have shown that both type 2 diabetes and obesity are very polygenic (hundreds of different DNA variants have been demonstrated to increase risk); many of these variants increase risk in all ethnic groups while others are ethnic specific. Our group has identified several DNA variants that uniquely affect risk for type 2 diabetes and/or obesity in our Indigenous population (N=8000 participants) and our current goal is to understand how these novel variants function within a cell to ultimately affect metabolic pathways that underlie these diseases. Some of our studies use *in vitro* model systems where we determine whether a disease risk DNA variant affects expression of a specific gene or alters protein structure. However, we also created a model system using induced pluripotent stem cells (iPSCs) that are differentiated into pancreatic beta cells to study *in vivo* how a variant affects development of beta cells which produce and secret insulin, a key hormone in diabetes. Once we understand how and when different genetic variants alter key metabolic pathways leading to type 2 diabetes, we assess various drugs to determine if a specific drug can be identified that can perform better in individuals who have a specific genetic variant.

Diversity Statement:
As routine medical care moves towards Precision Medicine (determining which treatment, drug, or dosage is optimal for a particular patient based on their ethnicity/genetics) it is important that people of all ethnicities participate in genomic research. If not, health disparities will only worsen. Yet conducting research equally among people of all races is complicated by a wide range of issues including funding of research in minority populations, access to patients who are not near major medical centers, etc. However, in the United States, a major issue that prevents some ethnic groups from participating in genomic studies is distrust of researchers and the U.S. government. It is important that we as researchers understand the history and basis of mistrust while seeking to strengthen our partnership/relationship with diverse communities. For the past 30 years my research has focused on an Indigenous community living near Phoenix Arizona who have a disproportionately high rate of type 2 diabetes and obesity. While it is exciting to make progress in understanding the genetic underpinnings of diseases that are prevalent in this community, it is important for me, and my trainees, to find ways to better partner with members of this Indigenous community to be able to communicate our findings to

individuals with a wide range of scientific backgrounds, some of whom may not trust in medical research. It is also important for me and my trainees to understand the stereotypes that can develop from long term studies of a specific population where a disease is common. I believe the best way to ensure that people of all ethnicities receive the best healthcare possible is to ensure that people of all ethnicities are represented in cohorts of medical and research professionals. While I fully embrace all kinds of diversity (religious, cultural, gender, health, etc.), given my research, I particularly try to recruit Indigenous trainees into my group such that they can become involved in research that affects their communities, interact with members of their families or communities to allay fears that arise from genomic terms or concepts, while at the same time I can learn about their culture, history, and perceptions to allow me to be a more compassionate and insightful scientist.

Rebecca J. Brown, MD
Diabetes, Endocrinology, and Obesity Branch

Keywords: Metabolic syndrome, diabetes, cardiovascular disease, insulin resistance, obesity

Project Description:
Metabolic syndrome, a cluster of risk factors linked to cardiovascular disease, is a global epidemic, with a prevalence of approximately 35% in the United States, and close to 50% after age 60 (1). Pathophysiologically, metabolic syndrome is caused by insulin resistance, which is in turn usually driven by obesity. The goals of my lab are to 1) Understand insulin signaling and insulin resistance by studying patients with rare disorders of severe insulin resistance; 2) Apply what we learn about pathophysiology to develop therapies for these rare and life-threatening diseases; and 3) Use what we learn from rare diseases to elucidate drug targets for more common disorders of insulin resistance, such as obesity and type 2 diabetes (T2D). Our patients include those with lipodystrophy, characterized by generalized or partial deficiency of body fat, and mutations of the insulin receptor gene (*INSR*).

Postbac IRTAs in my lab will take on one or more independent projects, thus gaining experience with reviewing scientific literature, generating hypotheses, study design, database management, statistical analysis, scientific writing, and oral presentations. Independent research in the lab is supported by bi-weekly one-on-one meetings, weekly lab meetings, and journal clubs. Postbac IRTAs also work on clinical and translational research protocols studying the natural history and effects of pharmacologic interventions in patients with severe forms of insulin resistance. During these projects, postbacs learn numerous metabolic research techniques, including how to measure insulin resistance using the hyperinsulinemic, euglycemic clamp studies, stable isotope tracer techniques, measurement of energy expenditure using indirect calorimetry, measurement of body composition, and assessment of blood vessel (endothelial) function. Postbacs will learn to work as part of an interdisciplinary healthcare team including other postbacs, physicians, nurses, nurse practitioners, and patients. Postbacs are also provided ample opportunity to shadow physicians within and outside our team.

Below are proposed projects to assess the role of insulin resistance in cardiovascular disease:

1. *Effects of insulin resistance on in vivo endothelial function (Clinical Project).*

Methods: The postbac will assist in running a clinical study in patients with lipodystrophy, *INSR*, and healthy controls before and during hyperinsulinemia induced by oral glucose, and serially measure nitric oxide (NO), endothelin-1 (ET-1), and vasodilation. The postbac will work with lab members and collaborators to recruit subjects, conduct studies, and analyze data. In this role, the postbac will learn about clinical trial design and conduct, including regulatory aspects of human subjects research, working with patients to conduct complex physiology studies, and collecting and analyzing data.

1. *Effects of insulin resistance on clotting and inflammation (Data and Sample Analysis Project).*

Methods: The postbac will use biobanked specimens and previously collected data to compare biomarkers of clotting and inflammation in patients with lipodystrophy, *INSR*, and healthy controls. In this project, the postbac will gain experience with reviewing the scientific literature, database management, statistical analysis, scientific writing, and oral presentation skills. If desired, the postbac can also learn wet lab skills by conducting assays for the biomarkers of interest.

Diversity Statement:

My group studies insulin resistance and metabolic syndrome, conditions that disproportionately affect communities of color and socioeconomically disadvantaged populations, and thus will be of interest to trainees who want to find solutions to health disparities in metabolic disease. I endeavor to promote diversity in my hiring practices and actively promote the career development of trainees of diverse backgrounds. Trainees will find a welcoming and respectful environment in a diverse group in which all voices are heard. In addition, I encourage my trainees to engage in research projects that specifically address issues of diversity and inclusion (see example abstract, below, from the Endocrine Society annual meeting, 2021),

1. Brent S. Abel; Elaine K. Cochran; Megan Startzell; Rebecca J. Brown. Racial Disparities Among Clinical Trials for Inherited Forms of Lipodystrophy. Poster presentation at Endocrine Society Annual Meeting, 2021.

I encourage my trainees to participate in discussions related to diversity and inclusion during our weekly lab meetings, including presenting relevant journal articles. Examples of recent topics are:

1. Health impacts of weight discrimination (January 20, 2022)
2. Minimal Model–Derived Insulin Sensitivity Index Underestimates Insulin Sensitivity in Black Americans (November 18, 2021)

Susan Buchanan, PhD
Laboratory of Molecular Biology

Keywords: mitochondria, outer membrane protein, protein biogenesis, protein crosstalk, structural biology

Project Description: Supercomplex assembly between mitochondrial TOM and SAM Facilitates Protein Biogenesis

The majority of the mitochondrial proteome is translated in the cytosol and imported into mitochondria as unfolded precursors. Mitochondrial outer membrane β-barrel proteins are imported by the translocase of the outer membrane (TOM complex) then folded and inserted into the membrane by the sorting and assembly machinery (SAM complex). We solved the first structures of the SAM complex and showed that it is composed of three subunits: a β-barrel core (Sam50) that spans the mitochondrial outer membrane, and two accessory subunits (Sam35 and Sam37) that associate on the cytosolic side of the membrane [1]. Sam50 and Sam35 are essential for cell viability and specifically interact with a conserved sequence motif on the precursor protein, called the β-signal. How the β-signal is recognized by the SAM complex, and the mechanism of precursor folding and insertion into the mitochondrial outer membrane, remain unclear. Biochemical data demonstrate that SAM and TOM interact in the outer membrane, likely to facilitate protein import, folding, and insertion. We have data showing that Tom22 interacts with Sam37, and this project will further characterize the interaction, delineating the protein-protein interface at high resolution. We will use this information to design a stable supercomplex consisting of the TOM core complex and the complete SAM complex for structural studies using cryo-Electron Microscopy [2]. Ultimately, this work will improve our mechanistic understanding of SAM complex function and mitochondrial outer membrane β-barrel biogenesis.

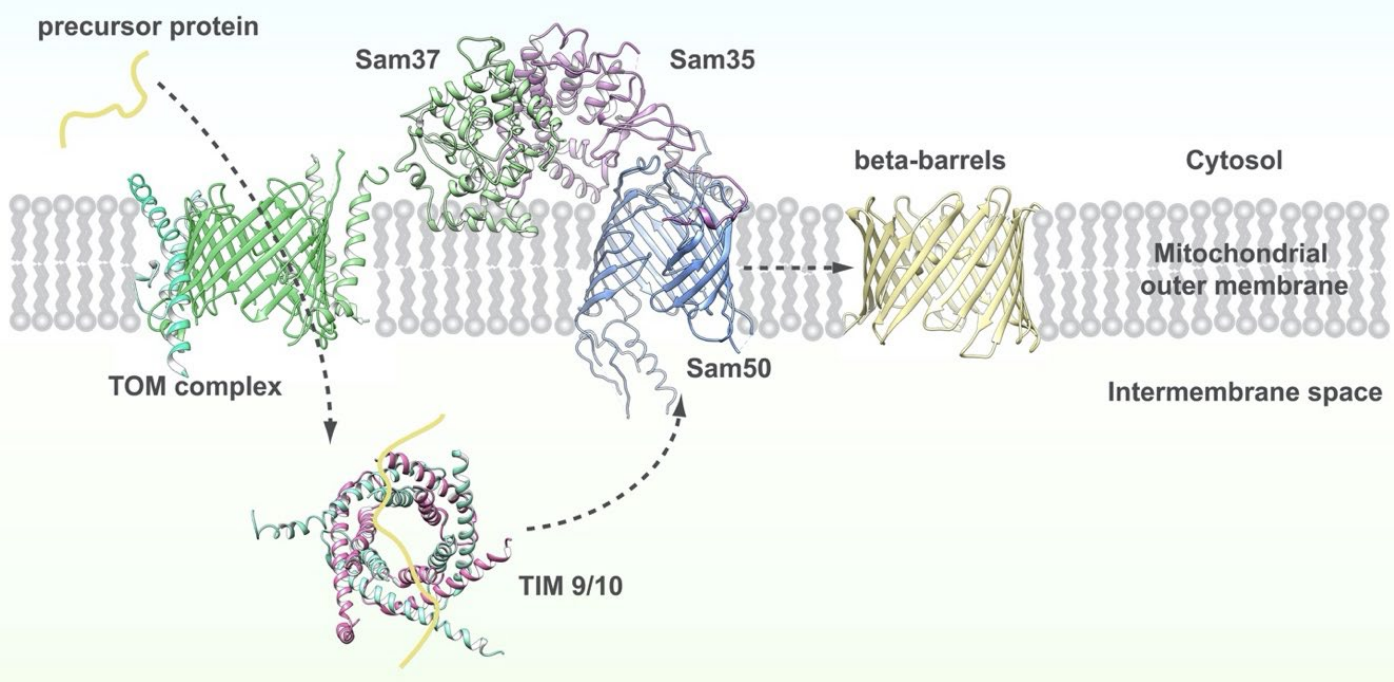


Figure 1. Schematic of b-barrel outer membrane protein biogenesis in mitochondria. Mitochondrial outer membrane b-barrel proteins are synthesized in the cytosol (yellow), then imported into the intermembrane space of the mitochondria by the translocase of the outer membrane complex (TOM complex, green). Once in the intermembrane space, the precursor protein is
bound by chaperone proteins (TIM9/10, magenta/cyan) and directed to the sorting and assembly machinery complex (SAM complex, blue/pale green/orchid). The SAM complex facilitates outer membrane b-barrel precursor protein folding and insertion into the outer membrane.

[1] Diederichs, K.A., Ni, X., Rollauer, S.E., Botos, I., Tan, X., King, M.S., Kunji, E.R.S., Jiang, J. & Buchanan, S.K. (2020). Structural insight into mitochondrial β-barrel outer membrane protein biogenesis. Nat Commun 11(1): 3290. doi: 10.1038/s41467-020-17144-1. PMCID: PMC7335169
[2] Diederichs, K.A., Buchanan, S.K. & Botos, I. (2121) Building better barrels: b-barrel biogenesis and insertion in bacteria and mitochondria. J Mol Biol 433(16):166894. PMCID: PMC8292188

Diversity Statement:

Promotion of diversity and inclusion starts with the composition of my own research group. I currently have six trainees: three postdocs, one graduate student, and two postbacs, with a gender distribution of
three women and three men. Over the course of my 20+ year career at the NIH, I have trained scientists from Belgium, Czech Republic, Dominica, Ethiopia, France, Hong Kong, Jamaica, Japan, Nigeria, Sri Lanka, UK, and USA. I believe that providing early training opportunities to fellows from diverse backgrounds produces the best cohort of young scientists to become our future leaders. I am very active in DEIA initiatives at the NIH. As the former chair of the Women Scientist Advisors (WSA) and long-time member of the executive committee, I have been involved at the NIH-level in developing policies that foster diversity and inclusion. The WSA (and other NIH organizations) has significantly improved the NIH as a hospitable place for women to work, and the group's goal is to recruit, promote, and retain women at all levels at the NIH. Recent advances include several trans-NIH salary surveys that identified investigators

(both men and women) whose salaries were below the normal level for their institutes. The WSA was also the driving force in implementing new antiharassment policies at the NIH. In collaboration with the NIDDK Scientific Director, the NIDDK Executive Officer, and three other NIDDK WSA representatives, I worked to educate the NIDDK workforce on the new anti-harassment policy and expectations (through a poster campaign, mandatory all-hands NIDDK seminars, and in-person Conduct of Research Training that focused on various harassment scenarios). Three years ago, I helped my graduate student start a trainee-led seminar series recognizing diversity and excellence in science: TREaDS (https://www.niddk.nih.gov/research-funding/at-niddk/trainingemployment/choose-niddk). This excellent program was the first of its kind at the NIH, and we are starting the forth year of seminars. I secured funding for the program and serve on the advisory committee for the group. In addition, two years ago I co-initiated the Distinguished Postbac Scholars program to diversify our trainee population. My goal is to strengthen this program and to create a similar program for postdoctoral researchers at NIDDK. I am committed to making the NIDDK (and NIH) a positive, inclusive place to work for all of our researchers and I welcome feedback and suggestions on changes that will make a real difference to your training experience.

Rafael Daniel Camerini-Otero MD, PHD
Genetics and Biochemistry Branch

Keywords: Meiosis, Genetic Recombination, PRDM9, genome rearrangements, genetic disease

Project Description:

Meiosis is the specialized type of cell division that gives rise to reproductive cells such as sperm and eggs. Errors in meiosis are responsible for at least half of clinically recognized miscarriages, as well as a spectrum of chromosomal birth defects in humans. Children who inherit an extra chromosome due to these errors (Down Syndrome, for example) can sometimes survive, but suffer from various congenital abnormalities and such aneuploidy is a major cause of mental retardation and neurodevelopmental disorders. Meiotic division generates four daughter cells, each of which contains half the chromosomal complement of the originating cell. This is achieved through DNA replication, followed by two meiotic divisions (meiosis I and II). Most chromosomal mis-segregation events result from errors in meiosis I (1), when genetic recombination creates crossovers (COs) to facilitate the accurate segregation of homologous chromosomes.

Recombination is initiated by the programmed formation of DNA double strand breaks (DSBs), and COs are generated from subsequent DSB repair. The vast majority of DSBs occur at a subset of genomic loci and my lab has generated the first maps of such DSB hotspots in any mammalian genome (2). We also showed that the meiosis specific histone methyltransferase protein PRDM9, defines essentially all DSB locations in mouse (3) and human (4) and it is now well established that each allele of the PRDM9 protein binds different DNA sequences to define a unique DSB hotspot landscape.

Assessment of PRDM9 diversity is important for understanding the complexity of human population genetics, the inheritance of linkage patterns, and the predisposition to genetic disease. Aberrant DSB repair can result in both benign and disease-causing structural variants (SVs), and recently, we showed that indeed, meiotic DSBs occur disproportionately frequently at SV loci (4). For this project, we propose a detailed computational analysis of the sequence determinants that predispose DSB hotspots to aberrant DSB repair during meiosis. Developing a better understanding of these events at DSB hotspots has the potential to identify loci in the human genome related to genetic disorders that arise in the germline.

Diversity Statement:

My lab has a long-standing commitment to diversity and inclusion. Over the course of close to five decades, I've enrolled students from a wide range of backgrounds, and I consider this diversity to be the cornerstone of my group's achievements. At the same time, I recognize the systemic barriers of entry that students from underrepresented minorities encounter just to be in the running for consideration. My lab actively engages in several NIH programs like the summer programs that provides an opportunity to perform research at the NIH to individuals ranging from high school to college. This Distinguished Postbaccalaureate Scholar Program is an opportunity for both students and investigators with strong commitment to diversity to keep building a more inclusive research community.

Finally, in addition to my efforts in recruiting students I am a staunch supporter of recruiting from underrepresented groups at every stage of development up to faculty level. I am very involved in the Faculty Recruitment Turn-the-Curve Working Group (5/31/2022 onwards) which extends my previous efforts as part of our Intramural Diversity & Inclusion Working Group that was paused in anticipation of this exercise. Recently, our branch recruited the first tenure-track investigator from an underrepresented group in over thirty years in the basic sciences of the intramural program of NIDDK.

1. Ottolini, C. S. et al. Genome-wide maps of recombination and chromosome segregation in human oocytes and embryos show selection for maternal recombination rates. Nat Genet (2015)
2. Smagulova, F. et al. Genome-wide analysis reveals novel molecular features of mouse recombination hotspots. Nature (2011).
3. Brick, K., Smagulova, F., Khil, P., Camerini-Otero, R. D. & Petukhova, G. V. Genetic recombination is directed away from functional genomic elements in mice. Nature (2012).
4. Pratto, F., Brick, K. et al. Recombination initiation maps of individual human genomes. Science (2014).

Ross Cheloha, PhD
Chemical Biology in Signaling Section

Keywords: Chemical Biology, Antibody, Pharmacology, Immunology, Peptide

Title: Harnessing the power of antibodies and chemistry to control immune function
Project Description:
The Chemical Biology in Signaling Section has broad ranging interests in applying chemistry and protein engineering to interrogate protein receptors found at the surface of mammalian cells. These receptors regulate all aspects of cellular communication and are essential for homeostasis. One group of proteins of particular interest is the G protein-coupled receptor (GPCR) superfamily, which constitutes the target of >25% of all currently FDA-approved therapeutics. Despite the immense importance of these receptors, both for basic biomedical research and for therapeutic applications, there are many facets of receptor function that are not adequately addressed with currently available tools. Work in our laboratory seeks to develop new tools that will be useful for understanding how these receptors function in health and disease. Tools developed in these studies can serve as the basis for new strategies to treat diseases for which GPCRs are validated targets, which include metabolic diseases, cancers, and immunological disorders.

Antibodies are nature's solution to generating molecules that can bind to any target of interest with high affinity and specificity. Our laboratory uses a specialized type of antibody generated by camels, llamas and alpacas. These specialized antibodies are a simplified version of the antibodies produced by the human immune system. Their simplified nature allows us to apply these antibodies as building blocks for biological engineering approaches. To enhance the utility of these specialized antibodies, we modify them further using chemistry-based approaches. We link synthetic molecules, prepared in our laboratories, to these antibodies to make chimeric molecules that combine the binding power of antibodies with the biological activities of synthetic molecules. We have dubbed this approach "CLAMP" for conjugation of ligands and antibodies for membrane proteins. In past work we have shown that these chimeric molecules possess properties superior to either antibodies or synthetic molecules alone. Further, these chimeric molecules have been shown to induce desirable biological responses in mice.

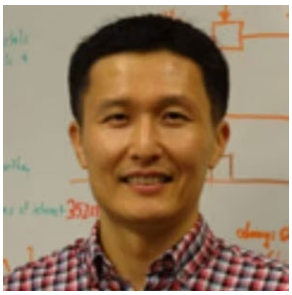
The specific project for the incoming postbaccalaureate will focus on applying this technology for creating new compounds to target a group of GPCRs known as chemokine receptors. The chemokine receptors are broadly responsible for regulating the movement of the cells of the immune system. The immune system is essential for combating an array of infections and battling tumors but can also act on normal human tissues to induce autoimmune disorders. Most of these actions rely on the ability of immune cells to move to sites in the body where they are needed. This is mediated in large part by signaling through chemokine receptors. There has long been interest in developing therapeutic molecules that stimulate chemokine receptors to promote immune responses against tumors or pathogens; however, the molecules used by nature (chemokines) are difficult to apply therapeutically because they stick to a variety of biological

surfaces before they are able to reach their target receptors. In this project we will combine the biological properties of chemokines with the targeting power of antibodies to create CLAMPs that target chemokine receptors with reduced issues of undesirable binding. As a long term goal, we will apply these new CLAMP compounds to promote the infiltration of immune cells into tumors for treating tumors.

A postbaccalaureate who participates in this project will gain experience in a variety of laboratory techniques including: recombinant protein expression, chemical peptide synthesis, enzymatic labeling chemistry, cell-based signaling assays, flow cytometry, and mammalian cell culture.

Diversity Statement:
I am committed to the promotion of diversity, equity, inclusion, and accessibility. These goals are pursued both through the way that I construct and run my research group and in how I engage with the broader NIH community. I seek to foster a culture of belonging and inclusion through purposeful communications with coworkers and trainees to ensure that their preferences and ideas are heard and applied. Individuals who work as scientists come from a wide variety of backgrounds and cultures. Differences in experiences and perspectives shape how scientists engage with their employer and coworkers. It is not possible to forge a one size fits all approach to accommodating these varied perspectives and preferences. As such it is crucial to communicate with my colleagues and trainees to ensure I effectively contribute to a workplace in which they are comfortable and primed to excel, both as scientists and as individuals. I have sought to improve my awareness of cultural, racial, and societal biases through participation in a variety of training opportunities provided by NIH. I have completed the OIR/COSWD 7 Week Workshop on Diversity, Equity, Inclusion and Accessibility as well as the Groundwater Immersive Experience two-day session on structural racism, among other smaller seminars and workshops.

As I am aware of my own membership in groups that have been historically privileged with respect to scientific endeavors, I have consciously worked to hire members into my research lab that provided diverse perspectives with respect to cultural and racial background, gender identity, disability status, and level of training. Many members in my group come from at least one underrepresented group, with several members intersecting with multiple underrepresented groups. Efforts to construct a diverse team have been facilitated by participation in NIH sponsored programs including the Distinguished Postbac Program and the Postdoctoral-Postbac mentorship program. I will continue to work to strengthen the culture of belonging and inclusion within my group. I am proud of the diversity within my current group, and I intend to make active efforts to ensure that future hires maintain the culture that now exists.



Hoi Sung Chung, PhD
Laboratory of Chemical Physics, Single-Molecule Biophysics Section

Keywords: Single-molecule fluorescence spectroscopy, Protein conformational dynamics, Protein aggregation, amyloid, apolipoprotein

Project Description:
The APOE ε4 allele, which encodes one of the three isoforms of apolipoprotein E (ApoE), is the major genetic risk factor for sporadic, late-onset Alzheimer's Disease (AD). ApoE4 differs from the other isoforms, ApoE3 and ApoE2 only by one or two amino acids and increases the risk of AD development. We aim to investigate the conformational dynamics of the ApoE isoforms during interaction with lipids and the amyloid-β (Aβ) peptide, the major amyloid component of senile plaques in AD patient brains, using single-molecule fluorescence spectroscopy. ApoE isoforms are known to interact with Aβ and modulate the kinetics of its fibril formation; therefore, molecular-detail characterization of these interactions is crucial for understanding the AD disease mechanism.

The student will be mentored by Dr. Jae-Yeol Kim (Staff Scientist) and the PI (Hoi Sung Chung), and will be involved in the following activities:

- Expression, dye-labeling, and purification of ApoE proteins
- Conventional biophysical characterizations of expressed proteins using various instruments such as UV-Vis, fluorimeter, and microplate reader.
- Performing single-molecule fluorescence experiments of ApoE proteins using a confocal microscope
- Data analysis using custom programming codes
- Research presentation (group meeting, NIH postbac events, and conferences)

Diversity Statement:
I understand very well the importance of promoting diversity in race, ethnicity, and gender in scientific research fields to create an environment where all talented individuals can have equal opportunities to do research. I have tried to maintain my research group as diverse as possible and consider this issue when recruiting group members. In line with NIH efforts, my group has participated in various activities related to promoting diversity. One of my postdocs received the Summer Mentor Award program to mentor two community college students as summer interns and we participated in an outreach program, NIDDK School Outreach Program Pilot in 2019, to engage children from lower income families and expose them to biomedical sciences.

Stephanie T. Chung M.B.B.S.
Section on Pediatric Endocrinology, Obesity, and Metabolism, NIDDK, NIH

Keywords: youth-onset type 2 diabetes, pediatric obesity, health disparities, transition care

Project Description:
Our Section's research and clinical goals are to improve early detection and treatment of diabetes, obesity, and cardiovascular disease in women and children, especially those from under-represented groups. We conduct clinical trials in youth and adults, advocate for our youth through community outreach in schools, and collaborator internationally to generate population-specific evidence to help shape obesity and diabetes prevention strategies. My post-bac IRTA fellows are integral team members and team leads during their 2-year fellowship. My IRTA training program provides an educational, enriching, and fun experience in clinical metabolic research that will lay the foundation for future success in medical or graduate school and beyond. My post-bac IRTAs are participant advocates, study coordinators for 2-3 clinical research protocols, early career investigators, and peer mentors. The fellows receive on-site training for all activities including basic clinical research skills, protocol implementation, and data management and statistics. In addition to performing daily tasks, it is my hope that every post-bac IRTA will contribute to our research mission by learning to write and presenting their findings at scientific meetings, teach and supervise fellow and summer students, and earn co-authorship depending on their involvement and expertise. Two examples of clinical projects are outlined below.

1. <u>The Youth-onset Type 2 Diabetes and Heart Disease Study: The Young at Heart Prospective Cohort</u>

This study evaluates the pathophysiological features of cardiovascular disease in youth-onset type 2 diabetes using a multi-level, multi-domain approach to socio-ecological risk factors (societal, community, and individual). This prospective, observational study design in youth aged 12-25 years will compare youth with type 2 diabetes with age and BMI-matched youth with overweight or obesity and age-matched healthy lean peers. Participants will be enrolled for inpatient/ outpatient metabolic visits annually. Post-bac fellows will have multiple opportunities to engage with participants for research study visits and shadow and assist in our joint NIDDK/ Children's National Hospital multidisciplinary diabetes clinic. Fellows will master metabolic phenotyping tests including glucose tolerance testing, endothelial function testing, biopsychosocial questionnaires, and ecological momentary assessments. Selected abstract topics—for which data are already available—are "Allostatic load score and cardiovascular disease risk in youth-onset type 2 diabetes" and "Heterogeneity in metformin responsiveness based on biopsychosocial determinants of health".

2. <u>Time Restricted Eating and Ketone Metabolism</u>

This is a clinical translational study designed to evaluate ketone body biology on $CD4^+$ T cell immunoregulation in response to early time restricted eating (6-h TRE) in women. Intermittent fasting dietary interventions including TRE have anti-inflammatory effects. Although the exact metabolic mechanisms remain elusive, they may be related to ketone body metabolism that differs by biological sex and obesity status. This protocol will evaluate ketone body turnover using stable-labeled isotopes in a domiciled metabolic unit. Post-bac fellows will become proficient in administering and analyzing stable isotope methodology for the analysis of glucose and ketone pathways. Selected abstract topics include "Continuous glucose monitoring and glycemic changes during early time restricted eating and the relationship with immune biomarkers".

Diversity Statement:

Winston Churchill penned "Success is going from failure to failure without losing your enthusiasm". This simple phrase embodies the tenacity and drive that most scientists share in their pursuit of excellence. As a tenure-track investigator, a woman, a mother, and a pediatric physician-scientist, I am on a daily quest for excellence. This process of pushing myself personally and professionally has only strengthened my belief in one of the guiding principles of diversity—namely, that the ideas, approaches and successes of medicine are strengthened when people from different backgrounds—with a variety of experiences, abilities, and world views—work together in furtherance of success. My tenacity and commitment to diversity is exemplified in my past and current research questions, the success of my trainees, and my track record of leadership in both community and national outreach programs.

The goal of my post-bac training program is to help this next generation of scientists think creatively and broadly to minimize biases and promote innovation. For me, this process begins with endeavoring to be an open-minded role-model and clinician for my patients, the majority of whom are from minority or disadvantaged backgrounds. Our research and clinical programs support self-sufficiency and resilience for these youth and young adults, while simultaneously training our IRTA fellows. One of the pillars of my research program is the student learners at varying levels in their academic careers, who range from undergraduate and postbaccalaureate to post-doctoral fellows. Students from all socioeconomic and cultural backgrounds have been attracted to my Section because of my emphasis on excellence through diversity. Over the last 10 years, I have mentored over 25 fellows from diverse culturally and ethnic backgrounds. I also a long-standing mentor for the NIDDK Diversity Summer Research Training Program and The Annual Biomedical Research Conference for Minority Students. To date, over 90% of my trainees have received scientific merit-based awards during their respective NIH appointments.

My inclusive mentoring philosophy is rooted in creating an environment which fosters scientific learning through a balance of individual and team-based learning, continual self-evaluation, and mutual respect. Core to the foregoing is an acknowledgement that people from diverse backgrounds often have different learning and communication styles. By focusing on a guided learning approach—with an emphasis on each trainee's unique abilities—my Section promotes freedom of thought, open discussion, and productivity. In the spirit of Churchill, we strive for success, learn from our everyday failures, and embrace scientific rigor with enthusiasm.

Ann Dean, PhD
Chief, Section on Gene Regulation and Development
Laboratory of Cellular and Developmental Biology, NIDDK

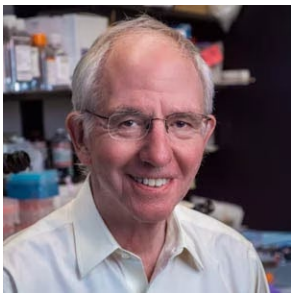
Keywords: Enhancers, Chromatin, Epigenetics

Project Description:
Epigenetic regulators play important roles in gene expression and developmental progression of multi-cellular organisms. Hematopoiesis has been a key model that has been exploited to gain insight into epigenetic functions during cellular differentiation. However, only a limited number of epigenetic factors have well studied roles in the differentiation of erythroid progenitor cells into mature red blood cells. Fully understanding regulation of blood cell development can suggest novel therapeutic approaches to treat anemias such as Sickle Cell Disease and β-thalassemia and blood cancers. We carried out a genome scale knock-out screen (GecKO) in murine erythroleukemia (MEL) cells to identify epigenetic factors that play important roles in erythropoiesis. Among the strongest hits was the epigenetic regulator and histone H3.3 chaperone HIRA. We aim to test the role of HIRA in erythroid differentiation using MEL cells by CRISPR-Cas9 deletion and in erythroid progenitor cells. CUT&Tag has been performed to localize sites of HIRA binding. The results of this study will allow us to comprehensively determine the role of HIRA in erythroid differentiation. As an extension of these results, we will use Promoter Capture-HiC to determine whether HIRA is involved in long-range contacts between erythroid genes and their enhancers.

Diversity Statement:
Promoting diversity in and inclusion in science has been a strong goal for me for decades. I served as the first Women Scientists Advisor (WSA) to the NIDDK Scientific Director in the mid-1990s when the position was established. I advocated for pay equality for women with their male comparable investigators, advancement of very accomplished women scientists and efforts to raise the number of women scientists in NIDDK and at NIH. I advocated for increased childcare options at NIH and for lactations rooms for nursing mothers, having experienced, as the mother of four children, how challanging it is to maintain a career in science and juggle family responsibilities. About half of my trainees (13/30) have been women and all are now MDs. Three trainees have been underrepresented minorities, which is another area I am committed to change. Regrettably, the pool of under-represented minority applicants for post-doctoral positions remains small and I feel strongly that our efforts to change this need to focus on younger students in high school and middle school to increase their exposure to the excitement of science. I have hosted middle school children from a local school that has primarily underrepresented minority students. I have hosted high schoolers from underrepresented minorities for student internships. These are one-on-one interactions, and I feel I can make a meaningful contribution in this way. I am especially pleased to have mentored Luis Diaz, the first college graduate in his family, as a postbaccalaureate fellow in the lab and seen him successfully gain

admission to the MD-PhD MSTP program at Oregon Health and Science University for Fall 2019. I have served since 2009 as a member or chair of the Chromosomes/epigenetics/transcription Stadtman Investigators Award recruiting committee at the NIH, through which most appointments to the tenure track are now made, and this has been an opportunity where I feel I have been able to make more of a difference in assuring the recommended candidates include a high number of qualified women and members of under-represented minorities. There is still a long way to go in these efforts. The number of women investigators at NIH is still only about 20%, the same as in the 1990s, and under-represented minorities are a very small fraction. Still, there is a lot of determination at NIH to change this.

This year I have two Distinguished Post-Bac Scholars in the lab. We are participating in planning and carrying out a visit to NIH by local school children who are mostly from under-represented groups in scientific careers. We are all interested in showing children what doing science is like and connecting them to people who have chosen this as a career.



Jurrien Dean, MD
Laboratory of Cellular and Developmental Biology, NIDDK

Keywords: Women's health, Reproductive biology, Fertilization, Early development, Mouse genetics

Projects Description:

Chromatin remodeling necessary for embryo implantation in the mouse uterus: Embryo implantation on the wall of the uterus is a critical step in mammalian reproduction. In humans, the maximal fecundity for natural births per menstrual cycle is ~30%. Over 40%-50% of conceptions are lost in the first 20 weeks of gestation and ~75% of unsuccessful pregnancies are due to failed implantation. Success requires synchronization between a competent embryonic blastocyst and a receptive uterus. There is a temporally restricted "implantation window" regulated by proliferation and differentiation of endometrial epithelium and stroma under the control of progesterone (P4) and estrogen (E2). Uterine epithelial–stromal crosstalk involves endocrine, paracrine and juxtacrine interactions that are critical for successful implantation. Developmental programs are precisely controlled by chromatin regulators that maintain specific gene expression through epigenetic modification of the genome. However, the details of chromatin remodeling and spatiotemporal expression of genes that guide proper epithelial–stromal interactions to ensure uterine receptivity remain largely unexplored.

We discovered that the SWI/SNF remodeling complex containing PBRM1 and BRG1 is essential for implantation of the embryonic blastocyst on the wall of the uterus in mice. Although pre-implantation development is unaffected, conditional ablation of *Pbrm1* in uterine stromal cells disrupts progesterone pathways and uterine receptivity. *Hand2* is a bHLH transcription factor required for embryo implantation. We identify a new enhancer of *Hand2* in stromal cells that requires PBRM1 for epigenetic histone modifications/coactivator recruitment and looping with the promoter. In $Pbrm1^{cKO}$ mice, perturbation of chromatin assembly at the promoter and enhancer sites compromises *Hand2* transcription, perturbs fibroblast growth factor signaling pathways, prevents normal stromal-epithelial crosstalk, and disrupts embryo implantation. The mutant female mice are infertile and provide insight into potential causes of early pregnancy loss in humans.

Post-fertilization block to polyspermy: One sperm is necessary for fertilization, but two are embryonic lethal. Thus, the post-fertilization block to polyspermy is equally important to sperm-egg fusion. Using the mouse as a model system, we have focused on two aspects of this block that involve the ~4,800 cortical granules in mouse eggs. Ovulated eggs are surrounded by an extracellular zona pellucida composed of three proteins (ZP1, ZP2, ZP3) to which sperm bind. A definitive block that prevents sperm binding arises from the post-fertilization cleavage of ZP2 by ovastacin, a zinc metalloendoprotease. However, complete ZP2 cleavage takes time, and a second block, mediated by the inhibitory effect of zinc on sperm motility, occurs within minutes of fertilization. Both ovastacin and zinc are stored in separate sub-populations of egg cortical granules which are exocytosed following fertilization. We would like to determine if there are additional populations of cortical granules and the biologic impact of their cargos. We have established gene-edited mice that accumulate either ovastacin^{mCherry} or zinc

transporter^{GFP} in distinct populations of cortical granules. With these genetic tools, we plan to isolate these subcellular organelles and determine their contents by mass spectrometry.

Depending on the interests of the Distinguished Postbaccalaureate Scholar, she/he would select a project and we would anticipate carving out sub-projects for increasingly independent studies as the Scholar gains experience.

Diversity Statement:
Promoting diversity and inclusion in science has been a strong personal goal over my years at the NIH. More than half of my fellows have been women, and many have become leaders in academe and philanthropy. The pool of under-represented minority applicants for fellowship positions remains small, but I have been able to recruit a Visiting Fellow (male) from Mexico and a Post-bac Fellow (female) who is Haitian-American. Last year I hosted an outstanding NIDDK Distinguished Postbaccalaureate Scholar who is African-American (female) and is applying to medical school. These one-on-one interactions with fellows/scholars in the lab make a meaningful contribution to recruiting more women and under-represented minorities into the scientific pipeline. I also have served as a member or chair of the Developmental Biology Stadtman Investigators Award recruiting committee at the NIH. This is the mechanism for most appointments to the tenure track are made and has been an opportunity for me to make more of a difference in recommending a high number of qualified women and members of under-represented minorities. In recent years, there has been considerable determination on the part of the NIH to remediate these under-representations and I would like to be part of this change. To that end, I have participated in multiple lectures/workshops including: NIDDK Listening Circle – Societal Injustices, June, 24, 2020; Conversations on Social Justice and Diversity, July 8, 2020; NIDDK Town Hall, February 2, 2021; Picture a Scientist, March 22, 2021; First Virtual Town Hall on Achieving Racial Equity at NIH, April 30, 2021; The Racial Equity Institute Groundwater Training, September 15, 2021; National Academies of Sciences, Engineering, and Medicine (NASEM's) Committee on Addressing Diversity, Equity, Inclusion, and Anti-Racism in 21st Century STEMM Organizations, October 25, 2021; The OIR/COSWD Diversity, Equity, Inclusion, and Accessibility Series (7 sessions), May 3, 2022 – June 21, 2022; Women's Community DEIA Listening Session, November 9, 2022; Conversations on Racial and Ethnic Equity, January 11, 2023; NIDDK Speaker Series: Race, Racism, and Health: Advancing Health Equity, April 12, 2023; 2nd Virtual Town Hall on Diversity, Equity, Inclusion, and Accessibility, May 18, 2023; OIR/COSWD Diversity, Equity, Inclusion, and Accessibility Workshop Series (Roland Owens, PhD), July 11, 2023;

I also serve on Advisory Committees for four tenure-track Stadtman Investigators (2, NICHD, 1 NHLBI, 1 NIDDK) which provide me with the ability to strengthen the commitment to diversity and inclusion goals across the NIH.

Douglas Forrest, PhD
Laboratory of Endocrinology and Receptor Biology

Key words: Endocrine system, Neurodevelopment, Genetics and Genomics

Project Description: ***"Endocrine and transcriptional control of sensory development"***

The senses are our interface with our habitat, our community and the wider world. From neonatal and even fetal stages of development, sensory epithelia on the surfaces of the body detect information in the environment in the form of light, chemical and mechanical cues. In the retina, cone and rod photoreceptor cells detect light. Cone photoreceptors mediate daylight vision and color vision. Color vision requires cone populations with sensitivity to different regions of the light spectrum, typically medium-long (M, "green") and short (S, "blue") wavelength regions of the light spectrum in mammals. Despite the importance of color vision, the generation of M and S cone diversity is poorly understood.

We identified a rare thyroid hormone receptor (TRb2) that is unexpectedly critical for M cone development. In the absence of TRb2, all cones are of the S type suggesting that TRb2 switches a population to acquire an M type identity. This surprising link between the endocrine and sensory systems has novel implications. How does this switch for cone diversity work? How does an endocrine signal control color vision? What are the implications for vision loss in retinal disease? TRb2 is widely conserved, including in humans, pointing to a fundamental role in cones in vertebrate species.

Thyroid hormone receptors act as ligand-regulated transcription factors and are thought to bind chromatin control sites, or enhancers, that regulate gene expression. However, little is understood of this step in cone differentiation. As cones are a small population of retinal cells, we have adapted genomic techniques to study scarce cell types. Our research offers training in molecular biology, genetics, single cell and bioinformatic analyses.

https://irp.nih.gov/pi/douglas-forrest

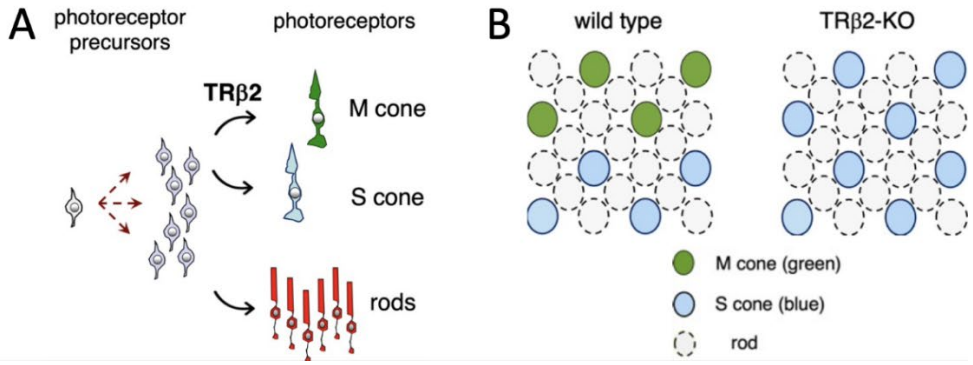


Figure 1

A, The generation of cone and rod photoreceptors during retinal neurogenesis.

B, Flatmount view of the retina showing loss of M cones in TRb2-KO. TRb2 controls a switch to generate M and S cone diversity.

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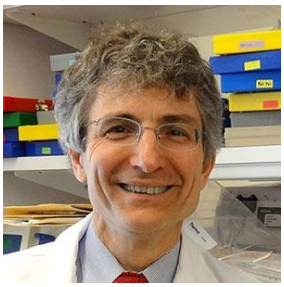
Diversity Statement:

Our research group has long been committed to diversity and inclusion regarding recruitment and support for each person in our group. The more inclusive the endeavor, the greater the benefit for research and ultimately for society. My mentoring philosophy is to support each individual to achieve their training and career goals. Our research progress depends on cooperation. We aim to help each individual achieve their potential for a scientific career. Trainees work with more experienced researchers to learn techniques and concepts while gaining experience and making their own contribution to our research program. Trainees are encouraged to take advantage of the wide range of career training workshops at NIDDK and to participate in other trainee opportunities at NIH.

At NIDDK, our group has long supported the Diversity Summer Research Training Program, working with students from a wide variety of backgrounds. A reward is seeing trainees then taking the next steps in their career. Recent trainees have progressed to enter graduate school, medical school, or masters research programs. As an example, one student returned to our lab as a post-baccalaureate trainee which helped her admission to medical school, the next stage in her long term goal of giving back to her community. We support various diversity programs at NIH and have assisted in NIDDK outreach. I have also served in career training and diversity activities in the American Thyroid Association. Our lab cultivates a supportive and stimulating environment for trainees at all stages of their career because it is people who make scientific discovery possible.



Gregory Germino, MD
Kidney Disease Branch, Polycystic Kidney Disease Section

Keywords: Polycystic kidney disease, Primary cilia, Proximity biotinylation (BIO-ID) protein interactome

Project Description:
Our laboratory studies polycystic kidney disease (PKD), a genetic disease caused by mutations in *PKD1* or *PKD2*, which encode polycystin-1 (PC1) and polycystin-2 (PC2), respectively. PKD is characterized by progressive replacement of normal kidney tissue by fluid-filled cysts and results in end-stage renal disease in about half of the affected individuals. Over the course of several years, our group and others have shown that PC1 undergoes several post-transcriptional cleavage steps required for normal function [1-3]. Furthermore, we generated several mouse models that mimic various aspects of PKD and used them to investigate transcriptional and metabolic changes associated with *Pkd1* deletion [4-10]. These studies helped uncover possible PC1 functions in primary cilia and mitochondria, but identifying the set of proteins that interact with PC1 and its cleavage products remained an elusive goal. More recently, we developed a knock-in mouse model in which the endogenous *Pkd1* gene has been modified to add GFP-HA tags to PC1 C-terminus [11]. Using this model, our group performed affinity-purification mass spectrometry (AP-MS) and reported an *in vivo* interactome of potential PC1 binding partners. Identifying PC-2 in our dataset served as a positive control, as this was a previously known, *bona-fide* PC-1 interactor. However, this study required large amounts of input material, so our initial studies were performed using newborn mouse heads, a structure that expressed high levels of PC1 and was substantially larger than newborn mouse kidneys (PC1 expression is significantly lower in adult mouse kidneys). Furthermore, confirming interaction with several of the other candidate binding partners and determining which, if any, of the PC1 cleavage products they interact with requires further studies. Since this study was done, we have been accumulating newborn mouse kidneys, and are now able to capitalize on our expertise in PC1 AP-MS to investigate the PC1 interactome in kidneys, arguably the most relevant tissue in PKD biology. To further characterize the interactome of different PC1 fragments, we will also use AirID [12], a recently published optimization of a BirA, an enzyme used in proximity biotinylation protocols, to identify transient and low affinity PC1 binding partners. In this technique, a protein of interest is fused with an enzyme that adds biotin to proteins in close proximity. These biotinylated proteins are subsequently immunoprecipitated using anti-biotin antibodies and identified by mass spectrometry. We will initially focus on PC1-CTT, a small PC1 C-terminal fragment that we showed traffics to mitochondria, a process requiring the presence of a newly identified mitochondrial targeting sequence (MTS) [13]. This part of the project will include generating constructs of PC1-CTT-AirID fusion protein and an MTS-AirID control, establishing cell lines expressing these constructs and performing proximity biotinylation assays followed by mass spectrometry. Candidate interactors will be compared to candidate interactors identified in the kidney PC1 interactome. A final step in the project will seek to validate true interactors biochemically and manipulate their expression to investigate functional consequences in cellular models.

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Diversity Statement: (one paragraph to one page; whole document not to exceed 2 pages)

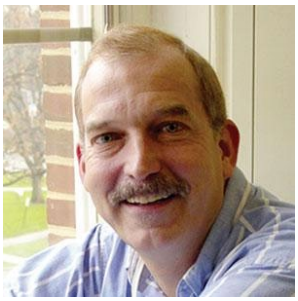
Diverse lived experiences and expertise is critical for the evolution of science, and particularly for NIDDK's ability to tackle some of its most consequential conditions. The PI has been co-leading NIDDK's efforts to diversify its portfolio of science, scientists/clinicians and staff on multiple fronts: a) he co-led the NIDDK Health Disparity/Health Equity Research Advisory Council Working Group, which produced an implementation plan for the 2021 NIDDK Strategic Plan entitled *Pathways to Health for All* (https://www.niddk.nih.gov/about-niddk/strategic-plans-reports/pathways-health-all). He is currently leading the Institute's efforts to develop initiatives to put the plan into action. b) He co-leads NIDDK's IDEA-C committee, which was established to promote inclusive excellence in our internal workforce. c) He is a member of the DIR Turn-the-Curve workgroup, which is seeking to promote diversity of the Principal Investigators of NIDDK's DIR program. d) He has taken the half-day (offered to all NIH Leadership) and the 2-day (NIDDK-supported) Racial Equity Institute "Ground-water" training programs as well as was a member of cohort 1 of the 5-day Race Ahead program. e) He has a long history of promoting diversity within his research group: *at Johns Hopkins*, he had an NIDDK-Diversity Supplement award for a trainee to work in his laboratory; *at NIDDK*, he has had several summer trainees from community colleges, a post-bac IRTA who was the first in her family to attend college, and a post-bac IRTA through the NIH Distinguished Scholars program.

Astrid D. Haase, M.D., Ph.D.
Senior Investigator

Project Description: A small RNA perspective on genome integrity
Retroviruses and transposons pose a threat to genome stability. In the ongoing arms race with these mobile genetic elements, host genomes suffered insults, accumulated scars, and in rare instances adopted transposon sequences for their own use. But above all, they established control. RNA-guided immunity -CRISPR/Cas and RNA interference pathways- restrict mobile genetic elements to protect genome integrity. Animal germ cells employ a specialized small RNA pathway-PIWI proteins and their PIWI-interacting RNAs (piRNAs)- to silence transposons and ensure genome stability. PIWI-piRNA silencing complexes (piRISC) degrade transposon transcripts in the cytoplasm and establish epigenetic restriction in the nucleus. Self/nonself discrimination is at the very core of successful defense and relies on complementary base-pairing in RNA-guided immunity. **How the millions of piRNA sequences faithfully discriminate between self and nonself and adapt to novel genomic invaders remain key outstanding questions in genome biology**. The Haase-lab studies mechanisms of piRNA biogenesis and function, and integrates genetics (in flies and mice), computational biology, and biochemistry.
Our project for a postbac student aims to characterize piRNA generating genomic regions (piRNA clusters) combining genomics and mouse genetics. Mammalian piRNAs establish epigenetic restriction of mobile genetic elements during a defined developmental window and contribute to genetic imprinting. Loss of all piRNAs results in germ cell death and sterility of the animals. However, it remains unknown which piRNAs are essential for this phenotype and which ones are modulators rather than key regulators. We have recently developed a computational algorithm to assemble and characterize piRNA generating regions. Using this novel computational tool, we systematically characterized piRNA clusters in flies, mice, hamster, and human. Results from our study revealed common features and species-specific variations, and identified topranked candidate piRNA clusters that can now be tested experimentally using mouse and fly genetics. Results from the proposed project are bound to reveal novel key regulators of germ cell development and fertility, and might reveal mechanisms of evolutionary adaptation. Interested students can find more information on our work, our team, and on general piRNA biology on our website (https://www.niddk.nih.gov/research-funding/at-niddk/labs-branches/laboratory-cellmolecular-biology/rna-biology-section) and in our recent review (https://mobilednajournal.biomedcentral.com/articles/10.1186/s13100-023-00298-2).

Diversity, Equity, Inclusion and Accessibility. Transformative research requires diverse teams. Our students and fellows come from different educational, socioeconomic, and ethnic backgrounds, and join at different stages of their careers. The combination of their unique strengths and problem-solving skills creates a collaborative environment. I would like to particularly encourage women from underrepresented backgrounds to apply to our group. There are many barriers for women in scientific careers, and it is particularly hard for women from underrepresented minorities and low-income backgrounds. Barriers for these students include the

practical cost of higher education, the lack of role models and insidious cultural expectations. I was fortunate to have met some amazing role models and supportive mentors throughout my career. Now, I want to use my voice to encourage other women, promote their training and welcome them into the scientific community.



John A. Hanover, Ph D.
Laboratory of Cell and Molecular Biology

Keywords: Nutrients, DNA methylation, Environmental epigenetics, Stem cells, O-GlcNAc

Project Description:
DNA methylation is an important epigenetic modification in regulation of gene expression, in which methylation of cytosines is generally linked to silencing of gene expression. genome wide DNA methylation is erased in early stages of embryogenesis and re-established as the development continues. The establishment of proper DNA methylation is crucial to activate necessary genes while silencing unwanted gene expression. Developing organism requires enormous amounts of nutrients. One of the routes of nutrients entering the cell is hexosamine biosynthetic pathway, which produces N-acetylglucosamine (GlcNAc). The intracellular levels of GlcNAc are therefore dependent on the nutrition levels in the cell. GlcNAc is substrate of O-GlcNAc Transferase (OGT) and added onto hydroxyl groups of Ser/Thr residues of target proteins, called O-GlcNAcylation. This modification is reversible and GlcNAc can be removed by O-GlcNAcase (OGA). Oga knockout animals survive the pregnancy but die at birth. Using these Oga knockout newborn livers, we determined cytosine, uracil and thymidine levels are altered, suggesting that DNA methylation levels are different in Oga mutants. Indeed, whole genome DNA methylation analysis revealed that the Oga knockout embryonic stem cells (ESC) exhibit significantly reduced DNA methylation levels compared to wild type ESC. Imprinted genes and miRNAs are among the hypomethylated genes. Both protein and transcript levels of DNA methyltransferases Dnmt3A, Dnmt3B and Dnmt3L, which are responsible for de novo methylation of cytosines, are downregulated in Oga knockout ESC. Moreover, the changes in DNA methylation affected gene expression. Over 2000 genes are upregulated, while 1000 genes are downregulated in Oga knockout ESC.

There are several potential projects that will give potential postbaccalaureate a chance to learn next generation sequencing and bioinformatics on top of molecular biology techniques. One of the potential projects is mapping genome wide O-GlcNAc and DNA methyltransferase sites, especially in correlation with Dnmt3A and Dnmt3B by performing chromatin-IP combined with next generation sequencing (ChIP-seq) experiments. The postbaccalaureate will culture ESC, perform immunoprecipitation of chromatin (ChIP), and prepare sequencing libraries and perform next generation sequencing. The second part of the project involves bioinformatic analysis of ChIP-Seq data, in which the genomic regions, or genes are co-occupied with O-GlcNAc and Dnmt3 genes will be mapped and compared. This project will identify the genes that are co-regulated with O-GlcNAc and Dnmt3A and Dnmt3B.

Another future project is related to miRNAs. We determined 75 miRNA genes are hypomethylated in Oga knockout ESC. The next step of this project is to investigate whether the transcript levels of miRNA's are altered in Oga knockout ESC. The project involves culturing ESC, isolating total RNA and performing next generation sequencing for miRNAs. Second step of this project is

bioinformatic analysis of miRNA expression. The miRNAs that display altered expression will be compared with miRNA genes that are hypomethylated.

Diversity Statement:

The Hanover lab has a long-standing commitment to diversity and inclusion. This commitment dates to at least twenty years. **As a mentor, Dr. Hanover seeks to train scientists who are unafraid of approaching important problems and, more importantly, who are prepared to identify those problems that ARE IMPORTANT.**

We participate in a few trans-NIH programs such as the NIH Academy, Summer enrichment programs and Post-bac IRTA programs. Our recent Academy graduates have gone on to Medical and Graduate School and we are proud of their accomplishments upon completing their training here. Our fellows also participate in the Threads Seminar program aimed at increasing awareness of under-represented minorities and health disparities. I am quite proud of the many fellows I have trained. It is a constant source of joy to see them progress in their careers after their brief stay here in NIDDK. Most have gone on to rewarding careers in academics, science policy, and industry. Many of my fellows also participate in FELCOM and/or the NIDDK Fellows Committee. This opportunity allows them to focus on their writing, communication, and managerial skills. I am proud to report that many of the editors for the FELCOM newsletter in recent years were from the Hanover lab. Please contact Dr. Hanover if you have an interest in this project.

Lothar Hennighausen, PhD/Hye Kyung Lee, PhD
SGP/LCMB

Keywords: cytokine signaling, gene regulation, hematopoietic cancers, genome editing, computational biology

Project Description:
Our research focuses on how cytokines (interferons, interleukins, growth hormone, prolactin) regulate complex genetic loci and the physiological impact of mutations that deregulate key regulatory components, such as transcription factors. Specifically, we address the role of transcription factors from the STAT family in executing cytokine action in mammary tissue during pregnancy[1] (see left panel of figure), in liver and in the immune system exposed to viruses and vaccination[2].

We are identifying genetic regulatory elements using tools of biochemistry and bioinformatics, followed by genetic investigation and validation through genome engineering[1,3]. Mutations in STAT5B, a transcription factor discovered by our lab, are frequently found in patients with specific T cell leukemias (see right panel of figure) and we investigate the underlying genetic mechanisms using genetic tools.

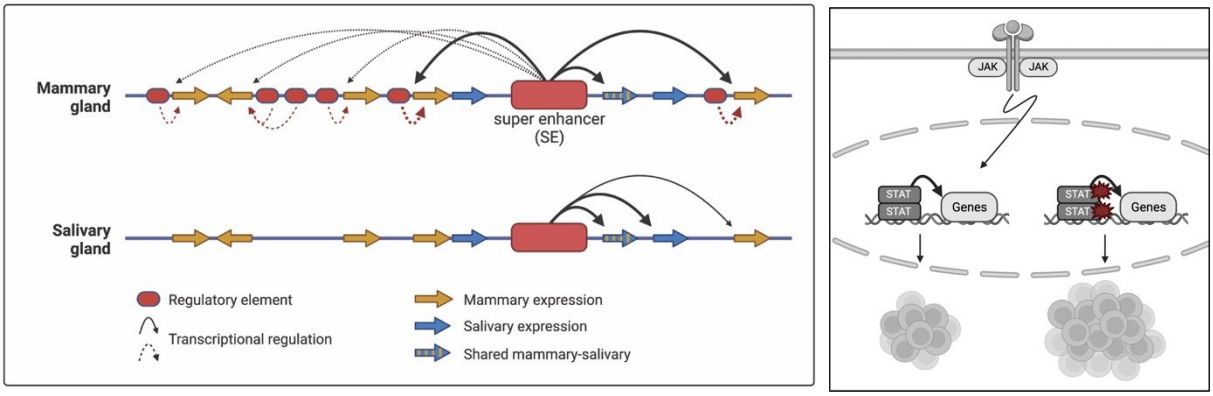


Figure
Left panel: expression of complex genetic locus composed of several genes is controlled by a super enhancer and several gene-specific local enhancers, all of which bind a plethora of transcription factors.
Right panel: cytokines activate genetic programs, a process mediated by membrane receptors, cytoplasmic tyrosine kinases and STAT transcription factors that shuttle to the nucleus and activate genes. Mutations in the STAT transcription factors can activate aberrant genetic programs that result in the development of disease.

Diversity Statement:

In hiring we look for enthusiasm for genomic research, character, scientific background and future promise for accomplishment. We work towards mentoring people to learn new skills as well as expanding their professional aspirations.

Our lab promotes the active involvement of individuals who demonstrate a steadfast dedication to fostering diversity, with a special emphasis on those hailing from underrepresented groups. This ethos closely aligns with the NIDDK unwavering commitment to advancing inclusion, diversity, and equity.

Our concept of diversity spans a broad spectrum of dimensions, encompassing but certainly not limited to race, ethnicity, gender, sexual orientation, disability, socioeconomic status, and cultural heritage. We firmly recognize that diversity is a dynamic catalyst for innovation and excellence. Our dedication extends to cultivating an environment that embraces individuals from all walks of life and perspectives, a commitment that is reflected in our recruitment practices.

The mission of NIH is to delve into the fundamental aspects of living systems and their behaviors, with the goal of applying this knowledge to advance health, extend life, and mitigate illness and disability. We hold a steadfast belief that realizing this mission necessitates the assembly of a team that mirrors the vibrant tapestry of experiences, viewpoints, and backgrounds woven throughout our society. In this spirit, we are proactively seeking Postbaccalaureate candidates who can actively contribute to our vibrant, diverse, and inclusive community.

1. Lee, H.K., Willi, M., Liu, C. & Hennighausen, L. Cell-specific and shared regulatory elements control a multigene locus active in mammary and salivary glands. *Nat Commun* **14**, 4992 (2023).
2. Lee, H.K. *et al.* mRNA vaccination in octogenarians 15 and 20 months after recovery from COVID-19 elicits robust immune and antibody responses that include Omicron. *Cell Rep* **39**, 110680 (2022).
3. Lee, H.K. *et al.* Targeting fidelity of adenine and cytosine base editors in mouse embryos. *Nat Commun* **9**, 4804 (2018).

Kenneth A. Jacobson, PhD
Laboratory of Bioorganic Chemistry

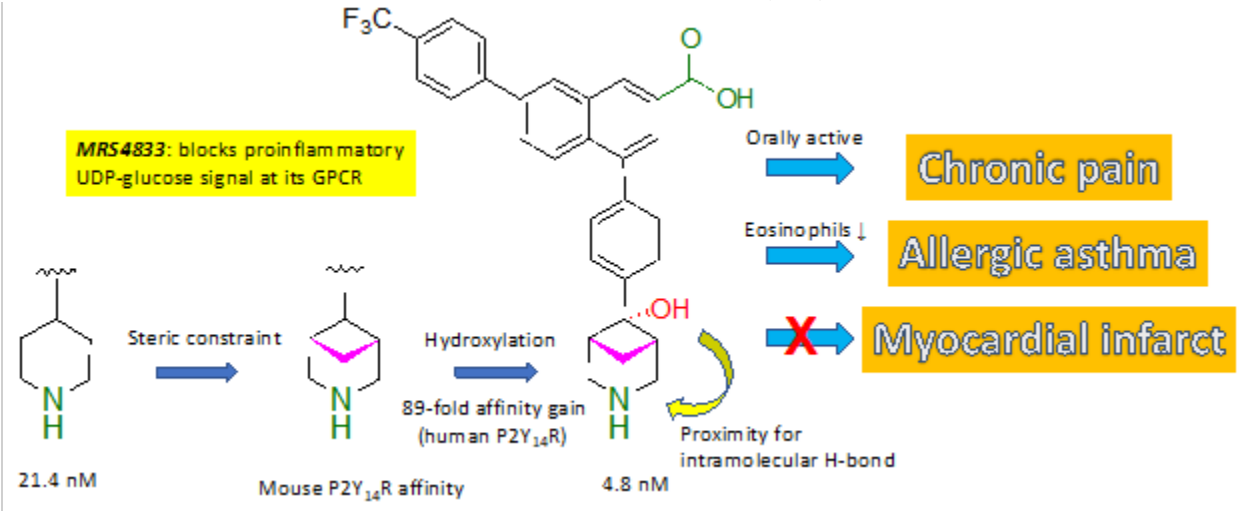
Keywords: GPCR, Medicinal chemistry, Drug discovery, Purinergic signaling, Adenosine, P2Y receptors

Project Description:

Title: Modulators of purinergic signaling

We emphasize four aspects of studying the purinergic receptors (including members of the adenosine and P2Y receptor families) by pharmacological and chemical methods: 1) design and chemical synthesis of novel and selective agonists and antagonists based on structure activity relationship (SAR); 2) protein structure-function studies; 3) exploring the novel biological role of such receptors; and 4) conceptualization of future therapeutics.

We are performing a comprehensive, medicinal chemical study of the SAR of PPTN analogues (in conjunction with molecular modeling), and we have discovered potent antagonists that have more favorable drug-like physical-chemical properties. Recently identified MRS4833, containing a cyclobutyl group, reduces chronic neuropathic pain in mice and inflammation in an asthma model, probed through our collaborations with researchers at St. Louis Univ. and NIEHS (NIH).



We are also very interested in continuing our exploration of adenosine receptor (AR) modulators as potential therapeutic agents. Synthetic selective ligands that either mimic the action of adenosine (i.e. agonists) in a fashion specific at a single subtype, or suppress it (i.e. antagonists), can be applied with great benefit in models of disease states, and therefore such agents are being explored as potential pharmaceuticals. For example, selective A_{2A} and A_{2B} AR antagonists can benefit patients suffering from neurodegenerative diseases. On the other hand, AR agonists are more applicable to treating other

chronic diseases, e.g. in inflammatory diseases and cardioprotection. Four of the small molecular ligands of the A_3 AR subtype discovered in our lab are already in clinical trials for psoriasis, nonalcoholic steatohepatitis, hepacellular carcinoma, stroke and glaucoma. Thus, we are constantly searching for the most viable disease targets and translational opportunities for our technology. Our collaborations include studies of the role of ARs in the central nervous system, inflammatory/immune system, cardiovascular system, skeletal muscle, and other systems throughout the body.

Diversity Statement:
As an elected member of the NIH Assembly of Scientists (AOS), I am active in the promoting the cause of diversity and inclusion, as well as the NIH-wide effort to reduce harassment of any sort in the workplace. The AOS acts as an advisory group to the Deputy Director of Intramural Research, M. Gottesman, with whom we meet monthly to discuss issues that affect the entire NIH scientific staff. The AOS interfaces with other senior NIH leadership, such as Dr. Alfred Johnson, NIH Deputy Director for Management, to get clarification of current NIH policy and to voice our opinions on key issues. One recent issue is how our constituents are being impacted, and whether there are different impacts by gender, race, or ethnicity, based on the NIH-wide COVID19 workforce impact survey. I am a member of three AOS Committees: Workforce, IT, and Travel (as chair). The Workforce Committee has been working on building a network with historically black colleges and universities (HBCUs) and is discussion other possible remedies for the current underrepresentation among NIH tenured researchers. I have created a list of HBCUs that have graduate programs in chemistry and biology for the committee. I also give lectures during the summer to various high school and college minority student groups to tell them about our work in medicinal chemistry.

Within my own research group, I also seek out underrepresented minorities as summer students and post-BACs and as post-doctoral candidates. I have a record of providing a diverse workplace, which I hope makes potential applicants from underrepresented minority groups feel comfortable about joining our lab. For example, a large fraction of our post-BACs is from underrepresented or disadvantaged groups. The fellows are highly diverse geographically, and with ~40% of the cumulative staff being female, and they have originated from 16 different foreign countries. For example, a female student trainee in my lab in 2011, from Howard University, has progressed in her career to Supervisor/Sequencing Specialist at the Institute of Genomic Sciences. Three of our recent female Post-BAC IRTAs have entered graduate school at Weill Cornell Graduate School, where they are currently studying, and two of whom belong to underrepresented minority groups. I have always been very supportive of my departing postdocs and have gone to lengths (such as allowing them to be co-corresponding author, when applicable) to facilitate their obtaining academic positions afterwards.

Andrew Lutas, PhD
Neuromodulation and Motivation Section; Diabetes, Endocrinology, Obesity Branch

Keywords: Appetite; Food addiction; Fluorescent biosensor imaging; Neuromodulation; Behavioral neuroscience

Project Description: Neuromodulator signals regulating cue-induced feeding
Almost 50% of American adults are obese, an alarming number considering the associated risks, which include heart disease and diabetes. External cues (e.g. food advertisements) and contexts (e.g. social gatherings) play an important role in motivating us to eat and together with the easy access to high-calorie palatable foods contributes to the obesity epidemic. Our ability to willfully override these cue-triggered food cravings is limited and necessitates therapeutic assistance. The brain contains neuromodulatory circuits that regulating both the learning and expression of cue-associated food seeking behaviors in humans and model organisms. Targeting these neuromodulatory circuits with pharmacological treatments is a promising avenue for suppressing unwanted food seeking. However, our mechanistic understanding of these neuromodulatory systems during cue-evoked food seeking is limited.

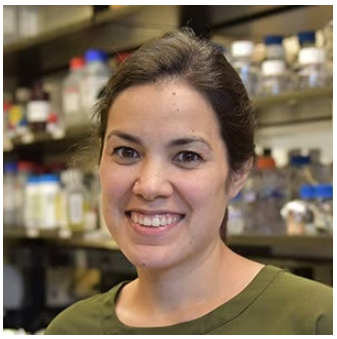
The amygdala is a critical brain area necessary for our ability to learn about the salience and value of cues and contexts. In addition, the amygdala and its interconnected brain areas is important for regulating on-going motivated behaviors, which can often be conflicting such as the drive to replenish energy while also avoiding predators. Animals learn and use external stimuli to make decisions about when to prioritize one motivated behavior over another. Neuromodulators such as dopamine, serotonin, enkephalin, as well as other hormones and neuropeptides can instruct the learning of these cues and their state-dependent salience.

Our goal in this project is to develop a causal mechanistic understanding of how neuromodulatory signaling in the amygdala controls the state-dependent learning and expression of food associated cues and contexts. We aim to achieve this goal by using fluorescent biosensors that report on either the presence of these neuromodulators or the postsynaptic biochemical and molecular signaling (cAMP, protein kinase A activity, transcription factors, and others). In addition, by using customized mouse behavior equipment and two-photon microscopes we can continuously track these fluorescence biosensors with subcellular resolution and high temporal precision across weeks. This allows us to watch neuromodulatory signaling as mice learn about food-associated cues, as motivation shifts to prioritize different goals, and as animals physiologically change (e.g. become obese). Finally, we can employ both optogenetic activators and inhibitors of neural and biochemical signals to causally investigate the role of neuromodulation in the amygdala.

Diversity Statement:
As a child of immigrant parents who fled a communist dictatorship, I am directly aware of how familial circumstances and societal inequalities can influence one's upbringing. Despite these challenges, being a white male has afforded me many privileges and shielded me from most forms of discrimination. I strive

to be a mentor that can contextualize my identities and use my agency to help others achieve success. Recruiting underrepresented minority scientists, passing on my research knowledge in a safe lab environment, and supporting career advancement of minority scientists are the most direct ways that I can make a significant contribution to DEIA issues in academia.

I have been fortunate enough to have mentored several incredible students that come from diverse backgrounds in the past two years. All but one identified as women and over half identified as underrepresented minorities in STEM. Remembering my early days in science, I have helped each student build self-confidence and battle imposter syndrome, all while maintaining a high standard of scientific excellence. As part of my mentoring philosophy, I entrust my students with important scientific studies—often resulting in co-authorship on publications—and provide opportunities for experiential learning to develop the independence to achieve their goals and the resilience to overcome their challenges. I emphasize that science is about developing exciting, yet rigorous, scientific goals and learning from failure. Having these insightful experiences early on is critical in the retention of scientists. I can always do more, which is why I will devote my time to personally training future scientists from all backgrounds while supporting an open and affirming lab culture.



Katherine McJunkin, PhD or MD
Laboratory of Cellular and Developmental Biology

Keywords: miRNAs, non-coding RNA, RNA decay

Project Description:
MicroRNAs (miRNAs) are endogenously-encoded small non-coding RNAs that regulate the expression of complementary mRNAs. Because of their roles in normal gene regulation, miRNAs are essential to most developmental processes, and their mis-regulation can contribute to diverse human diseases. Our lab is interested in how miRNAs are regulated post-transcriptionally. One aspect of regulation we are interested in is how miRNAs and their protein co-factor Argonaute are targeted for decay. We hypothesize that decay is a crucial point of regulation since the precise spatio-temporal expression of a miRNA in a specific stage and tissue is often crucial to its biological role. The post-bac project would be to investigate mechanisms of miRNA decay using techniques that include CRISPR/Cas9-mediated genome engineering, forward genetic screens, and next-generation sequencing.

Commitment to Diversity
I believe that problems are best solved by a group with diverse perspectives, which we are currently largely lacking in the scientific community. My primary contribution to increasing the diversity of the scientific workforce is my mentorship of a very diverse group of trainees. We regularly discuss diversity and inclusion as a group informally. As part of our Individual Development Plan annual review, trainees are also provided with a built-in opportunity to raise concerns about lab culture and inclusivity. Outside of my lab, I have volunteered as a mentor in two mentoring initiatives: the secondary mentor program in NIDDK which provides trainees with a second advocate/advisor beyond their own PI, and the Worm Board paired mentoring initiative which aims to support trainees and faculty from minoritized backgrounds. Beyond NIDDK, I serve as a member of the Stadtman Developmental Biology faculty search committee and the Johns Hopkins-NIH Graduate Partnership Ph.D. program admissions; in these capacities, I judge applicants with an acute awareness of implicit bias against minoritized groups (aided by annual NIH anti-bias training). Finally, as a woman in science, I serve as a positive role model for female trainees through publishing good science, providing supportive mentorship, and being a visible member of the scientific community.

Priyanka Narayan, PhD
Genetics and Biochemistry Branch

Keywords: Neurodegeneration, Alzheimer's disease, APOE, metabolism, iPSC-derived glia, cell biology, genetics

Project Description:
Diet has long been known to change brain function. Neuroinflammation is a characteristic of metabolic diseases. Metabolic alterations are increasingly being appreciated as a component of many neurological diseases. Microglia are a resident innate immune cell type in the brain involved in many neurological diseases. In our lab's preliminary work, we discovered that flux through the triglyceride biosynthesis pathway is necessary for microglia to mount a full response to immune challenge. We also discovered that we could modulate the protective vs. disease state of microglia by changing their internal lipid biosynthesis pathways. Finally, we observed that feeding microglia a fatty acid, oleic acid, increased their response to immune challenge.

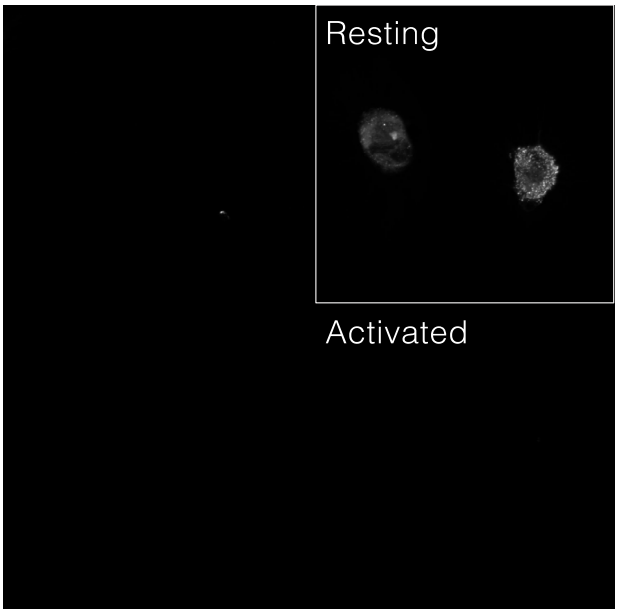


Figure 1. Human iPSC-derived microglia can mount a response to immune activation by changing their morphology (left) and accumulating lipids (right, white stain).

We would love to have postbaccalaureate scholar join the team to decode the relationship between fatty acid supplementation and microglial response to immune challenge. We would like to do this both in the context of healthy microglia and microglia harboring mutations associated with late-onset Alzheimer's disease.

The experimental strategy we plan to use is to expose human induced pluripotent stem-cell (iPSC) derived microglia to exogenous saturated, mono-unsaturated, and poly-unsaturated fatty acids of a variety of chain lengths. Then, we will profile the transcriptome and secreted cytokine profile upon exposure to various fatty acids in the presence and absence of activating agents like lipopolysaccharide. In parallel, we would like to characterize the metabolism of these fatty acids by profiling the cellular formation of fatty acid stores in lipid droplets, key organelles in mediating microglial neuroinflammation.

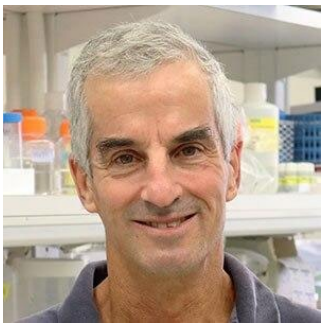
Once we have a greater understanding of how different fatty acids impact immune activation of microglia, we can use chemical modulation of biosynthesis pathways to steer microglia towards a protective state.

Diversity Statement:

Traditional structures within academia have historically excluded certain groups—women, racial and sexual minorities, individuals with visible and less visible disabilities. This is reflected in the composition of our scientific communities where those in positions of power and leadership tend to be white and male. These traditional structures reflect systemic discrimination present in broader society. DEIA-focused initiatives in academia present an opportunity to adjust the traditional structures to include and support individuals from underrepresented backgrounds in the academic enterprise. These initiatives are crucial for building and growing an academic community that better reflects the diversity of our country.

My approach to promoting DEIA in STEM fields occurs at four levels: 1) Building awareness of systemic discrimination within my own research group and within the larger institution, 2) Participating and designing DEIA-focused initiatives within my research group and larger institution, 3) Recruiting a diverse research team, and 4) Incorporating an awareness of diversity within my own research. To build awareness for myself and my team members, I've participated in initiatives like the Groundwater training and design data-driven journal clubs within my own lab to explore problems with systemic discrimination and innovative efforts to address these problems in academia. As a former member of the Assembly of Scientists, I advocated for more inclusive practices as a part of the Stadtman Recruitment Process. I also participated in summer research initiatives to introduce trainees from different backgrounds to the research at NIH. I've recruited a team from a variety of personal and professional backgrounds and helped build internal lab mechanisms to establish support and trust. Through societies like SACNAS, I've been fortunate to be able to share my work and recruit from diverse applicant pools.

I would like to discuss how I incorporate DEIA within my own research in depth. My group studies the biology behind Alzheimer's disease risk and resilience. One of the genetic mutations we study, APOE4, increases risk for Alzheimer's disease up to 12-fold in Northern European populations—it is commonly known as the strongest genetic risk factor for sporadic Alzheimer's disease. In populations of African descent, however, the effect of the *APOE4* mutation is far less potent with barely detectable association with Alzheimer's disease. For many years, genetics research has been performed exclusively in white, northern European populations and these genomic intricacies have been largely ignored. Even the functional research we do to understand these genomics-driven hypotheses has been largely conducted in iPSC-lines from White donors. I wanted to change the Alzheimer's disease research community addresses racial diversity. Through the NIH Center for Alzheimer's and Related Dementias (CARD), I am spearheading an effort called the iDA project (**i**PSCs for **D**iversity in **A**lzheimer's). We are generating 200 new iPSC lines from an assortment of patent donors. This repository will be far more diverse than any existing biobank. We are also generating foundational data on these lines to provide to the community a resource for studying genetic risk factors in diverse ancestral backgrounds.



Daniel C. Masison PhD
Laboratory of Biochemistry and Genetics

Keywords: Protein quality control, Protein chaperones, Amyloid

Project Description:
The overarching goal of our program is to understand how protein quality control factors and systems maintain cell health by protecting and managing proteins from synthesis to degradation and from optimal environmental conditions to extreme environmental stress. We are particularly interested in the structure/function relationships of protein chaperones, which help proteins to adopt and maintain their native structures, to protect them from misfolding caused by stress, to restore their functions after exposure to stress, and to promote degradation of irreparably misfolded proteins. We use yeast as a model eukaryotic cell.

Chaperones Hsp90 and Hsp70 are essential and among the most highly conserved of proteins. Human versions of both support all essential functions in place of their yeast counterparts. Both are intensely studied for therapeutic value in protein folding disorders. They help maintain integrity of the proteome by interacting with protein "clients" in ATP-regulated binding cycles, which depend on interaction with large cohorts of co-chaperones that regulate their activities. Hsp90 and Hsp70 undergo large conformational rearrangements during their client binding-release cycles.

The project aims to define more clearly the molecular mechanics involved in Hsp90 and Hsp70 reaction cycles and how co-chaperones fine-tune their activities to optimize them for diverse functions.

For yeast, human, and several disease organisms we showed binding of ATP, but not hydrolysis, is enough to promote the conformational changes needed for Hsp90 to support cell growth, which has forced the field to reconsider the role of ATP in Hsp90 function. We identified second mutations in the ATPase domain that improve efficiency of a hydrolysis-dead Hsp90. Current work using substitutions in the ATP-binding pocket with biochemical and biophysical techniques focuses on how certain residues influence the ability of the gamma phosphate to orient in a way that allows it to stabilize a "closed", substrate-bound conformation. We also are testing our hypothesis that the second mutations increase Hsp90 activity by promoting exchange of ADP for ATP, are confirming dispensability of ATP for human Hsp90 in human cells and assessing effects of amino acid substitutions on intrinsic and co-chaperone regulated activities. This work will provide important insight into Hsp90 function at a molecular level.

Human Hsp70 co-chaperone DnaJB6 has potent anti-amyloid activity that prevents disease-associated proteins A-beta (Alzheimer's), alpha-synuclein (Parkinson's), and polyglutamine (Huntington's) from forming amyloid. We showed that DnaJB6 counteracts propagation and toxicity of several amyloids in our yeast system, but it's potency varies considerably depending on differences in the structures of the

amyloids, even those composed of one and the same protein. Current studies that focus on structure-function relationships aim to identify and characterize the molecular mechanisms that underlie anti-amyloid properties of DnaJB6. We are finding that deletions or point mutations in various structural domains of DnaJB6 can affect its ability to inhibit amyloid propagation and are continuing to study how even subtle changes in structure can profoundly affect this activity.

Diversity Statement:
We are aware that DEIA biases together with underrepresentation in leadership positions pose difficult challenges to all trainees wishing to advance in their careers in science. We have not and do not discriminate by seeking out or declining applicants on the basis of any characteristic. Accordingly, we have taken on roughly equal numbers of evidently male and female trainees of very broad economic, age, education, and research backgrounds from India, China, Japan, Korea, Georgia, Turkey, France, Ireland, England, Latin America and the US. Their backgrounds include African American, American Indian, Asian, Caucasian, Hispanic and Slavic.

We have been proactively supporting underrepresented trainees for two decades. Much of this activity has been through participation in the NIH Diversity Summer Research Training Program (Office of Minority Health Research Coordination) and other summer training programs, although we also do so using longer training positions. Economic exigencies, which can affect people of any definition, lead to underrepresentation. We maintain awareness that applicants might face such difficulties. Our goal is the same for all trainees regardless of how they might be characterized: to understand their particular situations and prepare them as best we can for the next step in their careers.

Sushil G. Rane, PhD
Diabetes, Endocrinology and Obesity Branch

Keywords: Neuroscience, Metabolism, Pancreas, Insulin, Glucose

Project Description:
Title: The hunger games revisited: neuronal mechanisms underlying appetite and satiety.
Appetite is a desire to eat. Appetite can be classified into homeostatic or hedonic, reflecting a desire of eating to live versus living to eat, respectively. Homeostatic appetite reflects an overriding effort to combat hunger and restore the energy needed for survival and reproduction. Hedonic eating, on the other hand, reflects a desire for palatable foods, regardless of the energy needs of the body. Understanding the mechanisms that underlie homeostatic versus hedonic feeding and hunger versus appetite are at the forefront of basic neuroscience research. The knowledge is relevant to understanding the physiology of eating and eating disorders like obesity, anorexia, and diabetes.

In 1921, over a hundred years ago, a Nobel prize winning discovery by Banting, Best and colleagues identified insulin – a hormone that lowers blood glucose levels. Since then, insulin has been a lifesaver for diabetics. Insulin is synthesized and secreted by the pancreatic islet β-cell. Well before insulin's discovery, the work of Claude Bernard and Ivan Pavlov established that blood glucose levels and pancreatic secretions can also be controlled by the central nervous system.

The brain has a selfish interest in glucose-level regulation considering that glucose is the primary energy source for the brain! Persistently low glucose levels could be fatal, depriving the brain of its fuel. To guard against that possibility, there are mechanisms in place to sense glucose levels via glucose sensing neurons in the brain. By virtue of its ability to lower glucose levels, it was logical to consider that the brain would also be able to control insulin levels. Indeed, the possibility that the brain would have a say in when and how much a glucose-lowering hormone like insulin is secreted made logical sense. However, this hypothesis remained untested.

Recently, our lab identified and characterized a subpopulation of pre-autonomic neurons in the paraventricular hypothalamus region of the brain that communicate with pancreatic β-cells via the sympathetic nervous system (*Cell Metabolism*, 2022). Activation of these neurons suppresses insulin secretion and increases glucose levels. Conversely, inactivation of these neurons results in hypoglycemia. These neurons get activated upon sensing hypoglycemia, presumably to suppress insulin secretion and restore glucose levels back to normal. Our brain elicits such protective mechanisms to overcome extreme and uncontrolled hypoglycemia that can be fatal.

The incoming graduate student will expand on the above-mentioned findings. Specifically, conditioning experiments will be designed where mice will learn operant tasks to related to feeding behavior. The behaviors will be correlated with minute-to-minute fluctuations in glucose levels measured via *in vivo*

automated glucose telemetry. The experiments will unravel the neural circuits that respond to food taste, palatability, and reward value. Subsequently, viral tracing, imaging, and activity determination of the targeted neurons will be achieved via microscopy, chemogenetics and optogenetics techniques to interrogate circuit function and *in vivo* fiber photometry and calcium signaling response measurement to monitor neuronal activity. Finally, single cell sequencing approaches will decipher the transcriptomic changes that underlie these fundamental neural circuits.

Diversity Statement:

Commitment and contributions to NIH efforts related to diversity and inclusion

Scientific progress is critically dependent on a community of open-minded individuals with varied perspectives. Yet, certain ethnic, gender and socio-economic groups are unequally represented in the scientific workforce, whether it be at the trainee or at the faculty level. Underrepresented groups face unique challenges ranging from isolation to bias and discrimination. Ensuring that all scientists are equally encouraged and supported is critical for real scientific progress.

A fundamental component of promoting diversity and equity is to acknowledge that the playing field is uneven. Structural and implicit biases undermine diversity. It is tempting to judge someone based on their GPA, place of training, amount of research experience, and the quality of their publications. However, these metrics discriminate against students who were unable to acquire training at top-tier research institutions or with influential mentors and were unable to publish in high impact journals due to circumstances beyond their control. This issue became most obvious to me when I arrived at the NIH. Given that, I have learned to evaluate candidates holistically. As is obvious from my CV, the contributions of motivated trainees with diverse and underrepresented backgrounds are the foundation of my labs research program. The learning curve for my students and fellows is a bit steeper than usual as a result, but I believe their less privileged background contributes to a stronger work ethic, remarkable maturity, and broader perspective.

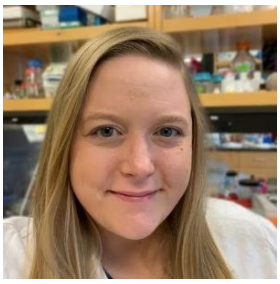
Increasing diversity is counterproductive if underrepresented groups do not feel supported. I have participated in outreach efforts to inspire scientific interest in students from disadvantaged backgrounds. I have received multiple awards from the NIH Diversity Summer Research Training Program (DSRTP) for undergraduate students. By sharing my expertise, I hope to level the playing field so that underrepresented trainees are better equipped to succeed. I also hope that my success as an underrepresented scientist will further encourage trainees about their potential path to success.

Effective mentorship is critical in promoting scientific productivity. My mentoring approach focuses on recognizing each lab member's unique background, goals, and needs. I work with each person to make short and long-term plans to work toward our mutual goals, ranging from scientific projects to learning new skills. I meet with trainees frequently to assess their progress. I promote a healthy work-life balance and I care about each lab member as a person. All my former mentees have made tangible scientific contributions and continued to academic, research or healthcare careers.

This year my lab is hosting Ms. Ashley Monique Bolds who received an NIDDK Distinguished Post Baccalaureate Fellowship and Mr. Benjamin Darko an international student from Ghana who is studying at Colgate University.

Summary. My strong commitment to diversity, equity, and inclusion is demonstrated by my mentoring history via promoting diversity and gender equality in trainees (26 women, 29 men over the past 21

years). By combining this commitment with my scientific vision, I hope to make a significant impact in the training experience of all my mentees.



Margaret Rodgers, PhD
Laboratory of Biochemistry and Genetics

Keywords: RNA, RNA-protein complexes, Single-molecule fluorescence

Project Description:

Ribonucleic acids (RNAs) are versatile and dynamic biomolecules and major players in gene expression. RNA not only encodes for proteins (mRNA) but also it fulfills numerous other cellular functions including comprising major portions of the protein synthesis machinery (ribosomal RNA). To fulfill their cellular function, RNAs must fold into complex three-dimensional structures and are often complexed with protein co-factors. Virtually all RNAs interact with RNA-binding proteins which help RNAs fold, direct modification, carry out processing, and protect RNAs from degradation. RNA-binding proteins can interact with RNAs for short periods of time (e.g. RNA chaperones, modification enzymes) or they can bind stably to form a ribonucleoprotein particle (RNP). In my lab, we aim to understand how RNAs and RNA-binding proteins come together to form RNPs and how RNP assembly is integrated into gene expression.

My lab utilizes a combination of genetics, biochemistry, and biophysics to characterize the mechanistic details of RNP assembly for a variety of different RNPs. One area of the lab focuses on the assembly of a bacterial RNP that regulates gene expression in response to environmental stress. When bacteria encounter stressful conditions, such as a change in temperature, specific mRNAs need to be up- or down-regulated for rapid adaptation. To regulate a specific mRNA, bacteria overexpress a small RNA (sRNA) that contains a sequence complementary to the target mRNA (Fig. 1). The sRNA and the homohexameric protein, Hfq, seek out and bind to a target mRNA by base pairing of the mRNA-sRNA complementary regions. Base pairing and formation of the Hfq-sRNA-mRNA RNP changes the structure of the mRNA and influences its translation (Fig. 1). Importantly, recent evidence suggests that Hfq and the sRNA assemble with an mRNA while it is transcribed, thereby guiding the structure of the mRNA as it is initially formed. The mechanism for how Hfq and the sRNA find the complementary region in the target mRNA as the mRNA is transcribed is still not well understood.

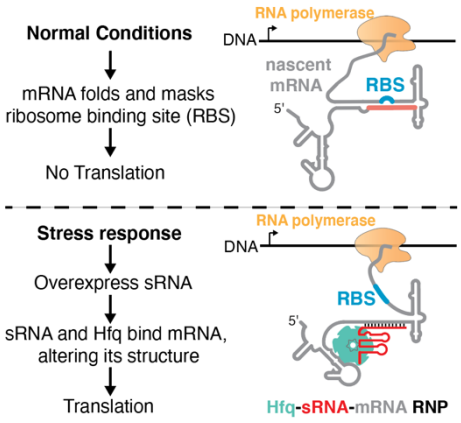


Fig. 1. The Hfq-sRNA-mRNA RNP regulates mRNA expression during transcription.

This project will examine how mutations in the mRNA predicted to change its structure influence assembly of the Hfq-sRNA-mRNA RNP and ultimately regulate translation of the mRNA. The major questions we will address are:

1. How do mutations in the mRNA-sRNA complementary region influence the timing of Hfq-sRNA-mRNA RNP assembly during transcription of the mRNA?
2. How do mutations in the mRNA-sRNA complementary region alter mRNA regulation *in vivo*?

Using single-molecule microscopy, we will examine how mutations within the complementary region affect recruitment of the Hfq and sRNA to the mRNA as it is transcribed. To do this, we will use a method that I developed called single-molecule co-localization co-transcriptional assembly which enables monitoring of both transcription of the mRNA and binding of Hfq and sRNAs in real time (1). Using this method, we will examine the timing of binding of Hfq and sRNAs relative to when the complementary region in the mRNA has been transcribed and compare the change in recruitment between different mRNA mutants. We will examine the effect of these mutations *in vivo* using gene reporter assays (2) to measure changes in regulation and determine if RNP assembly during transcription hastens regulation.

References: 1. Rodgers,M.L. and Woodson,S.A. (2019) *Cell*, 179, 1370-1381. 2. Peng,Y., Soper,T.J. and Woodson,S.A. (2014) *J Mol Biol*, 426, 275–285.

Diversity Statement:

My lab is dedicated to increasing diversity in science. I believe that everyone regardless of their race, age, gender, socioeconomic status, sexual orientation, or ability/disability should have the same opportunities to succeed and I am dedicated to work towards achieving this goal.

I believe that success in science is predicated on enthusiasm and creativity and I am focused on fostering an environment that celebrates these values. Creativity thrives in a diverse setting with people from different backgrounds, both personal and scientific, who can share their experiences to grow as individuals and as a team. I intend to increase diversity in my lab by utilizing recruitment resources that target underrepresented groups, like the Distinguished Postbac Scholars Program, as well as actively work towards eliminating unconscious bias in hiring at any level.

In addition to creating a diverse workforce, my lab values inclusivity. I believe one of the best ways to establish an inclusive environment as a mentor is to ensure that all ideas are shared and honesty about mistakes is encouraged. This attitude towards the act of science is something that inspired me to be more creative and allowed me to flourish as an independent scientist. As the PI, I will continually evaluate how well the lab grows and changes to ensure that the lab environment aligns with these core values. Specifically, I will evaluate the lab environment with check-ins like anonymous lab surveys to better understand feelings about lab climate and propose possible changes.

Increasing diversity in the workforce also necessitates that mentorship styles are adapted to effectively reach all students equally. Mentoring style is an adaptive skill that needs to be developed on individual basis and altered throughout the course of the student's career. I have been trained on developing the mentor/mentee relationship through the Delta program, an extension of the Center for the Integration of Research, Teaching and Learning (CIRTL). I have used several strategies from this course when I mentored students from different backgrounds. These experiences have helped me not only develop as a mentor but also increased my awareness of the challenges underrepresented groups face.

As my lab grows, I will continue advocating for underrepresented groups in my own lab and the broader scientific community. I am committed to advocating for underrepresented groups of different races, genders, ages, sexual orientations, ability/disability, or socioeconomic backgrounds. I strongly believe that building an inclusive, diverse research group will promote creativity, engender enthusiasm, and therefore will be a catalyst in achieving our short and long-term scientific goals.

Arthur Sherman, PhD
Laboratory of Biological Modeling

Keywords: Mathematical modeling, Diabetes, Insulin resistance, Beta-cell function,

Project Description:
My group studies how and why people develop diabetes, usually as a consequence of weight gain over many years. Diabetes is a complex disease, with a wide range of patterns that differ for individuals and for groups, such as racial/ethnic groups. We described this in a paper entitled, "Type 2 Diabetes: One Disease, Many Pathways" (PMID: 32663101). We argued that the complexity can be understood by keeping in mind that diabetes is mainly determined by the balance of two factors. First, as people gain weight, their bodies do not use insulin efficiently, a phenomenon called insulin resistance. This tends to make their blood glucose rise. Second, in response to the rise of insulin resistance, the beta cells of the pancreas secrete more insulin to compensate. Diabetes results when the compensation is inadequate to handle the degree of insulin resistance. Our contribution was to make these widely understood verbal descriptions precise by incorporating them into a mathematical model using differential equations.

The balance of insulin resistance and insulin secretion varies among different groups, with insulin resistance dominating among African Americans and Native Americans, for example, while inadequate insulin secretion is dominant among people from East and South Asia. A paradox that has generated a lot of controversy is that African Americans have high risk of developing diabetes yet have high levels of insulin. The high insulin levels arise from a combination of increased secretion and reduced extraction of insulin from the circulation by the liver, relative to insulin resistance. This has led to the hypothesis that the high level of insulin is itself a risk factor because insulin has been shown to increase insulin resistance in addition to responding to high insulin resistance. In the Pathways paper mentioned above, we showed by mathematical simulations that reduced clearance probably plays only a small role in diabetes risk because the benefit of higher insulin outweighs the harm of a further increment in insulin resistance, but more work is needed to study this systematically. The net effect of increased secretion is more subtle because increased secretion makes the beta cells work harder, which may make them more likely to fail over time.

I am looking for someone with a background in mathematics, physics, engineering or other quantitative discipline that includes differential equations, linear algebra, and programming in a language like Matlab, R or python to help in solving this important public health and health equity issue. A background in statistics will also be helpful in this work.

Diversity Statement:

I grew up in a blue-collar family and know what it is like to be one of the only students in a graduate school class whose parents were not college educated professionals or academics. I myself worked in a variety of non-professional blue- and white-collar jobs before deciding to go back to school for a Ph. D. in mathematics. My last job before graduate school was teaching high school math in an urban school district where 52 languages, prominently including Spanish, were spoken. These experiences gave me the opportunity to learn to work effectively with people from a wide range of backgrounds. In addition, being a mathematical modeler swimming in a sea of experimental and clinical biologists necessarily requires being able to communicate across barriers of scientific culture and thinking styles.

My recent activities include serving as a mentor to Dr. Stephanie Chung, an Afro-Caribbean Lasker Clinical Scholar on the tenure track in NIDDK. I contribute to mentoring Stephanie Chung and Anne Sumner's fellows, a group enriched in minority fellows and visiting trainees from Rwanda. I participate in their joint semi-monthly journal club, and I instructed Dr. Chung's post-bac fellow Mirella Galvan de la Cruz in using Matlab for mathematical modeling, resulting in authorship for her on an important publication. This year I co-mentored Nathan Sala, a DSRTP summer intern with Dr. Chung. I am also mentoring trainee Vijaya Subramanian, who is a non-traditional scientist from South Asia returning to research after fulfilling many years of family responsibilities.

My work on diabetes has a major health equity component, as described in the project statement. In May of this year, I was invited to speak at the NIH Asian American Pacific Islander Research Conference about my modeling work on improving diabetes screening for this group. Their deficit in insulin secretion would not be picked up by current standards of the American Diabetes Association, which are based on studies mostly of people of European descent. African Americans similarly have a different profile than European Americans, which makes standard screening standards less than optimal. Dr. Chung's data from minority youth in Washington, DC and her clinical insights will be central in pursuing the proposed project. I have also played a supportive role in Dr. Sumner's studies of African immigrants living in the US and her planning for large-scale diabetes prevention initiatives in Africa.

Anne E. Sumner, MD
Senior Investigator
Chief, Section of Ethnicity and Health
Director, NIH-Rwandan Health Program

Keywords: Diabetes, Health disparities, Social justice, African Americans, African immigrants

Distinguished Postbac Research Plan

The goal of the Section of Ethnicity and Health is to recruit trainees who will become health disparity researchers with the knowledge and skills to design new protocols which lead to improved health care for underserved populations. The program is directed towards recent college graduates who are planning to apply for an MD or an MD-PhD or a PhD in the social, nutritional or physiologic sciences. The training goal for postbac fellows in the Section of Ethnicity and Health is that in a 2-year period they will become Clinical Investigators with the skills and tools to set up and run a clinical investigation where none previously existed. The Postbac will gain experience with recruitment, screening, enrollment, scheduling, informed consent documents, patient interaction (often called bedside manner), administering psychosocial questionnaires, collecting blood samples at the bedside, aliquoting them and transporting them to the proper laboratory for analyses and storage. Additionally, they will learn how to organize, enter and analyze data, as well as write abstracts and manuscripts for publications. In short, with this training they will have the tools, confidence, and experience to design new research protocols and successfully compete for funding nationally and internationally.

The Section of Ethnicity is specifically focused on determining ways to improve detection and prevention of diabetes in African descent populations. Currently, we are working with both African American and African immigrants and through collaborations, with Africans living in Sub-Saharan Africa. Our research questions address key metabolic, social and genetic issues. In the metabolic arena, we are focused on screening for diabetes and designing protocols which could lead to remission. In the social arena, we are examining the social determinants of health including behavior, stress, sleep, resilience, the experience of discrimination and spirituality. Our genetic research is done in collaboration with NHGRI. Within these metabolic, social and genetic arenas, each Postbac chooses a specific focus area.

While our Postbacs will work in the field of diabetes screening, the experience will give them the skills to work with diverse populations across a broad range of health conditions. In short, the skills gained working with the Section on Ethnicity and Health are designed to be foundational for a career in medicine, social justice, and health disparities research.

Diversity Statement

The Diversity focus of the Section on Ethnicity and Health is divided into three spheres:

1) The research goals are directed towards eliminating health disparities relative to diabetes risk and complications in African descent populations with a specific focus on African Americans, African immigrants and Africans living on the African continent
2) The goal of the training program is to develop a diverse workforce able to conduct health disparities research, to formulate key clinical questions and then set up and run new clinical studies where none previously existed.
3) Ensuring that trainees develop a sensitivity and inclusiveness for colleagues and trainees with disabilities.

For Sphere 1, I have personally enrolled over 1000 individuals of African descent into Section on Ethnicity and Health protocols. This kind of enrollment demonstrates engagement, trust, and communication between communities of African descent and the Section on Ethnicity and Health. Our success is this arena can be demonstrated by the fact that previous participant referral has become our leading recruitment method.

For Sphere 2, as our protocols are of direct and immediate relevance to people of African descent, trainees of African descent often seek us out for training. In addition, because of our program's emphasis on clinical training relative to health disparities, we welcome and attract trainees from many different backgrounds.

In the last 23 years the Section has had 69 trainees (72% women). The race/ethnicity of the trainees in the Section of Ethnicity and Health are provided in the table.

Diversity of Section on Ethnicity and Health Trainees 1999 to 2023

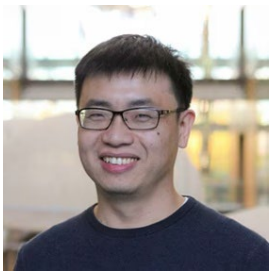
Race/Ethnicity	Number	Percent
African descent	37	54%
White	12	16%
Native American	8	12%
Hispanic	6	9%
Asian	6	9%

For Sphere 3, as a person with a mobility impairment, I walk with 2 forearm crutches and 2 leg braces and use a manual wheelchair and scooter to do my work as a physician investigator. Therefore, I seek out opportunities and inclusive policies across the NIH campus for people with disabilities. The trainees in the Section become familiar to working with people with disabilities and appreciate our outreach to the deaf community and others.

Due to the Section of Ethnicity and Health's commitment to Diversity, I have received 8 NIH Awards for improving diversity and inclusion on the NIH campus and 2 Awards for mentoring, including the Nancy Nossal Award from NIDDK and the Ruth Kirschstein Award from the OD.

In addition**,** I have been awarded adjunct faculty positions at Howard University and two African universities, specifically the University of Global Health Equity in Rwanda and the NorthWest University in South Africa.

In short, for the Section on Ethnicity and Health training a diverse and committed workforce is our highest value.



Quan Wang, PhD
Section of Nanoscale Single-molecule dynamics, Laboratory of Chemical Physics, NIDDK

Keywords: Single-molecule imaging; Phase separation; Synthetic biology; Biophysics; Physical chemistry

Project Description: Nanoscale probing of molecular organization in biological condensates
Recently, liquid-liquid phase separation was found to drive the assembly of many cellular compartments that lack membranes (also referred to as biomolecular condensates) and became an emergent new paradigm in cellular biology. While most studies of biomolecular phase separation have focused on its biological function, much less is known about its fundamental nanoscale properties, including molecular composition, heterogeneity and dynamics. This knowledge gap is largely due to technological limitations that preclude direct imaging at the nanoscale. This project aims to probe the nanoscale organization and dynamics of biological condensates using state-of-the-art, single-molecule imaging and spectroscopic tools developed in the PI's laboratory (Wilson and Wang, *Nat. Method* 19, 816; Wang and Moerner *Nat. Method* 11, 555), with the goal of comprehensive understanding of the general biophysical and biochemical principles that underpin biological phase separation and its dynamics.

Initial focus will be on synthetic systems with tunable interaction motifs (e.g. SIM and SUMO). We first aim to elucidate the dilute-phase composition following our recent publication (He et al. *Commun. Biol.* 6, 1-10). We will then explore the role of valence and stoichiometry in complex formation by generating synthetic proteins with varying number of binding subunits and controlling the concentration ratio of the components. These measurements will provide the opportunity to test a recently developed simple theory of condensate formation (Zhang et al. *eLife* 10, e62403).

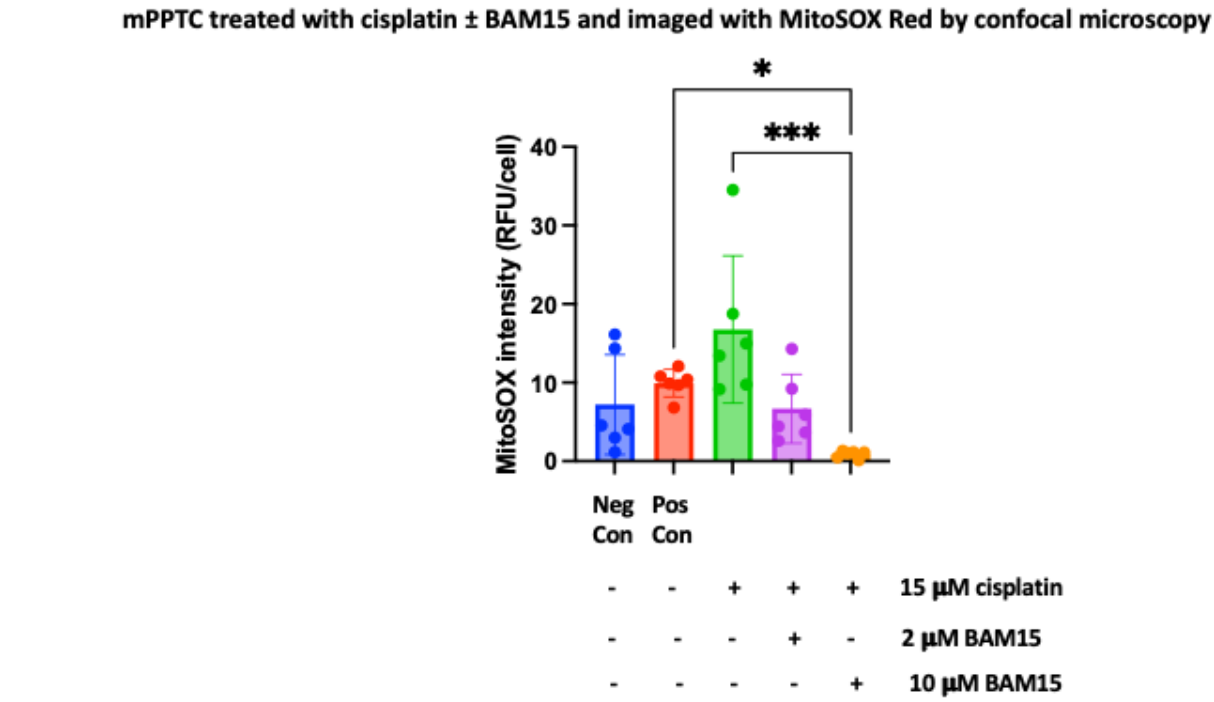
Students taking on this project will develop a wide range of experimental techniques in modern biophysical and biochemical research, including protein expression and purification, microscopy, bioconjugation, single-molecule imaging and FRET spectroscopy. He/she will also have the opportunity to develop non-conventional instrument to answer new biological questions, as well as interacting closely with theoretical collaborators.

Diversity Statement:
As an NIH investigator, beyond my roles of a researcher, I am also proud of my leadership role in furthering an equal, inclusive and diverse learning environment. Throughout my scientific career, I have been directly responsible for training and managing people from a highly diverse background, including trainees from Brazil, Turkey, Korea, Vietnam, China, India, New Zealand and underrepresented minorities with 40% of them being woman. I have also worked closely with and learned from mentors who place high values on diversity and inclusion. I strive to continue maintaining a diverse research group, promoting respect, increasing diversity in my scientific field, and urging all to continue educating ourselves about existing issues on diversity and inclusion.


Peter Yuen, PhD/Robert Star, MD
Kidney Diseases Branch

Keywords: Acute Kidney Injury; Cisplatin; Vancomycin; Mitochondrial Reactive Oxygen Species; Confocal Microscopy

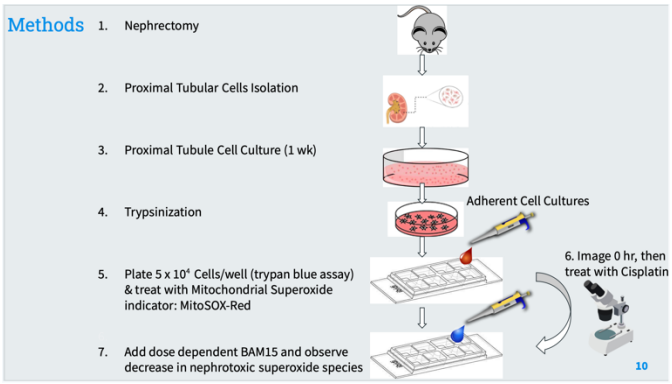
Project Description:
We have recently published a paper (Tsuji et al. 2023 JCI 133: e152401i-xvii) demonstrating that a mitochondrial protectant BAM15 is effective to treat a preclinical mouse sepsis and acute kidney injury (AKI) model, even well after the insult. We showed in vitro that BAM15 inhibits mitochondrial reactive oxygen species (mtROS) and release of mitochondrial DNA (mtDNA), which in turn stimulates more mtROS production. Despite our success in interrupting this feed-forward loop, translation into the clinic will be very difficult, partly because sepsis is heterogeneous, and it is not currently feasible to determine retrospectively when sepsis initiated after a patient has been diagnosed. However, there are two drugs commonly used that can cause AKI, cisplatin (and vancomycin (used in 35% of all hospital infections and 40-50% of patients treated with vancomycin get AKI). Since we know when they are administered, we can develop BAM15 as a co-treatment to reduce side effects, including AKI. We (especially two summer students and a graduate student) have obtained preliminary data showing that in vitro that both cisplatin and vancomycin increase mtROS in primary culture mouse proximal tubule cells (mPPTC). We have also shown that BAM15 reduces cisplatin- and vancomycin-stimulated mtROS in these cells.



If we are to translate these findings to the clinic, we must test whether BAM15 affects the efficacy of cisplatin to treat tumors, or whether BAM15 affects the efficacy of vancomycin as an antibiotic.

We plan to test the following hypotheses during the year:

a. Whether cisplatin or vancomycin increase the release of mtDNA from mPPTC.
b. Whether cisplatin- or vancomycin-induced increase in mtDNA release from mPPTC is inhibited by BAM15
c. Whether mtDNA released from cisplatin- or vancomycin-treated mPPTC can induce mtROS in naïve cells



d. Additionally we will test whether mice injected with cisplatin or vancomycin release mtDNA into plasma or urine, and whether the kidney damage is protected by BAM15 (these are established animal models)

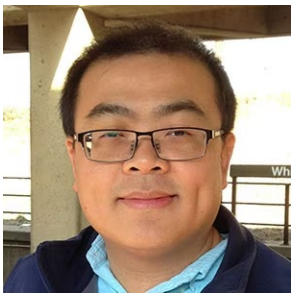
e. Most importantly, we will determine whether BAM15 affects the efficacy of cisplatin as a chemotherapeutic agent or vancomycin as an antibiotic. First these experiments will be conducted in vitro, and if successful will be validated in vivo.

f. If time permits, a similar set of experiments will be conducted by the postbac and one or two summer students for the nephrotoxin Tacrolimus, which is used to inhibit graft rejection for transplanted solid organs, including kidney.

Diversity Statement:

We have trained six African-American summer students (including one who got his PhD from UC Berkeley, and one who is getting his MD/PhD from Wash U-St Louis) and one African-American postbac (who is a medical student at Albert Einstein). Nicole Rainford was our first NIDDK DSRTP summer student, and she was a key part of the team that worked on the project described above and shown below, and given her success, we would like her to continue on this project as a postbac.

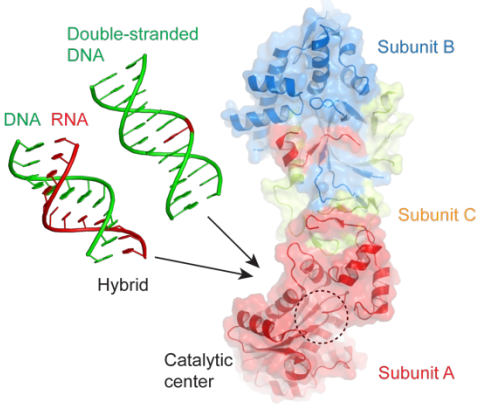
As members of the first NIDDK Race Ahead cohort, we are deeply committed to racial and ethnic equity. In our mentoring experience, there is great diversity among our African-American trainees, and we are sensitive to other forms of diversity in our efforts to provide an inclusive lab environment where everyone feels welcome and valued. We can only accomplish this by treating each person as the unique individual they are, in order to maximize their potential. We continually strive for as much transparency about our decisions as possible, with boundaries for personal/private information. To accomplish a sense of belonging, we are fostering more sharing of projects, which can be tricky and delicate, and we will continue to learn about each individual to fine-tune team dynamics and unlock each member's latent talents.



Jinwei Zhang, Ph.D
Laboratory of Molecular Biology

Keywords: Aicardi-Goutières Syndrome (AGS), RNA structure, RNase H2, RNA-protein interactions, Immunity.

Project Description:
Aicardi-Goutières Syndrome (AGS) is a severe neurological and developmental disorder that primarily affect newborn infants. Among the four human genes strongly associated with AGS, three map to the three subunits of the human Ribonuclease H2 (RNase H2) enzyme. RNase H2 is the principal nuclear enzyme responsible for the degradation of DNA-RNA hybrids generated during genome replication and transcription, and the removal of ribonucleotides (RNA) mis-incorporated into genomic DNA.



Human RNase H2

Although the crystal structures of human RNase H2 were previously reported, it remains unclear how this important enzyme achieves dual substrate specificity towards both the DNA-RNA hybrid ("A"-form geometry) and double-stranded DNA carrying RNA nucleotides ("B"-form geometry), a property unique to eukaryotic RNases H2. This gap in our knowledge is due to the unavailability of human RNase H2 complex structures bound to its substrates.

Therefore, this project aims to characterize the interactions between human RNase H2 and its two type of nucleic acid substrates using a collection of biophysical analyses. To this end we will employ rational RNA design and engineering, X-ray crystallography, single-particle cryo-electron microscopy, fluorescence-based RNase H catalytic and binding assays, etc. Once the structures are determined, extensive functional validation will be performed using site-directed mutagenesis and fluorescence-based in vitro assays. The incoming scholar will work closely with Dr. Zhang and postdoctoral fellows in the group in designing, planning, executing, evaluating, and documenting portions of the work, with the goal of publishing the research findings. Besides working chiefly with the Zhang lab in NIDDK, the incoming scholar will also collaborate with Dr. Robert Crouch's lab in NICHD on the project, to validate

structural and biophysical findings using in vivo techniques including yeast genetics, cell culture, and possibly mouse models. A second project objective is to design mutations based on the complex structures, to uncouple and disentangle the catalytic activity on the DNA-RNA hybrids from that on the double-stranded DNA with mis-incorporated RNA nucleotides. A third project aim is to use structural analyses and computer modeling to map known AGS-causing mutations onto the human RNase H2-substrate complex structures, to understand the molecular mechanisms of AGS pathogenesis. Overall, the project aims to uncover novel mechanistic insights into how human RNase H2 enzyme recognizes its nucleic acid substrates, and to expose the incoming scholar to basic science research in biochemistry, biophysics, structural biology, RNA biology, and auto-immune diseases.

Diversity Statement:
We as a research team are firmly committed to promoting diversity, equity, inclusion, and accessibility (DEIA) for all individuals in our shared workplace at NIDDK and NIH. We believe that an inclusive team that is diverse in gender, race, ethnicity, culture, religious beliefs, sexual orientation, and physical and mental abilities is inherently advantageous and conducive towards producing science and other work of the highest quality. Such diversity naturally creates an open, collegial, fair, and respectful environment that spurs and fosters creativity, innovation, and collaboration. This environment further welcomes and empowers people from a broad spectrum of geographical and cultural backgrounds and with distinct lived experiences to share, exchange and amalgamate a wide range of ideas, opinions, and perspectives.

Promoting and maximizing diversity and inclusion in our workgroup has been a significant consideration in making recruiting decisions. These efforts have produced and maintained a diverse group of trainees. Among the trainees at all levels we have had the pleasure to work with so far, more than 50% of them are women scientists and they originally come from 8 different countries. One minority summer student joined us as part of the Amgen Scholar at NIH Program on Health Disparities, and presented her research work here at the 2017 Annual Biomedical Research Conference for Minority Students (ABRCMS). Career development of the diverse trainees in our group has been a top priority. Anticipating the significant challenges that they face on the job market, we help prepare them by organizing regular group-based and one-on-one discussions about job searches, preparation of applications, and interview and negotiating strategies.

Inspired and encouraged by the strong NIH and NIDDK commitment to DEIA, we have proactively sought to further our education in understanding the origins and histories of structural and institutional racism in the U.S. and in the world, key characteristics of contemporary racial inequity in society and in the biomedical research enterprise, and in identifying solutions and actionable items to the problem. Among these learning experiences, we have particularly benefited from five days of in-depth, sobering “Groundwater” and “Phase I” training programs provided by the Racial Equity Institute (REI). We learned a great deal from the screening and group discussions of the “Picture a Scientist” documentary sponsored by NIH Office of Equity, Diversity, and Inclusion (EDI), and excellent presentations in the NIDDK Trainees Recognizing Excellence and Diversity in Science (TREaDS) Seminar series, such as key insights from the Nelson Diversity Surveys presented by Dr. Donna J. Nelson. Whenever possible, we try to attend the trainee-led TREaDS seminars and interact with the diverse speakers, even when the topics are distinct from our own research. Recently, I have had the honor of being accepted into the first cohort of participants in the inaugural NIDDK “Race Ahead” Program, an intensive months-long program designed to promote diversity and equity at NIDDK. This highly effective program combines multimedia, didactic teaching with frequent small-group activities, role playing, and sharing of personal reflections

with the group. Participants are further grouped in 4-person learning and action teams through which we support each other in regular meetings after the initial 5-day launch workshop.

To further advance and share our learning and contribute to the DEIA efforts at NIDDK, I have served as a member of NIDDK Inclusion, Diversity, Equity, Accessibility and Civility (IDEA-C) Steering Committee, and NIDDK Racial and Ethnic Equity in the Workforce (REEWork) Working Group (WG). These committees have helped design, launch, and support several highly effective DEIA initiatives including the creation of a LGBTQ+ community support working group and the aforementioned Race Ahead program.

In the future, we plan to continue, expand, and deepen our efforts, education, and services to further promote DEIA in NIDDK and NIH Intramural Research Program.