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**Arora, Himanshu**

**Title: Endothelial Cell-Derived Extracellular Vesicle’s MicroRNA serve as Biomarkers and Drivers of Prostatic Growth and Lower Urinary Tract Symptoms**

**BACKGROUND:**
Symptomatic Benign Prostatic Hyperplasia (BPH) affects 1 in 4 men and is associated with the progressive development of lower urinary tract symptoms (LUTS). There is little understanding of 1) why some prostate glands continue to grow while others do not, 2) why some men with normal prostate gland sizes still develop LUTS and 3) why some men do not respond to medical therapy. Understanding the underlying mechanisms that drive BPH can allow for novel therapeutic interventions for management of LUTS.

Hypertension, diabetes, abdominal obesity, and dyslipidemia have all been associated with increased risk of developing BPH (1-3) and endothelial dysfunction appears to be a common denominator (4-6).

Endothelial dysfunction can lead to release of endothelium derived - extracellular vesicles (ED-EVs), which contain high levels of protein and microRNA (miR) that have intricate effects on recipient cells (7). This project will result in more comprehensive understanding of which miRs can promote prostate growth and help elucidate the biological role of specific miRs from ED-EVs in men with both large and normal sized prostates.

**SUPPORTING DATA**
This is a pilot study, however there is a strong scientific premise to support the hypothesis and proposed project. Men with diseases strongly associated with endothelial dysfunction have an increased prevalence of LUTS/BPH (4, 8). Numerous animal studies have linked endothelial dysfunction and chronic ischemia to bladder and prostatic changes. Rabbits with induced endothelial dysfunction developed chronic prostatic ischemia with resultant stromal and capsular fibrosis, glandular cystic atrophy, impaired smooth muscle relaxation, and increased prostatic weight (9-11). Therefore, there appears to be a strong association between endothelial dysfunction/chronic ischemia to development of BPH/LUTS (12). Extracellular vesicles have the potential to serve as excellent biomarkers, and EVs arise in context of cytokine induced activation of endothelial cells in local and systemic inflammation.

**SPECIFIC AIM:**
Aim: To test the hypothesis that endothelial dysfunction will lead to upregulation of specific microRNAs (miRs) in endothelial derived extracellular vesicles that lead to prostatic growth in a small sample, feasibility study.

Rationale: Some prostates continue to grow excessively. Previous studies have shown that endothelial dysfunction is associated with prostate growth (12, 13). We will perform ED-EV profiling to identify microRNA (miRNA) transcripts from men with and without endothelial dysfunction (control group) to delineate potential biosignatures that could distinguish normal prostate (control, <40 g) vs. enlarged prostates (>100g). If ED-EV miR can be isolated feasibly, we will utilize isolates together with surgical specimen from transurethral resection tissue to study how ED-EVs may seed and be received by normal prostate epithelia, influence epithelial cell growth and proliferation, cytokine production and epithelium to mesenchymal transition.

Objective: To test the feasibility of determining how ED-EVs can affect prostate growth and whether these ED-EVs may be developed into diagnostic biomarkers and novel therapeutic targets.

Impact: We hope to have a more comprehensive understanding of studying endothelial derived EVs as potential biomarkers in the management of BPH-related Lower Urinary Tract Symptoms (LUTS) and provide insight to their potential use as therapeutic targets.
Atkins, Coleen

Title: Effects of Chronic Stress on Traumatic Brain Injury Outcome

DREAM Scholar Research Project

Mild traumatic brain injury (mTBI) is a major clinical problem in the United States. Although the majority of people with mTBI recover within a few weeks, a subset of people have persistent symptoms lasting for months. However, the factors that contribute to developing persistent symptoms after mTBI are unknown. One potential factor recently identified in a study of mTBI patients is pre-exposure to early stressful life experiences. Chronic early life stress is highly prevalent in the United States, and a major cause of early life stress in childhood is neglect. A key mechanism linking early life stress to neurological problems in adulthood is immune dysregulation. Exposure to stress results in an upregulation of the NLRP3 inflammasome, which enhances pro-inflammatory cytokine release by microglia in response to a subsequent inflammatory challenge. The goal of this project will be to determine if early life stress during development limits the recovery trajectory after a mTBI that occurs in adulthood by increasing inflammatory signaling through the NLRP3 inflammasome, leading to the worsening of hippocampal pathology and the development of persistent learning and memory deficits. To test this hypothesis, our DREAM scholar will investigate the following aims: 1) To determine if early life stress prior to mTBI experienced in adulthood increases microglia cell numbers, potentiates pro-inflammatory cytokine expression and increases NLRP3 inflammasome signaling within microglia, and 2) To determine if cognitive deficits after early life stress and mTBI are improved with an NLRP3 inflammasome inhibitor.

DREAM Scholar Training Plan

The DREAM scholar will be trained with a hands on approach. Our laboratory is staffed by a senior research scientist, Dr. Fabiola Placeres-Uray, who will directly train the DREAM scholar in the rodent model of mTBI, as well as the flow cytometry and qPCR experiments proposed for Aim 1. A research assistant in the laboratory, Ms. Maria Dominguez-Torres, will train the DREAM scholar in the behavioral experiments proposed for Aim 2. This direct one-on-one training and support from highly experienced personnel in the laboratory will support the DREAM scholar in completing the proposed experiments. The DREAM scholar will also participate in a one-on-one weekly meeting with Dr. Atkins as well as a weekly meetings with all personnel in the laboratory. Journal club meetings will be held every 2 weeks, and include two other laboratories led by Dr. Liebl and Dr. Brambilla, to broaden the research exposure of the DREAM scholar. The DREAM scholar will also have the opportunity to attend departmental and Neuroscience Graduate Program seminars relevant to the research project and the field of CNS trauma. The DREAM scholar will be mentored to produce a presentation at a national meeting such as the National Neurotrauma Symposium as well as contribute to the publication resulting from the research project.
**Beurel, Eleonore**

**Title: Th17 cells and depression**

Description of the research project for DREAM Scholars

There is a vital need to understand the causes of depression in order to develop effective treatments for the 11% of Americans who currently suffer from this debilitating disease. This project focuses on a new target, T helper 17 (Th17) cells, which we recently linked to depression susceptibility in mouse models and for which we identified feasible interventions. The overall objectives of this project are to identify characterize, localize and identify mechanisms of action of Th17 cells after stress and test the potential therapeutic impact of targeting Th17 cells to decrease vulnerability to depression, assessed by measuring depression-like behaviors in mice. This research evolved from the now well-established link between inflammation and depression. We reasoned that therapeutically targeting downstream, and prolonged, outcomes of inflammation may be more feasible than attempting to neutralize the multitude of cytokines that are transiently induced in the inflammatory response to stress. Inflammatory cytokines associated with depression drive the production of Th17 cells, and Th17 cells are already well-established to be toxic to the CNS. In mouse models, we found that Th17 cells are able to infiltrate mouse brain parenchyma after stress, these infiltrating cells exhibited characteristics of pathogenic Th17 cells. We also identified the gut as a likely source of Th17 cells that infiltrate the brain, and within the microbiome, Segmented filamentous bacterium are important for the development of depression-like behaviors. However, the mechanisms of action of Th17 cells in depression remain unclear. In this project, the DREAM Scholar will participate in the identification of the localization, the source, the characteristics and the mechanisms of action of Th17 cells in depressive-like behaviors. He/She will particularly focus on identifying the effects of Th17 cells on the connectome, using Thy.1 GFP mice receiving adoptive transfer of Th17 cells. We will also determine targeted strategy by which Th17 cell production following stress can be blocked in order to develop a new therapeutic strategy for depression, a prevalent, debilitating, and inadequately treated disease. The DREAM Scholar will participate in the use of engineered bacteria to target Th17 cells, and determine their effects on depressive-like behaviors. We found that molecules used by the bacteria to communicate (autoinducer2, AI-2) were increased after stress, and induce Th17 cell-dependent induction of depressive-like behavior. We will take advantage of this finding to engineer an E. coli strain containing a synchronized lysis circuit that will be activated in the gut by the bacterial quorum-sensing molecule AI-2 (signals through the LuxP circuit) to locally release an encoded nanobody antagonist of IL-17 to allow both local delivery and anti-IL-17 effects in the gut. Altogether, this innovative project at the intersection of immunology, neuroscience and microbiology will provide novel strategies to promote antidepressant actions.

**Dream Scholar Training Plan**

The aim of the training plan is to gain skills needed to become an independent investigator, and will requires both educational experience, as well as hands-on practice.

1. Acquire knowledge in neuroimmunology The DREAM Scholar will acquire an in-depth knowledge about the immune system and its effects on the central nervous system, including immune surveillance within the brain and immune interaction with glia.

2. Acquire knowledge in T cell physiology The DREAM Scholar will master techniques in immunology besides basic wet lab skills. He/She will gain experience in culturing primary T cells, differentiate Th17
cells, stain T cells for flow cytometry. Furthermore, he/she will learn how to design mouse studies to study Th17 cells, and perform tail vein intravenous injections, organ dissection and immune cell isolation.

3. Develop skills in behavioral and cognitive assessments The DREAM Scholar will receive training and guidance to effectively design, perform, and analyze behavioral measurements in mice related to mood parameters. Specifically, he/she will gain extensive experience in measuring behaviors associated with mood, cognition, and social processes.

4. Acquire knowledge in molecular microbiology The DREAM Scholar will gain basic experience in constructing and recombining plasmids, transforming bacteria to generate programmable bacteria. He/She will also learn how to perform bacterial gavage in mice.

5. Enhance scientific and professional skills The DREAM Scholar will tweak the basic skills that facilitate communication of science by strengthening his/her interaction with medical and research personnel to become the new generation of leaders in the field. He/She will improve oral presentation skills during lab meetings or by participating to conferences where he/she will develop a network of collaborators. Teaching skills will be fostered by mentoring undergraduates and rotation students in the lab. Writing skills will be improved by working on manuscripts and reviews, with feedback provided by the mentor. He/She will also participate in the various seminars and grand rounds offered at UM, or elsewhere.
Bhattacharya, Sanjoy

Title: Lipid metabolism and intraocular pressure homeostasis

Description of DREAM project:

Adult glaucoma refers to a group of irreversible blinding diseases with late onset and progressive loss of peripheral vision. Primary open angle glaucoma affects more than 70 million people worldwide and over 5 million people in USA rendering it a huge health burden. A group of people in their prime breadwinning years (35-60) experience sudden change in their quality of life and erosion of earning capacity due to unexpected and substantial loss of peripheral vision without any warning or pain. Rapid and progressive loss of peripheral vision affects them and their dependents. The elevated intraocular pressure (IOP) is frequently associated with primary open angle glaucoma as well as other forms of glaucoma. Secondary glaucoma refers to the disease which can be associated with a disease or illness and is also often associated with elevated IOP.

The anterior eye chamber is bathed with a clear liquid termed aqueous humor that provides nutrition to cornea and lens and clears away the excretory materials. The aqueous humor is produced by the ciliary body and exits through the structures in the anterior chamber through a filter-like region termed trabecular meshwork. The imbalance between aqueous humor production and exit or outflow determines IOP. It is often found that outflow is reduced due to aberrant impediment at the level of trabecular meshwork.

The outflow follows two pathways, conventional or through trabecular meshwork and uveoscleral or through sclera, which is a forced pathway usually forms due to elevated pressure and lack of conventional flow regions. The conventional flow regions often suffer aberrant blockage in glaucoma. The blockage is segmental with patchy deposits in trabecular meshwork, these regions in vitro demonstrates elevated elastic modulus.

In glaucoma suspects diurnal fluctuations in IOP are huge. It is unclear how the IOP homeostasis is maintained in the normal eyes. It is also unclear how the IOP homeostasis is decoupled in glaucoma suspects of in glaucoma. The extracellular protein deposition has been extensively investigated supporting patchy deposition. The focus thus far has been on finding targets to reduce elevated IOP in glaucoma. Prostanoid lipids have been found be effective in lowering elevated IOP.

Our laboratory is engaged in understanding the alteration in lipids in the trabecular meshwork between control and glaucoma. We find a few lipids of different classes that are able to reduce elastic modulus and hold them in reduced conditions. The elastic modulus in vitro correlate with medium term IOP homeostasis in vivo in mouse models. This project partly supported by NIH and DOD funding is available for Dream Scholars. Past medical scholars in the laboratory has successfully published multiple peer-reviewed papers and gone to residency and fellowships.

DREAM Scholar Training Plan:

The DREAM Scholar will be trained on background literature, experimental protocol, methods, techniques, experimental design, execution, interpretation, and packaging of data. The scholar will be mentored by the Principal Investigator (PI) Dr. Sanjoy Bhattacharya as well as senior members of the lab. The dream scholar will also be involved in mentored mentoring and teamwork designed to make the scholar a better team player with goals for larger academic outcome as outlined below.
**Scientific literature familiarity and background preparation:** The scholar will be provided three textbooks providing wide background in clinical and basic sciences literature. He/she will be followed once daily by the PI assessing progress on literature review. All yearly papers on trabecular meshwork is compiled by Prof. Ted Acott (OHSU, Oregon) as part of yearly Trabecular meshwork report for past 16 years. Dream scholar will have access to these reports and we will make sure that he/she has read the same. Dream scholar will be taught endnote, biorender for illustration, MetaboAnalyst and other software program as needed. He/she will be asked to participate in weekly journal club meetings, attend pertinent seminars.

**Experimental methods, protocols and techniques.** The scholar will be asked to review “At the Bench a Laboratory Navigator” By Kathy Berker prior to coming to the lab. He/she will be asked to review all methods videos online in the very week of the presence in the laboratory. Scholar will also take CITI Program pertinent courses for use of animals/mouse in research within the first week of laboratory. In the next week scholar will be put in a path to learn pertinent techniques such as cell culture, Western blot analysis, pertinent high-end instrumentation. During this period, he/she will be asked to learn step by step protocol writing following the style of *Methods in Molecular Biology* series (Dr. Bhattacharya is an editor of many issues in this series) and/or *Nature Protocols*. During this period Berker book tenets (as above) for meticulous record keeping will be emphasized. The scholar will be arranged to be trained in vivo work with Ms. Dona Olivo at Division of Veterinary Resource at this time. This may take up to two more weeks. Two different sessions are arranged for in vivo training. He/she will next be evaluated for training proficiency by a senior member of the lab. The scholar will next be trained on atomic force microscopy (AFM) elastic modulus measurement by Dr. Noel Ziebarth. Scholar will have a once every month meeting (minimum but more frequently as necessary) with Dr. Ziebarth and Dr. Sung Jin Kim (collaborators) to design advance experiments, which is then a problem-based learning. By the 4th week an experimental plan with boundary for a manuscript and mock power point figures. Scholar will be assigned junior undergraduate student(s) to impart developing a team.

**Responsible conduct of Research (RCR).** The scholar will be explained RCR points, meticulous record keeping, presentation of data and interpretation regularly with his studies as examples. Scholar will participate once every three-month session for review of mock F31 and K08 grants with MVSIO and TT-PhD students.

**Integration with clinical Sciences.** The scholar will participate on Thursday morning grand rounds. Lectures and didactics will be used for such integration as well.
Bianchi, Laura

Title: Genes that mediate the functional interaction between neurons and their accessory cells

The supporting cells of the mammalian olfactory epithelium, called sustentacular cells, have received a lot of attention lately because they seem to be responsible for the anosmia (loss of the sense of smell) caused by infection with SARS-covid-2. Given that sustentacular cells were thought to function simply as supporting cells, this finding raises questions on the true role of these cells in olfaction.

We are using C. elegans as a model to understand the function of the cells that in the worm functionally correspond to the “sustentacular” cells. In C. elegans, olfaction is mediated by the amphid sensory apparatus, which is composed of 12 pairs of sensory neurons and two pairs of supporting cells, called amphid sheath and socket cells. Work in my laboratory has demonstrated that amphid sheath cells are essential for olfaction. Indeed, C. elegans in which these cells are killed by expression of diphtheria toxin, experience profound anosmia.

To identify the molecular mechanisms that underlie the role of the amphid sheath cells in C. elegans olfaction, we performed single cell RNA sequencing. We identified 1,000+ genes enriched in the amphid sheath cells that are candidates for being part of the molecular mechanisms that mediate accessory cells participation to olfaction. Among these genes there are G-protein coupled receptors, ion/solute transporters, and ion channels. My lab is currently focusing on understanding the role of ion channels and transporters. We indeed predict that these proteins play key roles in olfaction because they are expected to control the concentration of ions and solutes in the microenvironment around the olfactory sensory neurons.

We have already identified six ion channels and transporters that are needed in the amphid sheath cells for olfaction. Interestingly, they are all involved in the transport of either K⁺ or Cl⁻, or both, underscoring the importance of these ions for the function for olfactory neurons. Among these, the K⁺/Cl⁻ co-transporter kcc-1 appears to be among the most critical for function. Indeed, its knock-out or knock-down, specifically in amphid sheath cells, significantly reduces C. elegans response to both attractive and repulsive odors.

The DREAM student that will be joining my laboratory will investigate how kcc-1, and the other ion channels and transporters we found needed for olfaction, regulate olfactory sensory neurons development, structural integrity, and function. To do so, the DREAM student will use a combination of techniques including molecular biology, C. elegans genetics, behavioral assays, functional imaging, fluorescent microscopy, and electron microscopy.

By answering these questions and others, we will begin to better understand the functional role of the supporting cells in olfaction. This work will also inform on mechanisms that mediate the functional interaction between neurons and other supporting cells, including glia, in the nervous system. The significance of this work is high because the accessory cells of the nervous system participate to injury and repair, and are involved in neurological disorders including multiple sclerosis, ALS, Alzheimer’s disease, Parkinson’s, epilepsy. However, the mechanisms underlying the functional role of these cells in the nervous system are not fully understood.
Title: Novel therapeutic targets for prostate cancer and COVID-19

My lab seeks to understand androgen receptor (AR) signaling, particularly in prostate cancer, and identify/evaluate novel drug targets including those regulated by AR. While androgen deprivation therapy for advanced prostate cancer results in tumor regression, eventually prostate cancer growth resumes in virtually all patients. Relapsed prostate cancer is termed “castration resistant” and is incurable. Androgen receptor (AR) and its constitutively active variants (such as the clinically relevant AR-V7) drive castration resistant prostate cancer (CRPC) progression. Our studies of AR-V7 regulated genes identified a new therapeutic target in CRPC, the arginine vasopressin receptor type 1a (AVPR1a) (Zhao N. et al. Science Translational Medicine PMID: 31243151; also see commentary about this article in Nature Reviews Urology PMID: 31346292). AVPR1a, a G protein-coupled receptor, is a druggable target with high potential for clinical impact because safe, effective and well-tolerated inhibitors (antagonists) of these receptors have already been successfully tested in humans for non-cancer disorders. We showed that an AVPR1a antagonist decreases CRPC growth in mouse models while exhibiting no toxic side effects. We are continuing to investigate the mechanisms of the anti-tumor effects of AVPR1a antagonists and determining their optimum use in preclinical models of CRPC and metastatic disease.

A second major theme in the lab is to use integrated “systems biology” and computational approaches to identify and target oncogenic pathways in CRPC. These unbiased and high-throughput methodologies utilize the extensive data available from men with prostate cancer and are coupled to experimental studies done in the lab to evaluate new proteins driving therapeutic resistance in prostate cancer. Using this “big data” approach, our studies revealed seven proteins functioning in interconnecting oncogenic pathways that had not previously been linked to constitutive AR variant signaling (Magani F. et al 2018 Molecular Systems Biology PMID: 30108134). Expression of these seven proteins is a strong predictor of prostate cancer aggressiveness in patients. The lab has also demonstrated that disrupting this gene network with pharmacologic inhibitors, potently decreases prostate cancer but not normal prostate cell proliferation. We are currently studying how these proteins promote prostate cancer therapeutic resistance and developing new combination therapies to block their actions.

TMPRSS2, one of the key human host proteins utilized by SARS-CoV-2 for viral entry into cells, is encoded by a well-characterized AR-regulated gene in the prostate. We recently obtained a grant from the VA to investigate whether AR regulates TMPRSS2 gene expression in lung epithelium, which are infected by CoV-2 and are known to express AR. We will test the hypothesis that AR up-regulates TMPRSS2 in lung epithelial cells and thereby promotes viral entry and infectivity. We propose that FDA-approved AR antagonists will decrease CoV-2 entry and spread and can be rapidly repurposed for COVID-19. Please note that while the molecular/cellular studies will be done at UM and represent a possible project for a DREAM Scholar, the live SARS-CoV-2 experiments will be performed by collaborators at the University of Colorado in their approved BSL3 facility.

DREAM Scholar Training Plan – Specific Project Descriptions and Methodologies

1. Examination of the anti-tumor effects of pharmacologic agents (AVPR1a antagonists – see Zhao N et al Science Translational Medicine 2019) in mouse xenograft and prostate cancer cell models. Techniques will include: generating mouse xenografts and monitoring tumor growth; examination of tumor-stromal cell interaction; immunohistochemistry; mammalian cell culture; viral
preparation and cell transduction; live cell imaging (IncuCyte Zoom); cell cycle, cell proliferation and apoptosis assays; reverse transcriptase-quantitative PCR, immunoblotting.

2. We identified a seven gene signature that drives AR V7 oncogenic activity in CRPC - (Magani F. et al. Molecular Systems Biology 2018). This project will deplete or over-express proteins encoded by these seven genes in prostate cancer cells and define the effects on AR signaling, cellular processes and tumor growth assays in mice. In a related project and based on our collaborative computational studies, we will establish patient-derived prostate cancer cell explant cultures and perform high throughput compound screens using liquid handling robotics. Techniques will include: cloning; mammalian cell culture; viral preparation and cell transduction; live cell imaging (IncuCyte Zoom); cell cycle (particularly mitosis assays), cell proliferation; reverse transcriptase-quantitative PCR (using TaqMan probes); immunoblotting.

3. For the VA-funded COVID-19 project discussed above, we will culture lung epithelial cells in a liquid/air interface and examine androgen/AR regulation of TMPRSS2 and ACE2 expression. The ability of the AR antagonist, enzalutamide, to block TMPRSS2 induction will be assessed. In addition to the techniques mentioned for the other projects, we plan to perform single cell RNA sequencing on primary lung epithelial cells to determine whether the relevant type II alveolar epithelial (AT2) cells exhibit androgen regulation of TMPRSS2 and/or ACE2.

DREAM Scholars will participate in our weekly lab meetings, relevant meetings with collaborators as well as have one-on-one weekly meetings with Dr. Burnstein. DREAM Scholars will be encouraged to attend seminars and career development activities offered by the Sylvester Comprehensive Cancer Center and the Department of Molecular & Cellular Pharmacology.
**Chaudhari, Nirupa**

**Title: Neural Identities, Functions and Circuits for Taste**

Description of DREAM project:

My lab, with long-term NIH funding, studies the innervation of the fascinating sensory system for taste. While the peripheral sensory organs and innervation for vision, hearing, smell and touch have been extensively examined, we are just beginning to understand the complexities of nerve-target interactions and circuits for taste.

One of the key projects that we are working on is documenting how peripheral receptor cells (the detectors) connect with afferent sensory neurons (which are the bridge between the peripheral and central nervous system). These neurons have cell bodies in cranial ganglia and send long projections into oral mucosa and other projections into the brainstem. What molecular mechanisms guide target selection at the peripheral and central terminals of these sensory afferent neurons? For these questions, we use transgenic strains of mice with inducible fluorescent reporters, immunofluorescence microscopy and single-cell transcriptomics (scRNAseq) to examine which molecules guide and specify nerve-target interactions.

Another question we are interested in is regarding the functional characteristics of gustatory afferent neurons. We have previously shown that these neurons are differentiated into several distinct molecular classes. How does this sensory system use neuronal diversity – to establish distinct circuits, to convey nutritionally important information to higher cognitive centers, to direct reflex behaviors – or all the above? For these questions, we are developing methods to efficiently transduce either neuroanatomical tracer labels, or functional reporters into selected neuron types using specialized Adeno Associated Virus vectors. We assess the in vivo function of labeled neurons in two ways. First, using a genetically encoded Calcium reporter, GCaMP6, visualized in the cranial ganglia, we analyze the responses to taste and other oral stimuli. Second, we will also be using these strategies to chemogenetically silence particular classes of neurons and examine behavioral and physiological consequences including ingestion, satiety, and insulin responses.

Each of these projects is large but a well defined sub-project can be dissected out, based on the DREAM Scholar’s interests and prior experience in bench research or even in computational directions.

Overall, our projects aim at a fundamental understanding of how the taste sensory system works, and discern interactions with metabolic and cognitive systems in mice. We hope to deploy these insights to inform strategies for better regulation of nutrition, body mass regulation and homeostasis in people.


DREAM Scholar Training Plan:

My lab interacts extensively and shares expertise and equipment with several different labs across the Medical School, and also shares equipment and expertise with that of Dr. Stephen Roper, another sensory researcher and collaborator in the Physiology & Biophysics Department. A DREAM Scholar who joins the lab would have ample opportunity to interact with two senior, NIH-funded Principal Investigators, 3-4 postdoctoral researchers, and several junior researchers as well.

The Graduate Program in Neurosciences and Department of Physiology & Biophysics include of ~80 research-active faculty and ~50 graduate students, to broadly enhance the scientific environment. Even in the current physically-restricted setting, there is significant intellectual support via video-conference seminars and a highly collaborative atmosphere. Students are always encouraged to take advantage of the many opportunities to learn from seminars, dissertation defenses and scientific presentations.

Oral presentation and writing skills: Weekly lab meetings are first order opportunities to begin this learning. Each lab member presents every 1-3 weeks, with a brief 1-2 sentence introduction of the goal of their project, followed by a review of the scientific premise and design of the current experiment. Results are presented after this, followed by discussion. PI will work with Andoni in advance of lab meetings to refine his ability to explicate rationales and results. The Q&A after each presentation is valuable practice for thinking on your feet, accepting and acting on constructive criticism, and incorporating other perspectives.

Every winter, the University hosts our Annual Neuroscience Research Day which includes a poster session during which researchers (from students to faculty) from several local institutions present current research. Students will have an opportunity to present research posters at this and other regional as well as national conferences.

Presenting a poster, of course, requires writing an abstract and later, the poster itself. These present opportunities to learn to write in comprehensibly, employing scientific logic, and presenting data with clarity to substantiate robust arguments. PI has achieved some success in this area -- working with mentees, from undergraduate students through faculty members, to improve writing skills. The oral presentation of every poster from PI’s lab is preceded by practice sessions for clear explication and smooth delivery. PI will personally work with Mr. Asencor in this area.

Research Seminars: Several departments at the Medical School have excellent active seminar programs. Currently, these are presented by videoconferencing, but will hopefully return to inperson sessions. PI will encourage Scholars to attend.
**Chen, Zhibin**

**Title: Preclinical and Clinical Study of Immune Cell Profiles in autoimmunity, Inflammation, and Cancer**

Description of the research project for DREAM Scholars:

Dream scholars can choose a number of projects in the areas of autoimmunity, gastrointestinal inflammation and cancer immunology. The projects may have a component of mechanistic discovery research using transgenic and knockout mouse models (pending the completion of all required trainings and regulatory approval of Dream scholars’ participation), as well as in vitro cell culture models. Moreover, the projects may also have a component of translational research using human peripheral blood or other tissue samples. The project will entail molecular and cellular approaches, such as quantifying mRNA and protein expression, and immune phenotyping by flow cytometry and microscopy. The specific projects will be tailored based on the experience level of the DREAM Scholars. The research areas will be in the broad scope of T lymphocyte and innate immune cell-mediated damage to tissues, mechanisms of tissue protection and regeneration, and inflammatory pathways that lead to either tumor development or tumor destruction.

**DREAM Scholar Training Plan**

The PI serves as the Director of Graduate Program in Microbiology and Immunology which currently has 31 PhD or MD/PhD students at the University of Miami and are well versed in the various aspects of research trainings.

The Dream Scholars will undergo their research training in a plan similar to what has been established for PhD students in regard to their research training. In brief, each trainee is expected to conduct a research project related to basic or translational immunological research. To foster independent activity and thinking within this project, each trainee is expected to present a weekly plan, attend weekly meetings to discuss their research project that includes interpreting data, trouble shooting and planning, as well as discussion of related and recent literature. As needed, there are also ad-hoc meetings to review research results and discuss future experiments. To develop writing skills, each trainee is expected to prepare research progress reports, and participating in manuscript writing. To develop presentation skills, each trainee is expected to actively participate in group meetings, present their data in departmental /center trainee seminars. Each trainee will be critiqued with respect to their writing and presentation activity. To develop networking skills and broaden their research knowledge, each trainee is also expected to attend session with guest lecturers invited to the medical school. The trainees may choose to present their work in scientific meetings if opportunity arises and funding permits. Trainees may also elect to take formal course work related to their research work, as needed, to facilitate knowledge and new techniques as it relates to their research project and/or future career goals. As appropriate, an experienced trainee may be assigned to help train a new trainee that enters the lab or for short-term rotating, or undergraduate students that seek a research experience. This aims to give a trainee a supervisory experience where they need to plan and evaluate the work of others.
Cocco, Emiliano

Title: Understanding the Biology of FGFR2 Fusions in Cholangiocarcinoma and their response to FGFR Inhibitors

Alterations in the genes encoding for the Fibroblast Growth Factor Receptors, FGFR1/2/3/4 are rare oncogenic drivers in multiple cancer types. These alterations include gene amplifications, activating mutations and gene fusions, all of which lead to the constitutive activation of the kinase domains of the FGFR proteins in a ligand-independent manner. FGFR2 fusions are recurrently found in intrahepatic cholangiocarcinoma (iCCA, 15%), an aggressive subtype of cholangiocarcinoma which arises in the bile ducts within the liver. Standard of care for patients diagnosed with iCCA includes surgical resection (when feasible) followed by systemic chemotherapy. Unfortunately, most cases recur even in apparently resectable disease. The 5-year overall survival for patients with iCCA is extremely poor (<10%). Thus, the identification of novel therapeutic options for the treatment of these patients is an urgent clinical need.

The recent discovery of FGFR2 fusions as targetable drivers in this malignancy has emerged as a promising approach for the management of the disease. A recent study showed that 35% of patients with iCCAs driven by FGFR2 fusions achieved an objective clinical response to pemigatinib, a pan-FGFR inhibitor. These results led to the approval of pemigatinib for the treatment of unresectable iCCA harboring FGFR2 fusions. Many other FGFR inhibitors, including isoform-specific drugs are currently in clinical development. These agents offer the potential to improve efficacy and limit adverse events, the most common of which is hyperphosphatemia, an on-target, off-tumor effect due to FGFR1 inhibition. Despite the impressive efforts that are ongoing to improve FGFR2-targeting specificity in the clinic, little is known about the biology of FGFR2 fusions. Moreover, just few mechanisms of resistance to FGFR inhibitors have been described to date. The main objectives of this proposal are to elucidate signaling pathways that mediate the activation and transforming capacity of different FGFR2 fusions when expressed in cholangiocytes, and to evaluate their response to different FGFR2 inhibitors.

We will do so following overexpression of some of these FGFR2 fusions in immortalized non-tumorigenic cholangiocytes of human (H69 and NHC) and rat (NRC) origin. These cell lines were obtained from Dr. Nicholas LaRusso (Mayo clinic) and will be transduced with vectors encoding for selected FGFR2 fusions. For this study, the following recurrent FGFR2 fusions have been chosen: FGFR2-BICC1, FGFR2-CASP7, FGFR2-KIAA1967, FGFR2-OFD1 and FGFR2-AFF3. In addition, H69 isogenic clones expressing the FGFR2-BICC1 fusion will be generated using a CRISPR-based strategy as previously described. The resulting models will be used to evaluate: 1) the transforming capacity and the oncogenic potential of each fusion, 2) the sub-cellular localization of each fusion (existing data in other fusion kinases showed that the subcellular localization of fusion kinases depends on the fusion partner), 3) the pathways that are preferentially activated by each fusion (proteomic and transcriptomic based-assays) and 4) the response of each FGFR2 fusion to different FGFR inhibitors. In addition, to identify additional mechanisms of resistance to FGFR inhibitors, the transduced cell lines will be cultured with increasing concentrations of FGFR inhibitors until resistance occurs. Sequencing will then be performed on the resistant clones.
Title: Harnessing the Adaptive Short Term Stress Response Induced During Cancer Surgery As A Predictor (and Partial Mediator) of Post-Surgical Healing and Recovery

Dr. Dhabhar will work with the scholar to define a project in the context of this study:

Rationale: Our preclinical studies showed that a short-term (minutes-hours) stress response (STSR) experienced during immunization, surgery, or tumor development, enhances protective immunity. In contrast, chronic stress (months-years) suppresses protective immunity. We defined a profile of STSR-induced changes in blood leukocyte numbers which indicates that an adaptive/protective STSR is underway. We subsequently showed that patients who naturally mount an adaptive STSR during surgery (meniscectomy), show significantly enhanced recovery (Lysholm score) and lower pain levels compared to patients who do not mount an adaptive STSR during surgery (Rosenberger et al., JBJS 2009). An independent editorial (Boyle, JBJS 2009) stated the following: “Could this be the holy grail that we seek – the simple, minimally invasive predictor of who will do well following surgery and who will not? ...I admire the authors’ diligence, completeness, and foresight. They may be on to something big.” These findings could be highly relevant for cancer patients who have inherent changes in innate and adaptive immunity while undergoing multimodality therapy and complex surgery.

Aims (A) & Hypotheses (H): A1: To test the generalizability of the above findings for pancreatic (primary focus), esophageal, and gastric cancer surgery. (We aim to leverage the study logistics that Dr. Merchant already has in place to target a wider range of surgeries in order to generate preliminary data for multiple NIH proposals.) H1-1: Patients who mount the a priori defined adaptive immune cell redistribution profile during the surgery-induced STSR will show enhanced recovery, and favorable oncologic outcomes. H1-2: Patients who show low resting state concentrations of cortisol ~3 weeks before surgery, peak concentrations just before and during surgery, followed by low resting state levels ~1-3 weeks following surgery, will show better recovery and oncologic outcomes. A2: To identify chronic stress related factors that inhibit recovery and lead to unfavorable oncologic outcomes, through direct mechanisms and/or by dampening/dysregulating the adaptive STSR. H2-1, H2-2: Higher levels of chronic stress will be associated with dampened or dysregulated surgery-induced STSR (H2-1) and impaired recovery (H2-2). H2-3, H2-4: High general anxiety will be associated with dampened or dysregulated surgery-induced STSR (H2-3) and impaired recovery (H2- 4). A3: To identify positive/protective psychological factors which serve as predictors of post-surgical recovery and favorable oncologic outcomes. H3-1: Patients who score high on social support and happiness will show enhanced recovery and more favorable oncologic outcomes. Exploratory Aim, A4: To characterize and quantify social and racial disparities with a focus on chronic stress and STSR related factors and mechanisms.

Study design: Similar to aforementioned study, JBJS 2009.

Potential clinical benefit: 1) To use a rapidly obtainable measure of surgery-induced immune cell redistribution as a predictor of postsurgical recovery and oncologic outcomes. 2) To identify additional psychological and biological factors that could serve as predictors and/or mediators of post-surgical recovery and oncologic outcomes. 3) To design interventions (administered before or during surgery) to optimize the surgery-induced STSR or restore it (in patients who do not naturally mount one).
Dr. Dhabhar will mentor the DREAM scholar according to the following Training Plan that will be modified as needed. The project scope will be reasonable keeping in mind the time available on a day-to-day basis and the one-year time frame.

1 or 2 months before start of project:

• Dr. Dhabhar will meet with the scholar to define a project in the context of a study, Harnessing the Adaptive Short Term Stress Response Induced During Cancer Surgery As A Predictor (and Partial Mediator) of Post-Surgical Healing and Recovery. This study will be a collaboration between Dr. Dhabhar’s and Dr. Nipun Merchant’s laboratories.

• Dr. Dhabhar will provide the scholar with background reading if requested.

• All outstanding safety/compliance training completed before, or within the first few days of the project.

1st month of project:

• The scholar will be trained in methods/techniques as required for the project (e.g. hematology, flow cytometry, cytokine/hormone quantification by high-sensitivity ELISA/quantitative multiplex protein assays, psychometric survey instruments to quantify stress, and psychosocial factors).

• The scholar will work closely with Dr. Dhabhar and Ms. Nisha Phogat (Study Research Associate II) and learn how to interface with Dr. Merchant and his team, collect samples from them, and analyze samples in the Dhabhar lab.

• The scholar will be trained to conduct all hematological/flow cytometric assays on the day of blood collection.

• Mentoring will continue through reading manuscripts chosen by Dr. Dhabhar or by the scholar.

• If the scholar is interested in writing, Dr. Dhabhar will work with the scholar to begin writing a review article of relevance to the project. Though not required, this would be a great experience and also provide material for the final project report.

Months 2 to 11:

• Work on research project by: picking up samples from the OR, bringing them to the laboratory and conducting hematological and flow cytometric quantifications, and optimally preserving serum, plasma, and cells for future analyses.

• If scholar chooses to work on quantification of psychological, social, and related factors, efforts will be made to enable the scholar to work directly with patients to collect this data (data is collected into an IRB-approved REDCap survey).

• Dr. Dhabhar will continue to work with the scholar through readings and writing the review article.

• The scholar will attend Grand Rounds, seminars and workshops that cover topics of interest.
• The scholar will also be exposed to other ongoing studies in the laboratory, and if possible, to Dr. Dhabhar’s collaborations with colleagues at Stanford, UCSF, and Berkeley.

• The scholar will have opportunities to meet with Dr. Merchant and members of his team. Dr. Dhabhar will work to ensure that neither the project nor the scholar are a burden on Dr. Merchant and his team.

• The scholar will make presentations if and where possible.

Months 11 & 12:

• Begin data analysis and start writing project report (month 11).

• If possible, convert project report to manuscript submitted to peer-reviewed journal (month 12) • If possible, present findings at a local or national meeting.

• Set stage for further collaboration or interactions if the scholar is interested
Dinh, Christine

Title: Income changes in relation to blood pressure, hypertension, and hypertension control

DREAM scholars will engage in a hands-on research experience in a basic science/translational laboratory whose vision is to identify and test new therapies for Schwann cell-related pathologies in Otolaryngology. DREAM scholars will participate in ongoing and new research projects that will foster their development and interest as a surgeon scientist in Otolaryngology. Current research projects:

Vestibular Schwannoma and Neurofibromatosis Type 2: Neurofibromatosis Type 2 (NF2) is a genetic tumor disorder that causes multiple central and peripheral nervous system tumors, including bilateral vestibular schwannomas (VS) that cause deafness, imbalance, and life-threatening intracranial complications. NF2 is caused by mutations in the NF2 gene that encodes the merlin tumor suppressor protein. Microsurgery and stereotactic radiosurgery are common treatments for individual tumors; however, these treatments often lead to hearing loss and nerve injury. Furthermore, stereotactic radiosurgery is less effective in NF2 patients and can lead to malignant transformation of benign tumors in this population. Although off label chemotherapies have been used with mild effect, there are no curative therapies for NF2. Our schwannoma laboratory investigates novel therapies for VS and NF2, studies the mechanisms of tumor resistance to radiation and chemotherapy, and develops new methods to improve surgical outcomes for VS.

Role of Schwann cells in Perineural Invasion in Head and Neck Cancer: The most common oral cavity cancer is squamous cell carcinoma (SCC), of which perineural invasion (PNI) is a significant prognostic factor associated with decreased survival and increased rate of locoregional recurrence. PNI requires reciprocal signaling interactions between tumor cells and nerve components, particularly Schwann cells. Specifically, head and neck SCC can express neurotrophins and neurotrophin receptors that may contribute to cancer migration towards nerves, PNI, and neuritogenesis towards cancer. Through reciprocal signaling, recent studies also suggest that Schwann cells may play an important role in promoting PNI by migrating toward cancer cells, intercalating, and dispersing cancer, and facilitating cancer migration toward nerve. The interactions of neurotrophins with their high affinity receptors is a new area of interest in the development of pharmaceutical therapies for many types of cancers.

Dream scholars will engage in multiple translational research projects during their research year. For the VS study, scholars will (1) consent patients undergoing surgery to participate in the tumor bank study, (2) harvest fresh tumors from the operating room, (3) process human specimens and develop personalized cell cultures for individual patients, and (4) conduct a variety of experiments on banked cells and tissue (2D and 3D cell-based assays, immunohistochemistry, western blot, time-lapse imaging, confocal microscopy). For the PNI study, scholars will (1) culture cancer, neurons, and Schwann cells, (2) develop and conduct migration and invasion assays, and (3) perform a variety of secondary cell-based experiments. Dream scholars will also engage in a multidisciplinary collaboration with otolaryngologists,
neurosurgeons, oncologists, radiation oncologists, neuropathologists, and neuroradiologists. Furthermore, scholars will learn to integrate laboratory findings with clinical data and pathology, analyze data and perform data visualization, draft, and publish original research manuscripts, and present at local, regional, and/or national meetings.

Dream Scholar Training Program
A personalized training plan will be developed based on individual goals and level of research experience. In the first two weeks, DREAM scholars will obtain proficiency and certification to conduct basic science, preclinical, and clinical research by completing online and in person courses. They will also complete online training in ethics in research and responsible conduct of research. Scholars will then meet with the mentor and mentoring team to discuss research background, study design, techniques, and timelines for completion. Throughout the year, scholars will engage in hands-on experiences conducting and troubleshooting experimental designs, including cell culture, protein/DNA/RNA extraction, immunohistochemistry, confocal microscopy, western blot, cell-based assays, migration and invasion assays, and time-lapse imaging. Preclinical skills can include writing animal protocols, animal surgeries, drug administration, behavioral testing (balance and hearing), and histology. Clinical research skills can include maintaining a database, writing research protocols, consenting patients, and collecting clinical and radiographic data. DREAM scholars will also learn to perform data visualization and data analysis using SAS or R software. DREAM scholars will participate in laboratory meetings and present research at local, regional, and/or national meetings. Scholars will also learn to work in multidisciplinary teams and write scientific manuscripts. Scholars will also receive one-on-one mentoring to achieve short and long-term goals toward becoming a successful clinician and physician scientist in the field of Otolaryngology.
Title: Income changes in relation to blood pressure, hypertension, and hypertension control

Description of research project for DREAM Scholars:

In the United States, the recent rise in income inequality suggests that a larger proportion of the population faces poverty and economic difficulties. While most adults experience some sort of income change over their life, income volatility has been on the rise since 1980 and has reached a record level, and continues to be a salient issue in the age of COVID. Income volatility is generally defined by a sudden and unpredictable change in income over time, and most often it consists of declines in income. The rise in income volatility is especially true for low-income households who experience a substantial number of income drops that exceed 25% of their average income. Income volatility is more common among African Americans compared with non-Hispanic Whites, especially and among African American women compared with African American men.

As recently as ten years ago, during the great recession in the US, the national unemployment rate increased as median family income and household wealth simultaneously decreased. Furthermore, increases in pre-retirement withdrawals from retirement accounts and increases in the percent of persons having negative home equity suggest that household assets in the US also decreased during the great recession. Recession-related shocks to financial wellbeing such as unemployment, income loss, and loss of assets have been found to be associated with several negative health outcomes. Thus, income volatility, especially in the context of the recent recession and the COVID-19 pandemic, presents a growing public health problem. This is exacerbated by changes, and mostly cuts, to federal programs, which are meant to help absorb unpredictable income changes.

The negative effects on health due to income volatility are potentially mediated by behavioral changes, psychological stress, and access to medical care. Increasing evidence suggests income volatility is associated with an array of unfavorable health outcomes, including increased risk of CVD and all-cause mortality. Income volatility may also contribute to acute and chronic health outcomes. For example, low income patients with chronic diseases, such as hypertension, may stop taking antihypertensive medication and not attend medical visits to cope with unexpected financial instability, consequently resulting in increased risk for heart attack and stroke.

In addition to being disproportionately impacted by income volatility, the prevalence of hypertension is higher among African Americans compared with non-Hispanic Whites and other race/ethnic groups in the US. Given the high burden of hypertension among African Americans, determining how changes in socio-economic factors contribute to hypertension in this group can help guide the implementation of targeted interventions to prevent the negative effects of income volatility.

For this DREAM project, we propose to determine how changes in income over three Jackson Heart Study visits (2000 – 2013), a timeframe which encompasses the great recession, is associated with blood pressure, incident hypertension, and blood pressure control among African American Jackson Heart Study participants. Participation in this project will directly result in mentorship and training with a final output of a high impact authored publication for the DREAM mentee.
DREAM scholar training plan:

The research project will be carried out by the trainee and with hands on support from Dr. Elfassy. There are three main training goals for the DREAM mentee: 1) Training and familiarization with basic epidemiology and applied epidemiologic research, 2) Training in social epidemiological concepts and health disparities research, and 3) Training in the presentation and dissemination of epidemiological research. To help achieve these goals, planned activities related to each goal are provided below. This will include formal and informal: one-on-one meetings, didactic coursework, seminars, group meetings/discussions, and online webinars (as outlined below):

**Goal 1:** Training and familiarization with basic epidemiology and applied epidemiologic research

1. **Directed readings:** Dr. Elfassy will guide readings on basic concepts in epidemiology and applied epidemiological research.
2. **Seminars:** Attend monthly Grand Round Seminars offered by the Department of Public Health Sciences at the University of Miami covering broad topics related to public health and health disparities.
3. **Weekly Lab meetings:** Attend Dr. Elfassy’s weekly lab group meetings to discuss on-going research in the lab and also report on DREAM research progress.
4. **Webinars:** enroll in the free webinar/lecture on epidemiology provided by the Centers for Disease Control and Prevention: “Introduction to epidemiology: [https://www.cdc.gov/publichealth101/epidemiology.html](https://www.cdc.gov/publichealth101/epidemiology.html)

**Goal 2:** Training in social epidemiological concepts and health disparities research

1. **Directed readings:** Dr. Elfassy will guide readings on foundational concepts in social epidemiology and health disparities research.
2. **Webinars:** Enroll in a free webinar related to hypertension provided by the American Heart Association Strategically Focused Research Network in Hypertension: “Spotlight series: Racial and Ethnic Disparities in Hypertension: Beginning the Conversation.” [https://learn.heart.org/activity/4325901/detail.aspx].
3. **Workshops:** Attend “Dialogues in Health Disparities Research” seminar offered each semester by the University of Miami which entails different themes such as studying cultural or social factors that impact multiple health conditions. [http://elcentro.sonhs.miami.edu/education-and-training/seminars-lectures-and-workshops/index.html].

**Goal 3:** Provide training in the proper presentation and dissemination of epidemiological research

1. **Scientific Meetings:** Attend the 2022 American Heart Association Epi Lifestyle Conference March 2022 and present DREAM project work.
2. **Hands-on research mentorship:** Meet on a bi-monthly basis directly with Dr. Elfassy to discuss research progress, interests, and presentation/dissemination of scholarly work.
3. **Biostatistics Collaboration and Consulting Core (BCC):** learn about BCC services and how/when to utilize consults.

In addition to the training goals listed above, Dr. Elfassy will discuss and provide constructive feedback related to: overall scholarly performance, leadership/management skills, collaborative/collegial skills, communication, presentation, and adherence to ethical standards. This DREAM project, will directly result in 1) submission of at least one authored peer reviewed publication, 2) training in epidemiological methods and health disparities research and 3) career development guidance and mentorship for the DREAM mentee.
Title: Treatment and Outcomes of Cutaneous Lupus Erythematos

Dream Scholar Training Program: A personalized training plan will be developed for the DREAM scholar based on individual goals and previous experience. The scholar will be provided with background literature in order to understand what is known regarding immune-signaling in cutaneous lupus. The scholar will apply this knowledge to understand treatments currently employed for management of CLE. The scholar will work one-on-one with Dr. Elman to complete a novel study in one of the identified gaps in knowledge in current CLE treatment. Dr. Elman will guide the scholar during weekly meetings in the creation of clinical hypotheses, project development, data analysis, and manuscript creation. The student will be supported in submitting research abstract to annual Dermatologic, Rheumatologic, and other appropriate meetings. Under Dr. Elman’s mentorship, the scholar will have the opportunity to participate in a variety of clinical activities at the Department of Dermatology and Cutaneous Surgery, including Dr. Elman’s general and rheumatologic-dermatology clinics, other Dermatology faculty clinics per scholar’s interests, attendance and participation in weekly departmental management conferences and grand rounds, and attendance at Miami Dermatologic Society meetings. Furthermore, scholar will be mentored by faculty member Dr. Andrea Maderal, who works closely with Dr. Elman in the field of rheumatologic-dermatology and is the chief of the UM/Jackson Hansens Clinic. Lastly, Dr. Elman will mentor scholar in discussing short-and-long-term career plans, plans for residency application and training, identification of residencies with strong research training, and will support scholar on their path towards becoming a successful physician scientist.
Fornoni, Alessia

Title: DREAM Scholar CKD Project

Chronic kidney disease (CKD) affects around 14% of the global population and the number of affected individuals is expected to continue to rise. Glomerular diseases account for a large number of cases of CKD.

Studies from our laboratory suggest that lipid accumulation in podocytes, which are highly specialized and terminally differentiated cells of the glomerular filtration barrier, contributes to the progression of glomerular diseases such as diabetic kidney disease, renal disease associated with Alport Syndrome, and focal segmental glomerulosclerosis. More precisely, we identified ATP Binding Cassette Subfamily A Member 1 (ABCA1) as an important mediator of podocyte injury and demonstrated that lipid accumulation in podocytes is primarily due to impaired ABCA1-mediated cholesterol efflux. In vitro, ABCA1 deficiency is associated with cardiolipin (CL) accumulation and increased CL peroxidation leading to mitochondrial dysfunction and oxidative stress. In vivo, we demonstrated that ABCA1 deficiency is not sufficient to cause renal disease but renders diabetic mice more susceptible to glomerular injury.

The DREAM Scholar joining my laboratory will be able to work on this NIH funded research study which is aimed at defining the molecular mechanisms by which ABCA1 deficiency leads to lipid accumulation and contributes to podocyte injury. As mentioned above, ABCA1 deficiency is not sufficient to cause renal disease and a “second hit” is necessary for kidney disease progression. The DREAM Scholar will work on a research project aimed at identifying novel factors and mechanisms contributing to the progression of renal disease. He/She will use a combined in vitro and in vivo approach, which will ultimately allow for the identification of new drug targets for the treatment of patients with kidney disease. Applying discoveries generated during this research in the laboratory and in the preclinical studies will allow the DREAM Scholar to acquire the essential research skills needed to accelerate a future career path as a Physician/Scientist.
**Franzmann, Elizabeth**

**Title: Early detection of HNSCC in underserved populations**

Our lab has been studying head and neck cancer in diverse populations in Miami and surrounding areas. Florida City is an underserved, low-income neighborhood in Miami-Dade County, Florida consisting of an overwhelming majority of black and Hispanic Americans. Racial disparities in particular play a major role in the demographics of oral and oropharyngeal cancer with significantly lower 5-year survival rates for black Americans in comparison to white Americans (45% vs 67%). Florida City exhibits a remarkable need for effective methods of cancer detection and prevention due to the increased risks factors of cancer created by such health disparities.

In general, oral cancers develop from precursor lesions, most often leukoplakia (white lesion) or erythroplakia (red lesion). Patients who present with precursor lesions have a significantly better outcome due to earlier stage diagnosis. Screening for such lesions has been shown to improve survival in high-risk populations in India. High risk populations include those who use tobacco and alcohol or have oncogenic HPV infection. However, screening for precursor lesions is fraught with challenges. Effective screening requires expert clinical exam and frequent follow-up which is associated with poor compliance. Moreover, some HNSCC arise de novo without a precursor lesion. Simpler and more effective screening programs are needed for populations at high risk for HNSCC such as Florida City.

Our lab has been investigating early detection markers for head and neck cancer for nearly 20 years. We have developed technology involving CD44 and total protein markers that have potential to detect head and neck squamous cell cancer at an earlier more treatable stage. P16 is another marker that may help distinguish at risk patients without cancer from patients that have disease. The Franzmann Lab plans to partner with industry to develop point of care tests that incorporate these markers.

Students involved in this project will have contact with head and neck cancer patients and subjects from diverse communities in South Florida. Students will be involved in study design, screening events, consenting, collection of samples from head and neck clinic patients and community subjects. They will learn how to process samples and test using home-grown ELISA, lateral flow, and related technologies. They will also assist in developing lateral flow and other point of care tests and basics of device regulation. Additional opportunities in device reader design also may be available.
Goel, Neha

Title: Genomic and Non-Genomic Determinants of Breast Cancer Disparities

The proposed research project for our DREAM scholar will involve:
1. Conducting in-depth structured surveys with patients enrolled in the Miami Breast Cancer Disparities Study.
2. Analyzing survey data to understand how structural barriers to care and social determinants of health impact breast cancer disparities, such stage at diagnosis which we know is a proxy for long term survival.
3. Writing manuscripts on how structural barriers to care and social determinants of health impact breast cancer disparities. Given my social epidemiologic background, we will also work to discuss potential interventions to tackle these disparities.

DREAM Scholar Training Plan

The DREAM scholar will be trained using a hands-on approach. Our translational disparities laboratory is staffed by research assistant Andrea Sparano, MPH who is trained in survey methodology and will teach the scholar how to conduct surveys in an unbiased approach. The scholar will be responsible for meeting patients in the clinic or via phone to complete the surveys. In addition, we will teach the Scholar how to properly enroll patients on studies and perform informed consent. The DREAM scholar will work with our lab biostatistician Dr. Lauren Nahodyl to learn how to organize data and perform univariable and multivariable analysis to understand how social determinants of health impact stage at breast cancer diagnosis. This direct one-on-one training and support from highly experienced personnel in the laboratory will support the DREAM scholar in completing their project. The DREAM scholar will also have one-on-one weekly meeting with Dr. Goel as well as weekly meetings with all personnel in the laboratory including basic scientists and computational biologists to understand how clinical data translates to tumor biology. The Scholar will attend monthly breast cancer journal club meetings and weekly breast surgical oncology case where the Scholar about the clinical management of breast cancer, putting their research into perspective. The DREAM scholar will also have the opportunity to come into the operating room, work with our Biospecimen Shared Repository to learn how to handle fresh tissue, and work with our pathologists to evaluate which samples go to research. The Scholar can also attend any educational meetings within our Division of Surgical Oncology, including our monthly disparities research meeting which I lead. The DREAM scholar will be mentored to submit an abstract for a national meeting and contribute to the manuscript from their specific project.
**Isom, Daniel**

**Title: Designing nanobody-based therapeutics for G protein-coupled receptors**

G protein-coupled receptors (GPCRs) are the largest and most therapeutically targeted class of receptors in humans. More than 800 GPCRs serve as transmembrane sensors for many chemical and physical signals (light, metabolites, neurotransmitters, hormones, chemokines) to regulate myriad physiological processes. In the Isom lab, we use and develop cutting-edge approaches to build a better understanding GPCR biology and to develop the next generation of GPCR therapeutic and pharmacological tools. One of the latest technologies developed for controlling GPCR function are nanobodies, which unlike conventional antibodies are small, single chain proteins that are easy to express in variety of physiological scenarios. As such, nanobodies that target GPCRs hold great promise as highly-specific drugs for much of the GPCRome. In this project, the DREAM scholar would design and profile nanobodies against one or more therapeutically-relevant GPCRs. Along the way, the DREAM scholar would be trained and gain expertise in variety of cutting-edge cellular technologies at the interface of GPCR biology, synthetic biology, and high-throughput nanobody profiling and drug discovery.

The DREAM project could provide experience with myriad cutting-edge techniques in the lab:

- High-throughput CRISPR engineering
- Nanobody design and profiling
- Liquid handling robotics and high-throughput screening formats
- The latest in plate reader and confocal technologies
- New methods in Fluorescence Activated Cell Sorting (FACS)
- New methods in Magnetic Activated Cell Sorting (MACS)
- Training in yeast and mammalian cell model systems
- Training in the use genetically encoded biosensors
- And much more ...

**DREAM scholar training plan**

Over the project period, the DREAM scholar would initially receive training in the aforementioned approaches (as needed), apply this training to design and execute their project, and package their results for publication using the following timeline.

**Months 1-3** The scholar will gain hands-on experience with the yeast and mammalian model systems and the approach for building nanobody libraries.
Months 3-9 The scholar will apply their training to do their main body of research with the goal of producing a high affinity nanobody against a GPCR target of the scholar’s choosing that it is compatible with our high-throughput GPCR profiling platforms.

Months 9-12 The scholar would perform any necessary follow-up validation experiments and work with Dr. Isom to begin formulating a stand-alone first author manuscript, or authorship contribution to a larger manuscript, depending on how the project progresses.
Larsson, Hans

Title: Development of novel treatments for cardiac arrhythmia

Project Description

The cardiac action potential is primarily generated by sodium and calcium channels, which depolarize the membrane potential, and by potassium channels that repolarize the membrane potential and terminate the action potential. One of the major cardiac potassium currents is the slowly activating potassium current $I_{Ks}$ that contribute to the action potential termination. Over 300 different inherited mutations have been found in $I_{Ks}$ channels that cause cardiac arrhythmias in patients. $I_{Ks}$ channels regulate the length of the cardiac contraction and mutations that decreases the activity of $I_{Ks}$ channels result in a prolongation of the cardiac contraction, leading to Long QT Syndrome. In turn, Long QT syndrome is a risk factor for ventricular fibrillation and sudden cardiac death. We have identified a family of compounds that activate $I_{Ks}$ channels and are antiarrhythmic when applied to cardiomyocytes.

There are three different types of experiments that the students can choose from that are associated with this project: 1) The student can test whether these compounds restore the length of the action potential in human cardiomyocytes from Long QT Syndrome patients. 2) The student can test the effect of these compounds on whole animal heart and in whole animals, in order to develop drug that restores the QT interval and that can be tested in future clinical trial. 3) The student can test variants of these compounds on heterologously expressed $I_{Ks}$ channels using two-electrode voltage clamp, to determine the important structure of these compounds for their effects on $I_{Ks}$ channels. The student will also make mutations of $I_{Ks}$ channels to determine the binding site of these compounds. Finally, the student will test the efficacy of these compounds to reverse different defects in $I_{Ks}$ channels caused by different types of Long QT syndrome mutations. This will be tested both in heterologous systems and in human cardiomyocytes.

The anticipated results of these experiments will provide proof-of-concept that this family of compounds can shorten the cardiac action potential and the QT interval and will provide preliminary animal model data to start clinical trials of these compounds. We anticipate that this development of new anti-arrhythmic drugs will lead to better treatments of cardiac arrhythmias and the prevention of sudden cardiac deaths in LQTS patients.

Training Plan

I will conduct most of the training in the different techniques used in this project with help from postdocs and senior graduate students in the lab, but I envision that the student will further develop these techniques as needed. The student will receive training in molecular biology (e.g. site-directed mutagenesis and Western Blot technique), electrophysiological techniques (e.g. two-electrode voltage clamp and patch clamp), and fluorescence techniques (e.g. using intracellular calcium-sensitive fluorescent dyes).

The student will present both in lab meetings (weekly) and in the Ion Channel Journal Club meetings (once a semester) in the Department of Physiology and Biophysics. In addition, the student will also present his research in yearly post sessions given by student and post-docs at the University of Miami Miller School of Medicine. If findings are found that merit publication, the student will be responsible for writing the first drafts of papers. I will go over the drafts with the student and polish the papers to publishable quality. The student will also be trained by me in the appropriate use of statistics to interpret data.
Responsible Conduct of Research (RCR) training is on-going throughout the year with two seminars about diverse topics in RCR per semester, led by faculty and attended by the whole department. PIBS 784 Professional Skills for Senior Graduate Students and Postdocs is a course that prepares students for independent positions. Topics include: Preparing a Dynamite Job Application, Giving Great Seminars, Career Choices, Writing Grant Applications, and Panel Discussions featuring faculty from different types of institutions and scientists with industry experience.

There are several experts in my group and at UM from whom the student will continuously obtain feedback and training. For example, Dr. Derek Dyxhoorn, the Director of the IPSC core facility at Univ of Miami MSOM, collaborates with Dr Larsson to produce IPSC-derived cardiomyocytes with KCNQ1 mutations to yield a cellular model of inherited cardiac arrhythmias. In addition, we have developed collaborations with clinical cardiac electrophysiology researchers at the Georgetown University/MedStar Heart Institute in Washington, DC (Dr. Nanette Bishopric, MD, previously at UM), from whom the student will get help with data interpretation on cardiac arrhythmias. In addition, new, interesting long QT mutations discovered at MedStar Heart Institute in Washington or here at UM could be available for the student to test.
Lee, Jae

Title: Regulation of gliosis and fibrosis by myeloid cells after spinal cord injury

Description of research project

After spinal cord injury, monocyte-derived macrophages that infiltrate the injury site regulate many aspects of the wound healing process. Previous studies have shown that macrophages activate astrocytes and fibroblasts to trigger gliosis and fibrosis, respectively. These scarring processes have both beneficial and detrimental effects on spinal cord injury pathobiology, but the underlying signaling mechanisms are poorly understood. By recently performing the first single cell RNA-seq of the spinal cord injury site, we identified oncostain-M (OSM) signaling as a novel mechanism by which macrophages may regulate both gliosis and fibrosis. Interestingly, OSM is expressed almost exclusively by macrophages (both tissue resident microglia and infiltrating macrophages), whereas the OSM receptor is expressed by astrocytes and fibroblasts. This study will test the overall hypothesis that myeloid-derived OSM promotes gliosis and fibrosis after spinal cord injury. This hypothesis will be tested in a mouse model of spinal cord injury where OSM or its receptor OSMR are genetically deleted in a cell type-specific manner. These mice are already available to be used in the laboratory. We will assess behavioral recovery over time, and perform endpoint histological analysis to assess the function and pathological effects of OSM or OSMR deletion. We will also use in vitro assays to study macrophage/astrocyte or macrophage/fibroblast interaction via OSM signaling. The student will learn how to use genetic mouse models, spinal cord injury surgery, mouse behavioral assessment, histology/microscopy, qRT-PCR, and primary culture.

Training plan

One year is not a lot of time to train a scientist, so the focus will be on providing a solid foundation of the scientific method with an emphasis on formulating and testing hypotheses, and making conclusions that are supported by the data. Along every step of the scientific process, there will be a strong emphasis on Responsible Conduct of Research (RCR) principles through both formal (i.e. classes/seminars) and informal (weekly meetings) settings. This foundation in the scientific method is provided by several ways. First is through an intensive research experience gained by performing the research project described above. The trainee will be required to formulate and test a hypothesis for every experiment to be tested. While the trainee receives training in specific protocols from members of the lab, he/she will be taught how to collect data appropriately using RCR principles including power analysis/statistics, randomization, and blinding methods. Through one-on-one meetings and lab meetings, the trainee’s data and conclusions will be discussed rigorously. Whereas I typically meet once per week with my trainees, this one year project leaves very little room for failure or mistakes, so I will meet twice per week with the trainee to ensure that weekly goals and long-term milestones are being met. If problems arise (and they always do), meeting more often will give us more time to address these issues directly or come up with alternative solutions.

In addition to the research project, the trainee will actively participate in other enrichment activities including journal club, department seminars, and RCR classes. My lab currently holds a joint journal club with Drs. Vance Lemmon, John Bixby, Pantelis Tsoulfas, Kevin Park, Hassan Al-Ali, and Nagi Ayad. This journal club covers diverse topics in regenerative neuroscience, and trainees rotate presenting an article of their choice. This meeting has evolved into more than just a journal club; it has become a fertile training ground with multiple faculty members providing invaluable input on everything from presentation skills and RCR to historical perspectives on the journal topic. The collective experience in developmental and
regenerative neuroscience in this group is truly amazing and will be one of the highlights for the trainee. The Miami Project holds department seminars every Wednesdays, which gives the trainee an opportunity to present his/her work in front of a large audience in a formal setting. The trainee’s seminar will be scheduled toward the end of the one year research period and will serve as his/her major public presentation of the research project (similar to a dissertation defense). In addition to this department seminar, the trainee will present in poster format at local, national, and/or international conferences. For formal RCR training, the trainee will attend the Neuroscience graduate program’s RCR classes (NEU700). Lastly, another major training goal will be to submit the trainee’s major research findings to a major scientific journal, and I will work with the trainee on how to write scientific manuscripts.
**Loewenstein, David**

Our mentorship focus would initially involve learning about new cutting-edge cognitive paradigms in our laboratories, assessment of clinical and neuropsychological assessment of a large cohort of culturally diverse older adults and state-of-the art diagnosis of Alzheimer’s disease and related disorders. A major strength of the program is the ability to sit in on clinical, neuropsychological and neuroimaging evaluations which garners an increased appreciation of the data collected.

A primary focus of our work at the CNSA is with culturally diverse older adults is deep phenotyping our research participants with advanced MRI, amyloid PET, and tau PET with longitudinal follow-up. This affords a tremendous opportunity to develop further knowledge about neuroanatomy and early structural changes in specific regions of the brains, to learn segmentation techniques using Freesurfer and receive state-of-the science training on analyzing quantitative amyloid as well as tau PET. We collect blood for genetic purposes and our now in the process of analyzing new blood-based biomarkers (p-tau 231; GFAP, NfL, AB42/AB49) of Alzheimer’s Disease and neurodegenerative disorders using new technologies such as SIMOA or mass spectroscopy that provides over 1000 times the resolution of existing technologies.

It is tremendously important to us for mentees to be involved in research that is meaningful for them individually as well as to foster academic growth. As such, Dr. Loewenstein fosters an academic partnership with the mentee to establish their goals and assists them in operationalizing the steps required to meet timelines and objective. There would be a weekly one to one meeting with Dr. Loewenstein to gain familiarization with existing and newly acquired data. Further there will be additional opportunities for mentoring with our other distinguished MD and PhD level faculty in a team science atmosphere.

The trainee would participate in regular didactics and weekly diagnostic consensus meetings. We have specific laboratory space, a computer and biostatistical resources available for the trainee. For the primary project, the mentee would learn to gather, analyze and write-up data in a very collegial and supportive environment with frequent written and verbal feedback by Dr. Loewenstein and colleagues. That project would be written up for publication as an abstract by the trainee with the goal of submitting the paper to a peer-reviewed journal. The trainee would also have the opportunity to contribute and work on other ongoing projects to expose them to many facets of our research program (including NIH grant submissions) and to give them an opportunity of authorship on other peer-reviewed manuscripts.

Training Plan: It is important to note that this mentorship program is a collaborative exercise between Dr. Loewenstein and the trainee. As such, the sequence of events described below is a general outline.

Month 1- Directed readings, observe clinical and neuropsychological evaluation, and familiarize the trainee with study protocols and databases including neuroimaging. During their time with us, the mentee will be expected to attend CNSA general didactics (e.g., neuroimaging, aging, Alzheimer’s disease, neuropsychological assessment) weekly diagnostic consensus meetings for the ADRC and attend weekly research meetings with our post-doctoral fellows.

Month 2- After literature review formulate Primary Research Project with Dr. Loewenstein and create Specific Aims, Methods, and Analytic Plan for Primary Paper. Opportunity to shadow our attendings for duration of the mentee’s training.

Months 3-6- Compile and analyze data under the supervision of Dr. Loewenstein and Biostatistician. Written and verbal feedback regarding Introduction, Methods, Results and Discussion with Drs. Loewenstein and
other faculty. A scientific poster can be submitted during that time, but the primary focus is on the empirical paper.

Months 6+
- a) Submit paper for publication in a peer-reviewed journal
- b) Contribute and co-author other Peer-Reviewed manuscripts
- c) Conduct a seminar on trainees area of interest to CNSA faculty and staff
- d) Meet with Dr. Loewenstein, Curiel and other faculty to foster professional growth
- e) Acquire specific skills and specializations (PET tau, PET amyloid neuroimaging, MRI brain imaging, biostatistics, NIH grant writing)

The timeline above is generally employed in our Dream Mentorship program. However, Dr. Loewenstein, Dr. Curiel and the team adhere to a collaborative approach to tailor certain aspects of the program to the trainee’s goals and which maximize professional growth.
**Martinez, Claudia**

**Title: Multiscale Modeling of Elastin to Predict Vascular Aging for Early Detection of Cardiovascular Disease**

Description of the research project for DREAM Scholars

The process of vascular aging is characterized by alterations in vascular structure and function that result in arterial stiffness. Vascular aging is a major risk factor for age-associated cardiovascular disease (CVD). Early vascular aging refers to the detection of arterial stiffness before overt clinical manifestations. At the molecular scale, the main structural proteins that contribute to arterial stiffness are collagen and elastin, but while collagen is responsible for providing mechanical strength, it is elastin – several orders of magnitude more elastic than collagen – that confers the exceptional elasticity and recoil to vascular tissue, which can undergo more than 3 billion cycles of extension and recoil over a human lifespan. The loss of function manifested by vascular stiffening is fundamentally caused by changes to the structure and chemistry of elastin during inflammation and aging. The structure of elastin, which is composed of a disordered crosslinked network of tropoelastin precursor molecules, has, however, remained notoriously difficult to characterize experimentally. As a result, not much is known about how the mechanical behavior of elastin, crucial for healthy vascular function, is affected by its structure. Furthermore, how the main mechanisms underlying CVD change the structure of elastin, and therefore its ability to function, is not well understood. Here, we propose to use a multiscale approach based on molecular modeling techniques and experimental vascular measurements to elucidate how the main mechanisms that affect the mechanical function of elastin during inflammation and aging are responsible for the loss of function of elastic tissue that leads to vascular stiffening and subsequent CVD. We propose the following specific aims to achieve the overall goal: (1) identify the regions in elastin more prone to damage, (2) characterize how the various sources of damage affect the mechanical properties of elastin, and (3) correlation of the model with in-vivo measurements of vascular stiffness. The proposed work will provide unprecedented multiscale insight into how the structure and mechanical properties of elastin are affected by inflammation and aging; knowledge that will vertically advance our ability to predict early vascular aging for potential clinical applications to help prevent CVD at an early stage.

**DREAM Scholar training plan**

Claudia Martinez MD (Mentor). Associate Professor of Clinical Medicine. Dr. Martinez is an Interventional Cardiologist in the Department of Medicine at the University of Miami, Miller School of Medicine. She is currently the PI of five ongoing studies examining subclinical CVD risk in patients living with HIV as a model of premature vascular aging. Her research has focused on clinical measures of arterial stiffening and mechanisms of repair. Her role as a clinician and investigator focused on detection of vascular aging as a precursor for CVD is critical for the proposed study and will catalyze new synergy between molecular and clinical scales to contribute to the understanding of the pathophysiologic mechanisms leading to CVD with a focus on early detection. She will oversee the scholar training to become a physician scientist. The first step will be to train the mentee in grant writing. Through this we will develop application for the proposed project. We will have multidisciplinary meetings in with Dr. Luis Ruiz Pestana who is an Assistant Professor in the Department of Civil, Architectural, and Environmental Engineering at the University of Miami. With background in engineering mechanics and computational chemistry to gain insight into the fundamental mechanisms underlying the anomalous behavior of biological and synthetic materials at the nanoscale, with the ultimate aim of designing better engineering materials. Through this collaboration the mentee will learn of molecular modeling techniques combined with advanced sampling and free energy methods that will allow us to identify the regions in elastin that are prone to damage. Based on the clinical expertise
we will then expand the model to characterize how the various sources of damage affect the mechanical properties of elastin. The mentee will learn how to use a multiscale model of elastin to investigate its mechanical behavior. Once these models have been developed, we will correlate the Multiscale Elastin model with In-vivo measurements of vascular stiffness to validate the multiscale model. While in the process, the mentee will be trained on how to write manuscripts in order to disseminate the findings at the conclusion of the one year training period. The cross disciplinary expertise of the research team, which includes computational chemistry and cardiovascular research and clinical expertise, will be instrumental to train a MS3 as a physician scientist in translational medicine.
Project Description

The goal of the research project is to assess the efficacy of collagenase clostridium histolyticum (CCH) in men who have previously received platelet rich plasma injections for the treatment of pyronine’s disease (PD). CCH is the only FDA approved intrallesional injectable medication for PD. Unfortunately, it is expensive and carries the risk of penile corporeal rupture (<1%). Therefore, many patients seek out other options that are off label. This has led to many patients seeking out unproven restorative therapies such as shockwave therapy and platelet rich plasma injections. As these community-based therapies gain popularity, it is unclear how they should be managed after treatment failure and if they are at a greater risk of complications. Anecdotally, we are seeing an increasing number of men presenting with PD after PRP. We additionally, are finishing a clinical trial assessing the efficacy of PRP for the treatment of PD. We hypothesize that CCH will remain an effective and safe therapy for these men.

We will prospectively treat men with a history of PD initially managed with intralesional PRP. We will assess for changes in penile curvature, sexual function, and adverse events. Men will be treated with CCH using the protocol outlined by the manufacturer (8 injections over 26 weeks). We will compare baseline to 3 months after completing CCH.

This project will be perfect for a dream scholar interested in prospective observational trials. The scholar will learn clinical trial design, patient recruitment and retention, basic statistical analysis something other soft skills needed to be successful. During the training, the candidate will also become familiar with scientific writing, publication, and presentation. They will be enrolled in the Stanford online scientific writing course. I anticipate that the scholar will attend the American Urological Association (AUS) Meeting and Sexual Medicine Society of North America (SMSNA). These will be opportunities to present their research and network with other students interested in urology.
Mellon, Eric

Title: Improving Biomarkers of Brain Tumor Response

My laboratory studies brain tumors. We work to find new imaging and tumor biomarkers of response to better optimize therapy for poorly responding tumors.

I have projects available for students in the following:
1. Quantitative MRI evaluation – Our laboratory uses the world’s fourth combination MRI-linear accelerator to treat the brain cancer glioblastoma. We were the first to obtain daily MRI on these patients during treatment and we analyze quantitative imaging to find early response.
2. Blood and tissue biomarkers of glioblastoma – With our post-doctoral fellow and several collaborating laboratories in our department, we take tissue and serial blood samples from glioblastoma patients to find biomarkers of response or changes during therapy that correlate with response.
3. Clinical projects for students interested in medical physics or radiation oncology to improve radiation therapy delivery or to correlate treatment parameters with patient outcomes.
Meng, Zhipeng

Title: Roles of mechanotransduction in tissue regeneration and disease development

Project Summary

Environmental biomechanical cues play a critical role in cell growth and functional homeostasis. Many human diseases, such as organ fibrosis, cardiovascular diseases, and cancers, have been associated with aberrant biomechanical cues that promote disease progression. However, how cells sense and propagate biomechanical cues into biochemical signals, a process known as mechanotransduction, is poorly understood. In particular, the precise signaling transduction mechanisms and transcriptional outputs of mechanotransduction remain unknown. Unveiling the roles and signaling cascades of mechanotransduction is important for understanding fundamental development and disease mechanisms and for advancing therapeutic strategies.

We have been developing a research program to elucidate the roles and mechanisms of mechanotransduction in tissue growth control and disease development, with a current focus on how mechanotransduction controls regeneration and fibrosis during organ injury and repair. The main challenge in understanding mechanotransduction in this disease context is the lack of knowledge of mechanotranscriptomes and signaling cascades that are triggered by a combination of force-, cell-, and microenvironment-specific factors. In this proposal, we aim to answer 3 main questions to advance our understanding in the field: (i) what role does mechanotransduction play in regulating cellular functions and transcriptomes, particularly in the context of tissue repair? (ii) what are the signaling cascades that connect plasma membrane mechanosensors to mechanotranscriptomes? (iii) how do biomechanical cues and wound-healing signals integrate to control cellular functions and transcriptomes?

We will use endothelial cells and the liver as my main models to study these questions, as they are classical models for studying mechanotransduction and tissue repair, respectively. We will characterize endothelial mechanotransduction for its roles in liver regeneration and fibrosis mainly using (i) in vitro or ex vivo bioengineered models with human primary endothelial cells, and (ii) in vivo mouse models of liver injury. Our research program will also include similar studies of fibroblast mechanotransduction and lung regeneration and fibrosis.

We anticipate that my research program will advance the fundamental understanding of mechanotransduction in normal and diseased contexts, providing opportunities for identifying new druggable targets from mechano-signaling cascades for organ fibrosis and other diseases with aberrant tissue mechanics.
Title: Evaluating the impact of artificial intelligence and telemedicine in dermatology

With the growing inequities that persist throughout healthcare, telemedicine continues to play a larger role as a modality for treating patients. The onset of the COVID-19 pandemic has only contributed to the increased adoption of telemedicine services, as it provides an avenue for individuals across the world to receive subspecialty care from the safety of their homes. Many of the benefits include shorter wait times, optimizing in-person visits, and ultimately improved patient outcomes due to earlier diagnosis of diseases. The visual nature of many dermatologic conditions allows for telemedicine to play a key role in care delivery and diagnosis.

However, many of the concerns associated with adopting telemedicine also apply to teledermatology. Several studies have cited concerns with diagnostic accuracy, limited ability to operate technology, and barriers in the formation of empathy and trust, which are core values of any doctor-patient relationship.

The student will evaluate teledermatology from a variety of perspectives including patient perceptions of telehealth providers, treatment of disease over telehealth, and incorporation of technologies such as artificial intelligence in teledermatology services. This will be accomplished through complex survey design for prospective studies, retrospective chart reviews, and analysis of survey, clinical, and epidemiological data. The student will also undertake projects that are related to telemedicine as well as any new interests within dermatology that develop throughout the year.

The DREAM scholar will work directly under the supervision of Dr. Nouri on a variety of research studies throughout the year. Dr. Nouri will serve as a source of guidance as the scholar conducts research independently. The student will gain an understanding of all aspects of research including study design, data analysis, project management, and manuscript preparation. Ultimately, the student will be well prepared for an accelerated career as a physician-scientist.
**Paus, Ralf**

**Title: Do Human Scalp Hair Follicles have Functional Neuroendocrine GH-GHRH-IGF1 Axis Established?**

**Months 0-4**
Scholar receives extensive training in basic laboratory methods that are directly relevant to the proposed DREAM project (focus: microdissection and organ culture of human scalp hair follicles, IHC/IF, quantitative immunohistomorphometry, qRT-PC) and writing of a comprehensive literature review on recognized impact of GH excess or deficiency on human skin and hair follicles (subsequent publication in Exp Dermatol planned)
Scholar establishes, under close supervision, first basic IHC/IF staining and qRT-PCR protocols for GH, GRHR, somatostain, and IGF-1

**Months 5-8**
Generation of publication-quality data that determine:
  a) Exact distribution of mRNA and protein expression of GH, GHRH and cognate receptors in human scalp hair follicles?
  b ) HF response to GHRH stimulation: upregulation of intrafollicular GH expression (mRNA, protein; in which cells exactly?)?

**Month 9 (optional)**
Laser capture microdissection-based RNAseq in defined HF compartments at Monasterium Laboratory, Münster, Germany (www.monasteriumlab.com)

**Months 10-12**
Project wrap-up for publication (incl. additional controls, additional analyses/assays to reach level of significance, limited mechanistic work)

Manuscript writing & submission
Ramasamy, Ranjith

Title: Clinical and molecular characterization of COVID-19 associated orchitis

Supervision and Mentoring
The DREAM Scholar will receive research training under my mentorship. Specifically, they will be studying an intersect of genetics and SARS-CoV2 associated orchitis via two aims – aim 1 to determine if men with COVID-19 associated orchitis share a number of common susceptibility genes leading to differences in (1) circulating ACE2 plasma levels, (2) ACE2 binding site allostery, and (3) cytokine storm predisposition and aim 2 to test the hypothesis that men with COVID orchitis will have decreased circulating ACE2 levels compared to men without orchitis. As their primary mentor, I will provide my expertise regarding both global and technical aspects of their research proposal, including interpretation of data. I will review all presentations and edit any manuscripts prior to submission for publication. We will schedule to have weekly meetings, and my open-door policy will continue to lead to frequent dialog about their science. Given my appointment at the Department of Urology, I will continue to direct the DREAM Scholar to resources both within the University and outside that will facilitate their research.

The DREAM Scholar will also continue to be mentored by Dr. Himanshu Arora, an Assistant Professor within the Department of Urology at Sylvester Cancer Center who also currently works closely with all medical students. The student will also be working closely with geneticist, Dr. Anthony Griswold, who will provide valuable advice given the genetics focused aims of this specific project.

Responsibilities to and of the Candidate

The DREAM Scholar will have 100% protected time for research-related activities, regardless of whether this grant is awarded. Ultimately, their research career is strongly supported by me. Throughout this year, the DREAM Scholar will gain understandings in study design, experimental execution, project management, and report preparation geared towards ultimately accelerating a career path in academic medicine.
Women who smoke cigarettes while using oral contraceptives (OC) increase their risk for and severity of stroke compared to nonsmoking women who use OC. In recent years traditional cigarette users are switching to electronic nicotine delivery systems (e-CIG). Nicotine is the common addictive and toxic ingredient in traditional and e-CIG, that are especially popular among adolescents, when nicotine addiction often begins. Adolescence is also the critical period in life when young women may initiate sexual activities and begin the use of OC. The combination N+OC exacerbates the severity of ischemic episodes in females. Relinquishing the smoking habit reduces the risk for stroke and young women tend to give up smoking because of pregnancy. The impact, however, of smoking cessation on brain remains unknown, and thus serves as the focus of the current proposal.

Our published studies on young female rats show that nicotine toxicity is aggravated by OC via mitochondrial dysfunction and increased innate immune brain responses. Specifically, N+OC-exposure reduces brain energy metabolism, oxygen consumption, mitochondrial complex IV (CIV) activity, mitochondrial biogenesis and generates reactive oxygen species (mtROS). Recent studies corroborate that mitochondrial dysfunction and the release of mtROS and mitochondrial DNA (mtDNA) into the cytosol play a key role in inflammasome activation. The inflammasome is a main component of the innate immune response, and inhibition of nicotine-induced inflammasome activation improves post-ischemic neuronal survival. Our data clearly suggest that N+/OC-induced mitochondrial dysfunction and inflammasome activation are the processes at the fulcrum of severe ischemic brain damage in N+/OC-exposed female rats. Importantly, our pilot study shows that N+OC withdrawal (NW) for 30 days fails to reduce severity of ischemic brain damage in these female rats previously exposed to N+OC. These data indicate that N+OC-induced respiratory chain defects, energy metabolism alertations and inflammasome activation persist even after NW in female rats. Reducing mitochondrial dysfunction and inflammasome activation during NW can reduce nicotine toxicity to improve ischemic outcome in female rats.

Our pilot data show that pharmacological stimulation of mitochondrial biogenesis-using bezafibrate (BEZ; a PPAR pan-agonist) reduces N-induced mitochondrial dysfunction in the cortex of female rats. The use of BEZ to improve mitochondrial biogenesis has therapeutic implications, because this drug is clinically approved, successfully used for the treatment of hyperlipidemias and is currently being evaluated for treatment of mitochondrial diseases. Based on these findings, we hypothesize that the BEZ treatment after NW will abrogate the mitochondrial dysfunction, neuroinflammation and adverse ischemic outcome owing to N+OC observed in the young female rat brain. To test this hypothesis, we propose the following two aims:

**Aim 1:** To determine the effects of BEZ on brain metabolism after N+/OC withdrawal (NW).

**Aim 2:** To determine the effects of BEZ on neuroinflammation and stroke outcomes after NW.

Successful completion of this proposed study will show that maintaining the brain mitochondrial function constitutes a target for future therapy to reduce the severity of ischemic brain damage in women attempting to cease nicotine addiction.

Medical Student (MS) training in field of stroke at PI’s laboratory that is part of the Peritz Scheinberg Cerebral Vascular Disease Research Laboratory (CVDRL): The PI is committed to the training of medical
students and dedicates a significant portion of time and attention to training of MS in responsible conduct of research and to critically evaluating their progress. The mentorship will consist of guiding the medical student throughout her/his training tenure by means of the following approaches:

**Research training:** The PI will train student to design the experiments, identify appropriate experimental *in vitro* or *in vivo* animal model. MS will be trained to handle laboratory rodents, perform surgery to induce cerebral ischemia, behavioral testing and tissue collection. He/she will also be trained to perform histology, qPCR, western blotting, immunohistochemistry and ELISA or bioplex assays.

**One-on-one meetings with the mentor:** Apart from routine day-to-day interactions at the work bench, the PI will meet with the MS individually at least once a week to discuss experimental details, troubleshooting, to evaluate the significance of his/her experiments, discuss relevant literature and completion of data analysis, publication and presentation at lab/ intramural/extramural forums. We will also discuss opportunities for fellowship application(s).

**Weekly laboratory meetings and monthly journal club:** Lab meetings are conducted weekly at the CVDRL. In these weekly lab meetings members of Drs. Miguel A Perez-Pinzon (director of CVDRL) and Dave’s laboratory also participate. In this meeting, we critically discuss experimental design, approach, results obtained, technical difficulties and possible solutions. Importantly, experiments are performed by a blinded investigator and if the experiment is completed then the experimental groups reveal to the investigator. MS will also participate in a monthly journal club to develop the skills of critical review and presentation of the literature.

**Presentation of her/his work in intramural and extramural forums:** Once during the tenure in the lab, MS will present her/his data in a formal way in our Neurological Disorder Research Group meetings attended by Neurology faculties. In addition, funds are available for travel to participate one scientific meeting such as the Society for Neuroscience or the Brain meeting. Attendance in such meetings will give the MS exposure to other scientists in the field, and develop networking and skills in public presentation and discussion of research results.

**Research publications:** Publication of research is an integral and crucial part of research training. The genuine and mutual expectation between the PI and MS is to publish research papers in peer-reviewed journals, and the proposed study will allow the MS to generate enough data for a publication.

**Additional resources for professional development:** Training and resources are available at UM for MS to assist in the development of the “survival skills” needed for success in biomedical research. MS will be encouraged to attend grant-writing workshops, physician-scientist career development workshops, and speed mentoring sessions. These provide an immense opportunity to acquire the variety of skills necessary to survive successfully in the highly competitive world of stroke research and be productive.
One in five women having surgery for breast cancer continue to use opioids up to a year after surgery. Preventing immediate postoperative pain is a promising strategy to decrease the need for long-term opioid use in these women. Recent studies using “enhanced recovery pathways” have shown that a combination of non-opioid medications before, during, and after surgery leads to decreased opioid use. Specifically, a study of patients undergoing breast cancer surgery found that those receiving a combination of non-opioid alternatives had less pain than those who received opioids. Aside from their addictive potential, long-term opioid use negatively impacts the gut microbiome. The gut microbiome is composed of millions of good and bad bacteria. Recent studies have shown that a disruption in the balance between these bacteria, also known as gut dysbiosis, leads to inflammation that may increase the risk of cancer progression or recurrence. Therefore, clarifying the role of opioids given at the time of cancer surgery has the potential to improve patient survival.

Studying the negative impact of surgical opioids on the gut microbiome has been challenging because the surgery itself may lead to inflammation affecting microbiome bacteria. To overcome this problem, patients undergoing similar surgeries for breast cancer will receive either a previously-studied opioid-sparing protocol or traditional opioid-based care. The two patient groups will contain equal numbers of Hispanic and non-Hispanic patients to ensure that a diverse population is represented in the study findings. Microbiome samples will be collected at the time of surgery and one week later to determine whether opioids given during and after surgery lead to gut dysbiosis. Blood samples will also be collected to determine whether inflammation in the body is linked to receipt of opioids around the time of surgery. Opioid-related changes in the blood and the gut microbiome will also be compared between Hispanic and non-Hispanic patients to determine whether ethnicity or country of origin affects the negative impact of perioperative opioids. Determining whether surgical opioids lead to the same negative effects seen in long-term opioid users will confirm the importance of finding improved ways to manage pain without opioids. At the same time, connecting perioperative opioid use to inflammation associated with the negative changes in the gut microbiome suggests that opioids have the potential to worsen cancer survival, an important topic of future study.

DREAM Scholar Training Plan
The present project recently received funding through the Bristol Myers Squibb/National Medical Fellowships Diversity in Clinical Trials Career Development Program starting Nov 1, 2021 through Oct 31 2023. My translational mentor, Sabita Roy PhD, has a well-funded lab where the serum analyses for the inflammatory marker correlatives will be run using an ELISA. I now serve as a clinical collaborator and along with Dr. Roy and her team will mentor the DREAM Scholar during the study period. The Scholar will participate in the weekly lab meetings of Dr. Roy, as well as the biweekly Rojas Breast Surgical Oncology Virtual Lab meetings. The Scholar will be trained to perform and assist with the ELISAs for my funded study and will also be able to participate in additional laboratory projects during the time period. Furthermore,
as the surgeon clinical collaborator, I will be able to mentor the DREAM Scholar on the clinical side of translational science and provide clinical insight to these endeavors, along with how to pursue a career as a surgeon scientist. The DREAM Scholar will also have the opportunity to participate in an additional ongoing clinical research project, of which there are several in the Rojas Lab which focuses on studies looking at surgical decision-making with the use of preoperative MRI, opioid-sparing initiatives in breast cancer surgery, and managing sexual health sequelae after cancer treatment.

The specific aims of the funded study in which the Scholar will be assisting is shown below, with a focus on Aim 2:

Aim 1: To correlate measurable changes in the gut microbiome to perioperative opioid receipt in patients undergoing breast cancer surgery. The first aim will test the primary tenet of the central hypothesis, that perioperative opioids, and not process of surgery itself, lead to gut dysbiosis in breast cancer patients. Proving that changes in the gut microbiome are a result of perioperative opioids will be accomplished by comparing the changes in gut microbial colonies during the study period to patients that undergo similar surgery without opioids. Methods and analysis not included due to word limit.

Aim 2: To identify circulatory inflammatory markers correlating to gut dysbiosis after perioperative opioid receipt in breast cancer patients. The second aim will determine whether perioperative opioids, and not the process of surgery itself, lead to inflammatory systemic changes in patients undergoing surgery for breast cancer. Proving that increases in circulating inflammatory cytokines are a result of perioperative opioids will be accomplished by comparing serum blood samples during the study period to patients undergoing similar surgery without opioids. Differences in the systemic inflammatory response will be further stratified by ethnicity, comparing Hispanic vs. non-Hispanic patients. The tremendous diversity within the Hispanic population within our unique catchment area allows for additional exploratory analyses comparing differences in the downstream effect of opioid-based pain management. Hispanic women are less likely to participate in mammographic screening and are therefore more likely to present with later diagnoses and require more aggressive surgery. Therefore, exploring ethnicity-related vulnerabilities to perioperative opioids and their impact on the systemic inflammatory response will inform future interventional studies capitalizing on the plasticity of the microbiome through preoperative manipulation to prevent opioid-induced dysbiosis. Methods: Serum blood samples will be collected at the time of preoperative and postoperative microbiome specimen collection. Cytokine array will be used to elucidate circulating inflammatory cytokines, which will be subsequently correlated to perioperative opioid receipt and changes in the gut microbiome. Changes in inflammatory and immunomodulatory markers will be compared between cohorts that do and do not receive perioperative opioids. IL-6 and IL1-beta will be measured using a cytometric cytokine bead array, while sCD14, lipopolysaccharides, lipoteichoic acid, and FABP2 will be measured using ELISA. Analysis not included due to word limit.
**Roper, Stephen**

**Title: Functional Imaging of Pain: The Distress of Oral Cancer**

**DESCRIPTION**

Oral cancer is deadly and painful. Nearly 1/3 of Americans with oral cancer perish from the disease within 5 years of diagnosis [1]. In the US alone, this cancer kills roughly 1 person/hour, 24 hours/day [2]. Ironically, oral cancer pain is exacerbated by prolonged survival following improved chemo- and radiotherapy. Health disparity is an issue: in men, the highest rates of oral cancer occur in African-Americans [1,3].

The focus of this DREAM Scholar program is on the unique pain associated with oral cancer. Oral cancer patients do not go gently. This scourge generates more severe pain than any other cancer type [4]. The intensity of oral cancer pain escalates with disease progression. Opioids become less effective as patients develop opioid tolerance. The majority of terminal patients experience debilitating pain during their final months of life. Understandably, severe chronic pain from oral cancer reduces function and degrades quality of life. Important for understanding the underlying mechanisms of oral cancer pain for evaluating my proposal is the key observation that supernatant from oral cancer cells (but not other cancers) elicits intense pain when introduced into the tongue of experimental animals [5]. An unknown (at present) component of the tumor secretions appears to stimulate pain in oral cancer.

A critical limitation to studying the cellular and molecular basis for oral cancer pain has been the lack of appropriate animal models. To date, the most effective animal model has been oral squamous cell carcinoma (SCC) in mice. Oral pain in mice can be measured with devices to assay mechanical allodynia during chewing [6]. Over the years, researchers have conducted detailed cellular, molecular, and biochemical analyses of oral SCC in mice (e.g., [5,7-10]). Yet, despite all the advantages, oral tissue in mice is relatively inaccessible for direct experimentation, especially for recording neural activity in nociceptors that innervate the tongue. Moreover, equipment to measure oral pain behavior in mice must be custom-built and is expensive [6].

Given this lack of a suitable animal model for studying oral cancer pain, I propose that a DREAM Scholar and I will take a surprisingly novel, innovative approach; we will develop the mouse cornea as a model system for investigating oral cancer pain! As in oral mucosa, the cornea is covered by a stratified squamous epithelium. Moreover, the cornea is the most densely innervated tissue in the body, crisscrossed by thermosensitive, mechanosensitive, and nociceptive afferent fibers. Corneal afferents travel close to the epithelial surface [11-13] (Fig. 1). Importantly, by using confocal Ca2+ imaging and transgenic mice that express Ca2+-sensitive proteins (GCaMP) in sensory neurons, it is possible to record stimulus-evoked activity in corneal sensory fibers and their parent neurons in the trigeminal ganglion in living, anesthetized mice [14-18]. Preliminary experiments show that murine oral cancer cells implanted in the mouse cornea form tumors resembling tongue cancer. Experiments are underway testing xenografts of human oral cancer cells into the mouse cornea to further validate this new model.

**TRAINING PLAN**

I propose a systematic progression of the DREAM Scholar training, with 8 specific steps, or milestones, as follows:
Step 1, Introduce Scholar to the problem: provide a curated collection of publications and websites on nociception, corneal microanatomy, squamous cell carcinoma, confocal microscopy, and calcium imaging. Introduce Scholar to Dr. Brian Schmidt, NYU, and arrange weekly (virtual) meetings among the 3 of us to discuss and evaluate the readings.

The following milestones will be completed on the confocal calcium imaging rig in my laboratory:

Step 2, Train Scholar how to prepare mice for in vivo confocal calcium imaging, including anesthetization and mounting mice in the custom-built stereotaxic imaging frame.

Step 3, Instruct Scholar how to operate the scanning laser confocal microscope: collect in vivo imaging data from corneal afferent fibers in deeply anesthetized mice. [We use transgenic mice that express GCaMP6s (a calcium-sensitive fluorescent protein) in trigeminal sensory neurons, allowing us to image neuronal activity in corneal afferent fibers]. Explain how to (a) digitize images with ImageJ (NIH); (b) measure stimulus-evoked responses with MatLab; and (c) conduct statistical analyses (Graphpad Prism).

Step 4, Quantify pain responses in control animals: image afferent activity in naïve (control) mice and determine sensitivity of untreated corneal afferents to dilute solutions of capsaicin, a canonical nociceptor stimulus. Measure corneal afferent mechanosensitivity with von Frey hairs.

Step 5, Test ability of tumor cell secretion to elicit pain: determine sensitivity of corneal afferents to supernatant from cultured human oral cancer cells (HSC-3). Does supernatant stimulate nociceptors and enhance responses to capsaicin and mechanostimulation?

Step 6, Quantify oral cancer pain responses in experimental animals: Measure corneal afferent fiber activity (responses to capsaicin, mechanostimulation) in mice with corneal xenografts of human oral cancer cells. The following milestones will be completed using electrophysiological recording:

Step 7, Quantify pain behavioral responses in control mice: record blink responses to air puffs and von Frey hair stimulation of cornea, measured by electromyographs (EMGs) recorded from the orbicularis oculi muscle.

Step 8, Quantify pain behavioral responses in experimental mice: record blinkevoked electromyographs (EMGs) in the orbicularis oculi muscle in mice with corneal xenografts of human oral cancer cells. Are blink responses exaggerated in mice with human oral cancer cell corneal xenografts?

I myself will train and mentor the Scholar in each of the above steps and each step will be reviewed in consultation with Dr. Brian Schmidt, NYU. Dr. Schmidt will provide human oral cancer cell culture (HSC-3) supernatant, Step 5, and mice with corneal xenografts of human oral cancer, Steps 6, 8.

Furthermore, results will be presented and discussed in weekly lab meetings held with my longstanding collaborator, Dr. Nirupa Chaudhari (Professor of Physiology/Biophysics) and her lab staff. At these meetings, our trainees present progress on their projects on oral sensory mechanisms, including taste, touch, temperature, and pain.

Finally, under my mentorship, the DREAM Scholar will prepare oral presentations for the Department of Otolaryngology (Grand Rounds), the Department of Physiology & Biophysics (weekly seminar series), regional meetings, and appropriate national conferences to gain an introduction to other faculty (both clinical and basic science) and to nationally- and internationally-renowned physician/scientists. I will
mentor the DREAM Scholar in writing drafts of reports and one or more anticipated publications. The Scholar will assist in preparing the NIH MPI R01 proposal that Dr. Schmidt and I will be submitting in 2021 (see Biosketch, Section D). Findings from the Scholar’s milestones will provide crucial pilot data for that NIH MPI proposal; involving a DREAM Scholar will tremendously enhance the NIH proposal.
Sagen, Jacqueline

Title: Developing cannabinoid peptide and gene therapies for the treatment of chronic spinal cord injury pain

Chronic neuropathic pain is a debilitating condition often induced by spinal cord injury (SCI). SCI neuropathic pain is a particularly challenging and difficult target, as it generally responds poorly to most clinically available therapies. Cannabinoids (CB) are a promising and potent class of agents in the management of neuropathic pain, and preclinical studies as well as clinical observations suggest that cannabinoids may be particularly potent in relieving SCI neuropathic pain. Despite the positive benefits of cannabinoids, clinical acceptance has been limited due to CNS side effects at systemic analgesic doses and the fear of abuse potential. Marine cone snails produce a wealth of diverse and selective peptides (conopeptides) and have become a major focus for new drug development in the treatment of CNS injury and disease. Using cone snail venom extracts, preliminary screening in pain models in our laboratory has identified several potential candidates that can be characterized and developed into novel therapeutics for the treatment of pain. Since these are peptidergic, local spinal delivery is utilized, thereby avoiding widespread side effects. The overall hypothesis to be addressed is that unique conopeptides that target cannabinoid receptors can be identified and utilized for long-term alleviation of chronic SCI neuropathic pain using a gene therapy approach. To accomplish this, cone snail venom extracts from diverse Conus species are being tested in vitro for selective activity at the two distinct primary CB receptors, CB1 and CB2, using redistribution assays, and positive extracts progressively subfractionated until pure active peptides are obtained using HPLC and mass spectroscopy. This has resulted in several promising CB1 and CB2 conopeptide subfractions. The student project will evaluate these in the rat SCI clip compression pain model, using continuous intrathecal infusion via implanted Alzet minipumps. In addition, the project will include the generation of cDNAs from the promising pain-reducing peptides for development of a gene therapy using AAVs. These will be tested in the rat SCI pain model using a battery of sensory and locomotor behavioral tests. Potential side effects will be monitored, and selective pharmacologic antagonists will be used to determine cannabinoid activity. Sustained conopeptide transgene expression will be evaluated using neurochemical and immunocytochemical assays. If successful, this project should overcome barriers in harness the promising analgesic potential of the cannabinoid system in the therapeutic management of debilitating chronic SCI pain.

DREAM Scholar Training plan:
The student will be trained hands-on in all aspects of the research project, including rodent surgical procedures, rodent SCI pain and locomotor assessments, histological, immunocytochemical, and neurochemical assays, and microscopy. The student will also participate in design of the gene therapy and delivery systems, data and statistical analyses. Weekly lab meetings are held with in depth discussions of the lab projects, results and data sharing, trouble-shooting, and ideas for future experiments. All students are expected and encouraged to participate and contribute to these discussions. Frequent one-on-one meetings between the student and mentor are also arranged. Required courses such as lab biosafety and IACUC will be completed. Attendance at the weekly Miami Project seminar series and Neuroscience lectures will be encouraged to broaden the student’s scope of knowledge. In addition, the student will present their research findings at University of Miami student research forums and at national/international scientific conferences such as the Society for Neuroscience meeting when feasible.
The student will also participate as an author in the preparation and submission of project manuscripts upon successful completion.
Non-enzymatic post-translational modifications (NEM) are emerging as important determinants of protein function. Unlike conventional enzymatic modifications, these arise from spontaneous reactions between specific amino acid side chains and reactive by-products of cellular metabolism. Oxidation, acylation, and glycation are the three most abundant NEM found throughout the animal kingdom. Amongst them, glycation is currently the least understood and most abundant. Glycation broadly refers to the covalent attachment of glucose or reactive metabolites derived from its breakdown, such as methylglyoxal (MGO) onto proteins. Although the forward reaction, i.e. between glucose or MGO and proteins, is non-enzymatic their removal is catalyzed by highly conserved and specialized enzymes fructosamine 3-kinase (FN3K) and protein deglycase DJ-1. Glycation serves as a pathognomonic marker of diabetes. Importantly, we have recently described its role in liver and lung cancers (Sanghvi et al., Cell, 2019). However, our current understanding of glycation is limited to these few examples and its full extent and biological significance in normal and pathological conditions remains unknown. In principle, glycation should be proportional to the nutritional and metabolic state of cells as well as to the activity of deglycating enzymes. Our central hypothesis is that glycation is an evolutionarily conserved mechanism that senses nutritional and metabolic environment and modulates cellular processes accordingly. There are several open projects in the lab that are centered on understanding this process and its implications in metabolic gene regulation.

Project 1: Understanding glycation kinetics and stoichiometry: The glycated proteome has not been characterized in any detail. We will employ sophisticated and highly sensitive mass spectrometry combined with isotopomer based labeling to identify the proteins glycated by glucose, MGO, or both. Moreover, we will use pulse chase and Stable Isotope Labeling by Amino acids in Cell culture (SILAC) to precisely quantitate glycation kinetics and stoichiometry on individual proteins.

Project 2: Glycation and metabolism: The molecular link between glycation and cellular metabolism is poorly understood. We will investigate this by perturbing cellular metabolism in vitro and in vivo in several ways (different diets, suppression of one or both deglycation enzymes, or increasing intracellular concentrations of glycating metabolites) and examine the functional consequences of differential glycation.

Project 3: Targeting de-glycation in cancer: The hallmark of several aggressive and incurable cancers is their altered metabolism. Specifically, these cells meet their exceedingly high energy and biomass demand by increasing glucose uptake to subsequently fuels cancer-specific anabolic processes. Glycation is directly proportional to glucose levels, therefore we speculate that these tumors have evolved counter measures to avoid excess glycation and maintain proliferation. Glycation is reverted by two distinct conserved enzymes, FN3K and DJ-1, and this project will investigate whether inhibiting their action increases glycation burden and result in tumor regression in vivo. Specifically, we are interested in targeting deglycation in lung, liver, and B cell malignancies.

Our lab uses several in vitro and in vivo modalities. Specifically, we use genetically engineered mouse models, in vivo somatic gene transfer, genome editing by CRISPR/Cas9 system, genetic screens, high throughput genomics and proteomics, and temporal gene regulation strategies.
DREAM Scholar training plan

I am committed to providing top-notch mentorship and research training to students and postdocs in my lab. I aim to foster a collaborative and creative research environment and offer the same high-level training I received at the Memorial Sloan Kettering Cancer Center with the ultimate goal of developing trainees into independent investigators.

I understand that medical students may not have similar prior research experience as PhD students and may require extra time to familiarize themselves with wet lab research. Therefore, to ensure their immersion in the project and independence to conduct their research, I will take a more hands-on approach when they first join the lab. Specifically, I will comprehensively discuss the project, lay out a feasible and systematic experimental plan, navigate them through the technical challenges, and help them with data analyses. In addition, I will discuss with each trainee his or her short- and long-term goals in order to facilitate their actualization through more personalized mentorship.

I will then organize periodic meetings to make sure that the project is moving in the right direction. Particularly given the short amount of time, this will not only promote timely troubleshooting but also maintain research focus in order to ultimately enable trainees to make biologically meaningful contributions in the field. Importantly, while I will mentor and supervise the trainees, I will not micromanage but rather encourage them to be independent thinkers and creative scientists.

For development of professional skills, I will also encourage medical trainees to attend departmental and institute seminars to widen their scientific knowledge. Additionally, I will suggest they present at one or more works-in-progress or internal retreats to build their collaborative network within the institute. Moreover, I will send trainees to at least one prominent conference to present their research findings and establish contacts at other institutes. Finally, I will also encourage my trainees to participate in grant and manuscript writing to empower them to hone all skills needed for future research as an independent physician scientist.

Although I am a new PI, I have trained multiple graduate students and technicians during my postdoctoral training. Moreover, being a new and small group will allow me to dedicate ample time to each trainee ensuring their research success. Overall, I will provide a motivating and research friendly environment that will enable the trainees to confidently conduct their research and drive the field forward.
Schürer, Stephan

Title: Novel Prospective Targets for Cancer Therapy

This proposed project has specifically been developed for a medical student and can be completed in the one-year time frame. The project has no external dependencies. It will leverage medical knowledge and expand data science skills of the DREAM scholar.

Novel prospective targets for cancer therapy

The ability to generate and process huge amounts of data has given rise to a new discipline, Data Science, which has become an essential component in most industries. Data Science is quickly transforming medicine, from diagnostics to the development of new therapies. The future of cancer treatments will be highly individualized enabled by large reference datasets and among other technologies - scalable and inexpensive sequencing, image analysis, and artificial intelligence. Small molecule precision cancer therapy will require an arsenal of new drugs. Currently, there are less than 4,000 FDA-approved small molecule drugs (unique ingredients) [1]. They target less than 700 known mechanism-of-action proteins targets [2]. The human genome codes about 20 thousand proteins and the number of druggable proteins, defined as those that can be modulated by binding a small molecule with a resulting pharmacological effect, is at least 4,500; but this number is rapidly increasing with the development of PROTACS [3] and other technologies to target what was previously thought to be “undruggable”. The current drugs thus target at most 20% of the druggable proteome. The human Kinome is one of the most cancer-relevant protein families and less than 20% of kinases have been effectively “drugged” for cancer therapy [4]. Over 20% of human kinases are understudied with little to know knowledge. The same situation holds for other protein families such as GPCRs or ion Channels. Systematic efforts are under way to expand the scope of drug targets, for example via the European Open Targets or the NIH Illuminating the Druggable Genome (IDG) project in which we participate [2,5].

We have recently developed the Clinical Kinase Index (CKI) [4]. CKI is a comprehensive scoring system that utilizes differential gene expression, pathological parameters, overall survival, and mutational hotspot analysis to rank and prioritize clinically relevant kinases across 17 solid tumor cancers from The Cancer Genome Atlas. We have also developed an interactive Web App to facilitate interactive analysis of all kinases in each cancer [6]. Our work showed that understudied kinases have potential clinical value as biomarkers or drug targets that warrant further study.

In the proposed project we will carry out similar analyses for other protein families such as GPCRs and other enzymes. The project will extract and process gene expression, and protein expression data and clinical data, along with various additional information related to targets phylogenetic, functional, and target development level (TDL) classifications from databases such as TCGA [7], TCPA [8], CPTAC [9-11], LINCS [12,13], Pharos [14,15], and various ontologies [16]. These data will be harmonized, integrated, and analyzed to generate a predictive scoring function to rank the clinical relevance of these targets. The work will be performed in collaboration with a senior lab member. The medical student is expected to take the lead and curate, analyze, and interpret clinical parameters such as histological, pathological, and survival data thus leveraging their medical expertise. An App will be developed in collaboration with an experienced software developer. The project is realistic to be completed within one year with an
impactful publication, such as the CKI paper [17].

DREAM Scholar Training Plan
Stephan Schürrer Research Group
As data science is quickly transforming medicine and enables precision therapies, it is essential that future physicians and in particular physician scientists to understand and be able to apply data science methods in medicine. The proposed project is focused on the prioritization of new drug targets. The project will leverage several large public datasets such as TCGA, TPCA, target, tissue and disease ontologies, and drug target and mechanism of action data.
The DREAM scholar will work closely with Dr. Schürrer and a senior lab member to guide her / him through the various data resources, data harmonization, integration, and analysis. The development of the accompanying App will primarily be done by a software developer unless the DREAM scholar has the expertise and can perform this work.
Overall, the project will provide solid training in data science, including data and metadata standards, data wrangling, data harmonization, data integration, various statistics methods (basic knowledge is expected) for data aggregation, hypothesis testing, benchmarking, ROC AUC analysis, and correlation analyses. If the project timeline allows, we will also leverage explore machine learning methods. The project will also provide a deep understanding of available gene expression, proteomics, and associated clinical datasets, and how to access and process the data access. The required bioinformatics methods will be part of training for thus project. At least basic bioinformatics, statistics, and R or Python coding skills are required.
During the first three months, there will be heavy emphasis on learning the methodologies and datasets and will be DREAM scholar will be provided with relevant literature, online resources and if needed online coursework. Regular weekly meeting with a senior lab member and Dr Schürrer will evaluate progress; adjustments will be made as needed.
While gaining expertise in Data Science, the DREAM scholar will apply and leverage her / his medical knowledge to curate, select, filter, analyze, and interpret the results. The project thus aims to integrate data science and medical knowledge to be highly relevant towards future essential expertise and use cases of medical practice and research.
Following the first quarter, the data will then be queried, downloaded, annotated, harmonized and integrated iteratively in the second quarter. Deep analysis and augmentation, optimization of the datasets will follow in the third quarter. The Web App will be developed in the fourth quarter primarily by a software developer while the DREAM scholar will draft the publication manuscript. Throughout the project there will be weekly progress meetings with, the senior lab member and Dr Schürrer focused on technical issues and progress against the timeline. In addition, the DREAM scholar will have access to the significant expertise among the members in the SchürrerLab and will be able to work one-on-one with a senior bioinformatician or data scientist.
**Sharma, Umakant**

**Title: Efficacy of Synbiotics therapy on Attenuation of symptoms of Inflammatory Bowel Disease in the Context of Prescription Opioid.**

Description of the research project for DREAM Scholars

Opioids are the most prescribed analgesics for pain management in inflammatory bowel diseases (IBD). Opioid use has been linked with increased complications, hospitalizations, decreased quality of life and mortality in IBD patient. Recently, we demonstrated that opioids used for pain management in IBD accelerate progression of IBD by dysregulation of the gut microbiota, leading to expansion of pathogenic bacteria, translocation of bacteria, immune deregulation and sustained inflammation. The results of this study suggest that use of opioid potentially alters the gut microbiome which is closely involved in the pathogenesis of IBD. Current IBD therapies focus on antibiotic treatment and suppressing immune responses but here we propose that microbiological and nutritional interventions that are able to protect the gut against damaging inflammation offer the next source of IBD therapies in opioid using patients. Moreover, this understudied and underexploited area of research provides a tractable system that can be used to reduce damaging intestinal inflammation. Based on our recent published study and preliminary data, we hypothesized that “the restoration of gut homeostasis by modulating the gut microbiota with the use of probiotic and prebiotic treatment could be a relevant therapeutic strategy for IBD in the context of prescription opioid.” In this scenario, supplementation of probiotics and prebiotics will be beneficial to the recovery and reconstruction of intestinal microbiota. Under these circumstances, regulation of enteric flora will be beneficial to the repair of inflammation. Probiotics are live microorganisms that benefit host health when administered in adequate amount. Probiotics promote maintenance of the gut barrier function and modulation of the host immune system; therefore, dietary supplements containing probiotics may be beneficial for IBD. Gut commensal bacteria such as Lactobacillus and Bifidobacterium strains are commonly used as probiotics. The effectiveness of probiotics will be influenced by colonization ability and survival rate of viable bacteria using prebiotics such as inulin. A prebiotic is a non-viable food substance which could not be absorbed by the host but could promote the proliferation of one or more beneficial bacteria selectively and associated with modulation of the intestinal microbiota. A synbiotic, a mixture of a probiotic and prebiotic, has the advantages of both microbiological and nutritional interventions. Probiotic and prebiotic treatment has been shown to be a promising therapy to repair the gut microbiota and inflammation. Until now there are no published studies on the effects of synbiotics treatment on IBD in the context of opioids. This is the first study in which the therapeutic effects of synbiotics will be investigated on opioid induced intestinal inflammation and exacerbated clinical symptoms of colitis in a murine model of IBD. Herein, we will demonstrate that modification of the gut microbiome by synbiotics can modulate the mucosal immune response and suppress the damaging inflammation for the amelioration of IBD in dextran sodium sulphate (DSS)-induced colitis and spontaneous colitis (IL-10 knockout mice) mouse model of IBD in the context of opioid. The results of this study will help in the development of new therapeutics for the treatment of IBD patients that are on opioids.

**DREAM Scholar training plan**

Primary objectives of the Dream training plan is to:

1) provide trainees with a rigorous laboratory research experience that is translational in prescription opioids, IBD and gut microbiome research.
2) provide trainees with essential research skills and information regarding career development in substance abuse research through journal article presentations and invited lectures and seminars and attendance of the lab meetings.

3) Participation in appropriate supplemental didactic experiences that allows for the multidisciplinary understanding of drug abuse research and its associated co-morbidities at the bench side and clinical implementation of prevention and treatment strategies at the bedside.

4) The candidate will also learn how to perform scholarly reviews of the literature; formulate hypotheses and study design; developing essential skills in statistics, oral and written presentation of scientific findings and manuscript writing; understanding issues and defining potential problems of scientific integrity and ethics.

5) The candidate will learn very advanced molecular biology and Immunology research techniques.

Drs. Sharma and Roy will meet the trainee on a daily basis to discuss experimental plans and weekly to discuss data and data interpretation.
Shehadeh, Lina

Title: Blocking SARS-CoV-2 Infection in human cells and animal models

Description of Research Project

Patients with diabetes and poorly managed hyperglycemia hospitalized for Coronavirus Disease 2019 (COVID-19) have death rates and hospital stays four times greater than people without these conditions. We recently found that patients with diabetes and heart failure (HF) express significantly higher levels of the low density lipoprotein receptor (LDLR). While the entry of coronavirus including SARS-CoV-2 into cells is known to be facilitated by angiotensin-converting enzyme 2 (ACE2), our preliminary data indicate that LDLR is a novel receptor with low micromolar affinity for the SARS-CoV-2 spike protein (SSP) and increases SARS-CoV-2 pseudoviral infection in 293T cells. Therefore, we hypothesize that elevated LDLR in patients with diabetes and HF enhances SARS-CoV-2 infection and this contributes to the worse morbidity and mortality seen for coronavirus infection of these patients. Here we propose to determine the SSP binding domain on LDLR, and develop blocking peptides with the overall goal to generate a novel treatment to protect patients with diabetes and HF from infection with the SARS-CoV-2.

Goal 1. Determine the SARS-CoV-2 spike protein (SSP) binding domain on LDLR.

To identify the specific SSP binding domain(s) and determine the binding affinity (Kd = EC50), each domain or group of domains will be tagged and immobilized in an in vitro binding assay in the presence of increasing amount of labeled SSP. Results from Aim 1 will identify the specific SSP binding domain(s) on LDLR, EC50, and association/dissociation constants.

Goal 2. Determine the effect of LDLR on SARS-CoV-2 pseudoviral infection of human cells and identify peptide inhibitor(s) of LDLR-mediated SARS-CoV-2 infection.

We hypothesize that coronaviral infection in susceptible subjects is increased by elevated LDLR, and will be blocked by peptide(s) that compete with the spike protein binding domain on LDLR. Using the peptides identified in Aim 1, we will perform neutralizing assays in human cells ± LDLR, and quantify SARS-CoV-2 infection by live cell imaging. Results from Aim 2 will determine the effect of LDLR on the rate of SARS-CoV-2 pseudovirus infection of susceptible human cells and identify novel inhibitor(s) of such infection for possible therapeutic applications.

Goal 3. Test the best lead of LDLR peptide in blocking SARS-CoV-2 pseudoviral infection in hACE2 transgenic mouse ± high fat diet.

We hypothesize that lead peptides identified in Aim 2 significantly reduce SARS-CoV-2 pseudoviral infection in hACE2 transgenic mice, in a manner that is amplified by high fat diet (to induce obesity, cardiac dysfunction, diabetes, and dysregulated LDLR expression). Blocking peptides or PBS will be administered intranasally to 4-month old male and female Keratin-18 (K-18) hACE2 transgenic mice that express the human ACE2 gene driven by the K-18 promoter which is prominent in the lungs and present in the heart. Twenty hours after inoculation, mice will be sacrificed and lung, heart, kidney, and intestine tissues will be collected for quantification of GFP signal via flow cytometry and immunohistological staining. Results from Aim 3 will determine the efficacy of a novel LDLR peptide treatment for reducing SARS-CoV-2 pseudotyped viral infection in vivo.
Training Plan

The medical student(s) to join the Dream project will be trained in all technical and conceptual aspects of the project. The technical training will involve protein binding assays, molecular biology experiments, cell culture work, lentiviral work, live cell imaging and analysis, mouse dissections, mouse echocardiography, and mouse whole body plethysmography.

In addition, one of my key roles as PI is to coach and train the rest of the team members on the insights of verbal and written communications according to the laboratory and journal standards. All team members are required to participate in lab meetings to establish a detailed treatment/experimental timeline as well as timeline/design for technical skill acquisition of the scientific research projects they are currently working on. In our group, lab meetings are conceived as the first step in the path, which should ultimately lead to the submission of abstracts to scientific forums and journals. The first step in the research process would be to define the scientific problem and the hypothesis with base in different aims including the ones outlined in the project description. The second step is a formal Power point presentation of 30 minutes minimum, followed by an extensive discussion. With this approach we expect to visualize the results and interpretation of the data from different points of view and draw consistent lines of continued research work. The third step must present a formal seminar to our department once a year and the presentation of new ideas to future research studies and plans for manuscript presentation and future application of grants. We have a good success rate when submitting abstracts to annual conferences. For example, we usually have 1 or 2 presentations/posters each year in the American Heart Association (AHA) scientific sessions and/or American College of Cardiology (ACC). This is an invaluable preparation for the trainee’s writing skills and presentation rehearsals as part of my research team. In conclusion, the student will write a mandatory manuscript for his/her main project autonomously; consequently, we will work together to generate a final product for submission. Based on rigorous selection of the MD candidates, I trust that the student will have high probabilities of success in scientific and journal presentation as well as manuscript and grant writing. He/she will be asked to co-review manuscripts that I have been requested to evaluate, further expanding their appreciation of scientific design and data interpretation. Based on this, I am confident that the student will become a strong researcher nurtured under my research group.

In conclusion, this Dream award will give invaluable experience to the medical student(s) as part of my research team. The student will be requested to write a review manuscript for his/her main project autonomously, and consequently we will work together to generate a polished product for submission. The student will also be immediately placed on the department seminar schedule to attend our weekly group and Cardiology Rounds meetings.
**Starke, Robert**

**Title: Cellular dysfunction in cerebral aneurysm pathology**

Dream project:
The primary focus of our basic science research is on the pathophysiology of cerebral aneurysms. An aneurysm is a focal weakening of a blood vessel in the brain which leads to vessel enlargement or bulging. In some patients the aneurysm may grow leading to further vessel damage and rupture resulting in a devastating form of stroke. Therefore, many patients are treated to help stabilize the aneurysm before it ruptures. Our research aims to understand the molecular and cellular mechanism which leads to cerebral aneurysm formation, growth, and rupture and to investigate new avenues for cerebral aneurysm treatment. We have several ongoing research projects:

1. Endothelial and vascular smooth muscle cell dysfunction and death are associated with cerebral aneurysm formation, growth, and rupture. Although multiple inflammatory cascades are implicated in inducing vascular smooth muscle dysfunction and death, there is relatively little known about the mechanisms leading to endothelial cell dysfunction. Therefore, this study aims to understand the role of inflammatory pathways in endothelial cell dysfunction and how this relates to aneurysm progression.

2. An extensive body of clinical and preclinical data demonstrates that cigarette smoking enhances the risk of aneurysm formation, rupture and treatment failure. However, the mechanisms by which smoking increases the risk of cerebral aneurysms and treatment failure is not fully defined. Smoking is known to induce cellular dysfunction and death of endothelial and vascular smooth muscle cells, the two primary cellular components of the blood vessel wall. We have previously shown that cigarette smoke enhances vascular smooth muscle cell phenotypic switching and death resulting in increased rates of aneurysm rupture. However, it is not known if cigarette smoke induces endothelial cell dysfunction which in turn contributes to the enhanced aneurysm formation and rupture observed in patients who smoke. The goal of this project is to determine the effects of cigarette smoke on endothelial function and how this may contribute to aneurysm progression.

We also have a very active clinical research program where we study all forms of cerebrovascular disease, such as ischemic and hemorrhagic stroke, vascular malformations, cerebral aneurysms, and others. Part of this research involves clinical trials as well as numerous prospective and retrospective studies to investigate all areas of cerebrovascular disease.

**DREAM Scholar training plan:**
During medical school I was fortunate to receive a National Institute of Health Clinical Research Training Program scholarship which allowed me to spend a year doing research and receive a master’s degree in statistics and epidemiology. Therefore, I understand this unique opportunity for medical students and the importance of this research training. I am fully committed to mentoring the DREAM scholar in order to help them achieve their clinical and research career goals. I have mentored 3 medical students who spent a year working in my lab and were accepted into neurosurgery and interventional radiology residencies. The DREAM scholar will receive intensive training in cellular dysfunction in cerebral aneurysm biology. The scholar will be trained in basic science laboratory techniques, such as cell culture, western blot and gene expression analysis, and other standard laboratory techniques. If interested the scholar will also have opportunities to be involved in clinical database studies. The scholar will present their findings at lab meetings, and local symposiums and will be given opportunities to contribute to clinical publications. The scholar will also be encouraged to attend clinical grand rounds and neurosurgery resident meetings.
Title: Elucidating early genomic biomarkers of cutaneous radiation-induced fibrosis in cancer patients using murine and human skin models

Description of the research plan for DREAM scholars:

Radiation-induced skin fibrosis (RISF) is a late complication of radiotherapy for underlying malignancy, and a subset of patients develop devastating fibrotic disease years after undergoing treatment. Incomplete understanding of the molecular mechanisms driving radiation-associated fibrosis has slowed the identification of biomarkers indicating risk for severe fibrosis in patients, impeding development of mitigation strategies and targeted therapies to combat fibrotic damage. This project aims to perform comprehensive genomic profiling and pathway analysis of irradiated skin samples from ex vivo human and in vivo murine RISF models in order to define the core molecular signature specific to radiation-induced skin fibrosis. Identified pathways will be validated and explored in archived post-radiation patient biopsies with chronic fibrosis as a platform for the design of prospective clinical trials.

As a DREAM Scholar pursuing this project under Dr. Rivka Stone’s mentorship, you will master the core research techniques in skin biology (per list below in Training Plan). You will learn how to execute a hypothesis-driven translational genomic study, from sample acquisition to processing of next-generation sequencing data, network and pathway analysis, and in vivo validation of findings, as you study radiation-induced skin fibrosis in both a murine and human skin model. This project is intrinsically translational in design and in approach and will appeal to the DREAM scholar interested in pursuing the pathophysiology of a challenging clinical condition with unmet needs and negative impact on patient quality of life. Although the techniques and approaches in this research plan are applicable to the study of organ systems across most clinical disciplines, a DREAM scholar interested in pursuing Dermatology, Oncology, or Radiation Oncology may find this research project and associated mentorship from Dr. Stone particularly relevant towards defining their career path as a physician scientist conducting translational basic science or clinical research.

DREAM Scholar training plan:

As a DREAM scholar in Dr. Rivka Stone’s laboratory, you will receive your research training as an integral member of a team that focuses on genomics of inflammatory and fibrosing skin disorders. You will receive hands-on training on research techniques in skin science including:

- Processing of skin specimens
- Immunohistochemistry/immunofluorescence
- Techniques in molecular biology (Western blotting, qPCR, and more)
- Quantification of fibrosis in skin specimens from mice and humans
- Ex vivo human skin models

1:1 training in the principles of bioinformatics, pathway analysis, and “making sense” of genomic datasets derived from patient skin biopsies, provided by Dr. Stone

Dr. Stone's laboratory is under the umbrella of the Wound Healing and Regenerative Medicine Laboratory. As such, you will participate in the weekly joint laboratory meetings and learn about translational projects across the spectrum of acute and chronic wound healing. You will benefit from the camaraderie, support,
and collective wisdom of a dedicated group of researchers, postdocs, graduate students, and research technicians.

You will meet weekly with Dr. Stone to discuss your progress, troubleshoot any challenges, and outline next steps to advance your research. You will be supported in submitting research abstracts to the annual Innovations in Wound Healing meeting, Wound Healing Society meeting, and Society for Investigative Dermatology meeting.

As an aspiring physician scientist, under Dr. Stone’s mentorship you will also have opportunity to participate in a variety of clinical activities at the Department of Dermatology and Cutaneous Surgery, including but not limited to:

- Participation in Dr. Stone’s general and procedural dermatology clinics
- Dedicated discussion with Dr. Stone on opportunities to ask translationally relevant research questions (successful conduct of “bench to bedside” work)
- Attendance and participation in weekly departmental Management conferences and Grand Rounds
- Attendance at Miami Dermatologic Society meetings
- Participation in other Dermatology clinical faculty clinics, per scholar’s interests (COVID-19 circumstances permitting)

Finally, Dr. Stone will mentor you in discussing your short- and long-term career plans, plans for residency application and training (for example, identification of residencies suited for dedicated research training), and will support you as you investigate your path towards becoming a successful physician scientist.
Title: The Role of SMARCA4 Overexpression in Therapy-Related AML

Description of the project:
Patients treated with cytotoxic chemotherapies for a primary cancer are at increased risk for therapy-related acute myeloid leukemia (tAML). As cytotoxic therapies yield increased mutation burden in relapsed malignancies and leave evidence of activity via mutational signatures, we studied the genomic and temporal relationship between chemo-related mutations and progression of clonal hematopoiesis (CH) to tAML. We analyzed 32 tAML whole genomes for mutational signatures and copy number variations. Complex structural variants were observed in 7 tAML, and not in any of 21 primary AMLs. Complex SV included chromothripsis in 6 (19.4%) tumors, chromoplexy in 2 (6.5%), templated insertion in 1 (3.2%), and otherwise unspecified complex SV in 2 (6.5%). Notably, chromothripsis appeared more likely in tAMLs exposed to melphalan or platinum (5/6, 83.3%; p = 0.059) and, in 4 cases, involved chromosome 19 with universal focal hyper-amplification of SMARCA4 (³5 copies). We now plan to investigate the role of SMARCA4 overexpression in tAML by using retroviral overexpression in AML cellular models. This work could identify SMARCA4 as a novel oncogenic driver of therapy related AML and could drive discovery of inhibitors of the SWI/SNF complex as a therapeutic for this deadly cancer.

DREAM Scholar training plan:
The DREAM Scholar would join the Justin Taylor Lab and learn the molecular biology, cell culture and cancer biology techniques necessary to complete the research project. This will include training in cancer epigenetics and genomics, signal transduction, multiparameter flow cytometry, and development and assessment of murine models of AML. I will meet with the Scholar once a week for approximately one hour to review data and an additional one-hour meeting specifically to discuss grant application and career development plans. In addition, there are many seminars in our program for the Scholar to attend and eventually present, including the Cancer Epigenetics (CE) Seminar series, the CE Colloquium, and the Hematology/Oncology Grand Rounds Series. There is also a weekly lab meeting between my lab and Dr. Stephen Nimer’s lab. I will work to help the Scholar with manuscript writing skills by working together. As a physician-scientist and former recipient of similar fellowship awards myself, I know the importance of a program like the DREAM in advancing the careers of promising young Scholars and will be committed to their training and career development.
Title: Mechanistic Studies of SARS-CoV-2 Induced Hepatic Damage Using Primary Liver Cells, Induced Pluripotent Stem Cell (iPSC) Derived Hepatocyte-Like Cells (HLCs) and Kupffer Cells.

PROJECT: Rationale. Patients infected with SARS-CoV-2 may present with or develop laboratory abnormalities and other clinical indicators of hepatitis and acute liver disease. Understanding the mechanisms by which SARS-CoV-2 induces or exacerbates liver disease activity in healthy patients or in those with chronic hepatitis and/or cirrhosis is paramount. Furthermore, determining if SARS-CoV-2 induces significant pathology in specific liver cell types that express SARS-CoV-2 viral receptors and their contribution to hepatocyte dysfunction is an area in need of inquiry. Mechanistic Studies. The mechanisms by which SARS-CoV-2 induces liver pathology and the pertinent cell types these clinical outcomes are unknown. The aims of this application are focused on understanding the molecular mechanisms underlying the hepatic sequelae in those who have been infected with SARS-CoV-2, specifically focusing on innate immune responses activated in primary human hepatocytes (PHHs) and Kupffer cells (PKCs) utilizing innovative in vitro models and patients samples. A better understanding of the mechanisms through which SARS-CoV-2 infected patients manifest hepatitis will enable the development of targeted therapeutics to abrogate these poor clinical outcomes that may have long lasting implications for liver health. Hypotheses. Our over-arching hypothesis is that exposure of liver cells to SARS-CoV-2 activates RNA-dependent innate immune pathways that subsequently drive inflammation that causes the hepatitis observed in infected patients. In this study, we will specifically be testing the hypothesis that the robust viral RNA dependent innate immune response that we have characterized, that drives inflammation in HCV infected livers, is activated in liver cells through activation of viral RNA sensing pathways. Approach. PHHs and PKCs will be used to characterize the innate immune responses activated in in-vitro models of SARS-CoV-2/coronavirus stimulation. Specific RNA dependent innate and inflammatory pathways, such as RIG-I/TLR signaling, will be studied as well as additional pathways involving the production of interferon and chemokines including IP10/CXCL10, IL-1β and CCL5/Rantes that may drive subsequent hepatitis. SARS-CoV-2 will be used to study COVID-19 disease specific responses while the HCoV-NL63 strain will be used for studies that may provide insight for broader coronavirus inflammatory responses in the liver. Innovation/Impact. The proposed research is innovative because the effect of SARS-CoV-2 on the antiviral response present in the liver of infected individuals has not been studied in the novel models utilized here. Moreover, liver-specific innate immune responses to coronaviruses are poorly characterized and the contribution of specific cell-types to this response has not been investigated in primary cells from the liver as we propose including specific analysis of RNA sensing pathways and genes that control inflammatory responses to SARS-CoV-2, including HMGB1 and TREM1. Collectively, completion of these studies will provide the most detailed understanding of the roles of PHHs/PKCs during the inflammatory response in patients with SARS-CoV-2 infection and provide new avenues for therapeutic intervention to ameliorate liver disease in these patients.

TRAINING PLAN: I am an alumni of both the University of Miami MD and PhD programs. I am a Fellow of the American Association for the Study of Liver Diseases (FAASLD) and I am on the National Board of Directors for the American Liver Foundation. I am director of the Oncology Pathway for medical students that is one of the most popular pathways. I also have a secondary appointment in the department of Biomedical Engineering, Public Health Sciences and Internal Medicine. My training philosophy has been guided by my upbringing in the minority community of Perrine in South Miami, FL. In addition, I obtained elementary education at minority schools (Richmond Elementary and Richmond Heights Junior High, Miami FL). I am very aware of the challenges that individuals from disadvantaged backgrounds face when considering careers in the biomedical sciences and I am committed to assisting these individuals in
achieving their career goals to promote diversity in the academic setting. My mentoring plan for my current and future mentees are to capitalize on their foundation in research and data analyses and provide them with additional training that would subsequently develop them into a fully independent investigator with focus on translational and disease-oriented research. My philosophy in supervising research fellows is to encourage independence and career development as rapidly and appropriately as possible. I will maintain close interactions with my mentees on a daily basis, gauge their growth in obtaining skill in research and provide them with as much independence and support as they are capable of handling. As mentees moves through their training, I continue to counsel them on their career development and support their research projects on a daily basis. I will also support their career development by recommending them to various professional and scientific societies (e.g. AAI, AASLD, etc.) so they can establish themselves as a contributing member of the biomedical research community and possibly assume a leadership position in the future. I will introduce them to leading scientists and academicians in the field so they can establish a network of support and collaboration. I take great pride in helping my trainees succeed in pursuing an academic career and I will do whatever is necessary to ensure their career success. As part of the MD DREAM program, I will specifically be working with the medical school student on this project so that they receive both basic research and clinical research training. Opportunities for clinical research training will also be available through the Department of Pathology working closely with Dr. Carmen Gomez. The goals for the research project participation are to help the students get research experience, help them with their medical career choices and ultimately help them obtain the residency of their choice. As a medical school alumnus, I have the first-hand experience necessary to guide medical students on a path to achieve their career aspirations.
**Title: Targeting Inflammasomes in Substance Abuse and HIV**

This application aims to investigate the impact of prescription opioids and HIV brain infection on ischemic stroke, a major comorbidity in the infected population and opioid abusers. The proposal is based on novel and exciting findings from the PI’s lab that were recently published in part in *Nature Commun* (1) and *Brain* (2). We identified that brain infection by HIV increased susceptibility to ischemic stroke, leading to reactivation of HIV (1). Importantly, this effect was associated with activation of the inflammasome (Figs 5 and 7), providing strong scientific premise for the current proposal.

The PI’s laboratory has a long-standing interest in the cerebral toxicity of drug abuse (e.g., 1-14). Our important preliminary data demonstrate that chronic exposure to opioids can enhance tissue damage in ischemic stroke (Fig 4); the results that are consistent with clinical reports on opioid exposure and predisposition to stroke (3). In addition, we have evidence that opioids can activate the inflammasome (Figs 5B and 6) and induce inflammatory reactions. In line with these observations, the central hypothesis of the current grant is that HIV and prescription opioids activate inflammasome in the CNS that can worsen stroke outcome, including poststroke HIV reactivation in the CNS and egress into the periphery. The Specific Aims are:

**Aim 1.** Evaluate the hypothesis that opioid exposure potentiates HIV-induced CNS toxicity via inflammasome activation, worsening the outcomes of ischemic stroke and delaying post-stroke tissue recovery. We will study the mechanisms of activation of the inflammasome in the brains of EcoHIV-infected and opioid-exposed mice. We will evaluate both the priming and the activation stages of inflammasome activation. Specifically, we will determine the type(s) of pattern recognition receptor(s) (PRRs) that are activated in response to these stimuli and pro-IL1β, as well as the assembly of the inflammasome complex, pro-caspase-1 cleavage, and secretion of IL1β and IL-18. We will next identify the type of the CNS cells that are involved in inflammasome activation. Finally, we will link inflammasome activation to neuroinflammation and ischemic stroke outcome and recovery in the HIV-infected/opioid exposed mice.

**Aim 2.** Evaluate therapeutic effectiveness of targeting mitochondria for protection against HIV and opioid-induced inflammasome activation, leading to improvement of stroke outcome and recovery. HIV and opioids share mitochondria as a pathological target, and we hypothesize that mitochondrial dysfunction induced by these agents can predispose the brain to stroke-related ischemic injury and delayed recovery. Importantly, mitochondrial dysregulation is also a strong inducer of inflammasome activation. Therefore, Aim 2 will employ a novel nanotechnology approach to target mitochondrial delivery of antioxidants conjugated to nanoparticles for protection against inflammasome activation. Such an approach was highly effective in our recent publication (15), enhancing scientific premise for Aim 2.

**Aim 3.** Evaluate the impact of opioid-induced inflammasome activation on HIV reactivation in the CNS and egress into the periphery in ischemic stroke. The CNS is an important but poorly understood HIV reservoir. Our novel findings indicated for the first time that HIV can be reactivated from latently infected brains as the result of stroke (Fig 11 and [1]). These results may have huge translational implications; therefore, we will further explore this process, and will evaluate if reactivated HIV in the CNS can egress into the periphery. Mechanistically, we will explore the role of inflammasome in these events, linking Aim 3 to studies in Aims 1 and 2. Our preliminary data also indicate that inhibition of inflammasome has a protective impact on HIV infection (Fig 13), further supporting the rationale for Aim 3. Virtually all HIV-
infected patients receive antiretroviral therapy (ART); therefore, it is our belief that studies on long-term HIV-related comorbidities should also include treatment with ART. Aim 3 will compare the effectiveness of ART to the efficacy of anti-inflammasome-based therapy for protection against stroke outcome and HIV reactivation. In concert, Aims 1 and 2 will provide critical insight into the role of inflammasome in stroke development of HIV-infected patients who are opioid abusers. Aim 3 will provide important information on the reactivation of HIV from the brain and seeding into the periphery as the result of inflammasome activation in stroke. The proposed research is highly innovative due to its focus on novel mechanisms underlying vascular comorbidities, such as ischemic stroke, in the HIV-infected brain in the context of opioid abuse. These studies are also likely to identify new opportunities for therapeutic intervention.
Title: Innate and Adaptive Immunity in Wound Healing Infections

DREAM Project Description

One of the most devastating complications of diabetes, diabetic foot ulcers (DFUs) are characterized by deregulated adaptive and innate immune response. Persistent tissue level of pathogenic bacteria including Staphylococcus aureus (SA), coupled by impaired activation, recruitment and survival of immune cells mediated by downregulation of FOXM1 and antimicrobial Perforin-2 (P-2) results in prolonged unresolved cutaneous inflammation, persistent and reoccurring infection that often result in lower leg amputations. The long term goal of this project is to understand the mechanism and clinical significance of the antibacterial molecules in patients with wound healing disorders. We have already shown that wound infection with S. aureus results in P-2 downregulation in keratinocytes and gamma delta (GD) T cells, whereas S. epidermidis (SE) induces P-2. Loss of P-2 is associated with both, lower antimicrobial activity against skin pathogens such as MRSA, its intracellular accumulation and decreased epithelialization. Importantly, we have shown that intracellular MRSA killing is enhanced in skin after exposure to SE. Based on robust preliminary data we postulate that P-2 is necessary for the optimal wound healing process, i.e. barrier restoration. To gain greater insight into relationship between innate immune responses and wound healing outcomes, we propose to study how commensal microorganism (SE) modulates wound healing process in human skin through activation of antimicrobial protein P-2.

This project will focus on the clinically relevant question if the ratio of S. epidermidis to S. aureus correlates to clinical outcomes of healing in DFUs. Our hypothesis is that protective effect of SE can potentially predict DFU outcomes of healing. We will leverage DFU tissue samples already collected to correlate the ratio of SE:SA with P-2 levels (Aim 1) and to the clinical outcomes of healing (Aim 2). This retrospective study will utilize FFPE tissue preserved from 50 subjects with chronic DFUs. The patients will be dichotomized into two groups: “healers” and a “non-healers” based on week 4 surrogate outcome of healing. We have already established and successfully utilized this approach to quantify SA in DFU tissue, which assures feasibility. CFUs for both species will be determined using qPCR and already generated standard curves. Importantly, the project is clinically relevant but does not depend on prospective tissue acquisition and new patient recruitment. P-2 mRNA levels in all samples will be measured by real time qPCR. Freshly cut sections of FFPE DFU tissue previously identified as healing (n=24) and nonhealing DFU (n=26) will be processed for DNA isolation. DNA quantity and quality will be evaluated and used for further qPCR analyses with species specific primers and probes, nuc - thermostable nuclease for SA and SE specific SodA - superoxide dismutase. Based on our preliminary studies we expect to detect higher load of SE among healing DFUs, and higher prevalence of SA in non-healing DFU.

This project provides an ideal training platform for a medical student: it connects bedside with bench, offers exposure to multi-disciplinary research approach, and hands-on training in multiple molecular and cell biology techniques.

DREAM Scholar Training Plan

Wound Healing and Regenerative Medicine Research Program provides an exceptional multidisciplinary basic and translational research training opportunity for young physician scientists who bridge research into new paradigms of clinical care. DREAM Training Plan will include several stages: initiation, data acquisition and completion of data analyses/progress report. Initiation Stage (the first 2-3 months) will
include hands-on training of techniques required for the project, visits to wound healing research clinic, and learning basic background regarding wound healing biology and pathophysiology by reading and discussing existing literature and attending ongoing seminars. It is expected that a student becomes proficient in techniques and can proceed to the Data Acquisition Stage (7-8 months), which will focus on generating data as outlined in the project. It is expected that the student will conduct most of the experiments, with mentor’s supervision and minimal technical assistance. Dr Tomic-Canic will supervise bench research, provide research space and infrastructure, additional supplies and access to all necessary equipment, and provide scientific mentorship as the student progresses through experiments. Finalization Stage (last 1-2 months) will include final data analyses, drafting a manuscript and conference abstract(s) and finalizing progress report. Upon completion of the research year DREAM student will be expected to submit scientific abstracts to ESRF and one national meeting (such as Wound Healing Society) and encouraged to apply for travel awards when they are available. The student will present the final results at the Dermatology Annual Research Day that occurs at the end of every academic year, which will provide training in research presentations and critical thinking.

During this year of research, a student will be immersed in multiple educational activities as integral part of Dermatology Academic Training Program that includes lecture series (such as weekly Dermatology Ground Rounds; bi-weekly basic science seminars), Journal Club, and Innovations in Skin Biology Seminars. DREAM Student will attend and discuss her/his progress weekly at Wound Program Meetings attended by clinical and research teams (trainees, clinical and research fellows and program PIs), which will provide opportunity for discussing progress and troubleshooting. Student will also have the opportunity to participate in Wound Rounds (a bi-monthly discussions of complicated clinical cases related from wound clinic). Finally, twice a month a DREAM student will have one-on-one standing meeting with Dr Tomic-Canic to discuss progress and overall training experience. Taken together, mentorship, training and research environment that are available in support of a DREAM student and this research project are outstanding and will assure successful and meaningful training experience for a future physician-scientist in academic medicine.
**Verde, Fulvia**

**Title: Control of cell morphogenesis and chronological aging**

Defects in cell morphogenesis promote the onset of diseases such as cancer and neurological disorders. Loss of cell polarity and disruption of tissue architecture is a common histological feature in cancer, playing an important role in the alteration of tissue organization. Although substantial progress has been made, the molecular mechanisms coordinating cell morphology and cell growth are still poorly understood. The long-term goal of our laboratory is to understand the cellular functions that govern emergence of cell shape, and in particular the signaling networks that coordinate cell polarity with cell growth.

The conserved NDR kinase plays a key role in the control of cell morphology and cell proliferation in several organisms ranging from yeast to mammals. Studies have shown that NDR kinase protein levels decrease in gastric cancer and lymphoma. Loss of NDR kinase has also been linked to defects in cardiac and neuronal cell function. Currently however, there is a very limited understanding of the cellular functions of this conserved kinase and of its targets. We have previously discovered that fission yeast NDR kinase Orb6 spatially regulates the activity of Cdc42 GTPase, a key morphology control factor. Recently, we have shown that Orb6 kinase also negatively regulates mRNA degradation and translational repression, promoting polarized cell growth. Using genomic-scale and proteomic approaches we have identified novel targets of Orb6 kinase, and discovered a novel role for Orb6 kinase in promoting cell adaptation and regulating chronological lifespan during quiescence.

The objective of our current projects is to define the mechanisms whereby NDR kinase spatially regulates cell shape, promotes cell growth, and fosters cell resilience in both yeast and human cells. Our research aims to establish the role of NDR kinase in enabling alternative physiological states of the cell, such as active cell growth versus cell quiescence, in response to environmental stimuli. The results of this research project will provide insight into a still poorly characterized signaling pathway with a conserved function in the control of cell morphogenesis, cell growth, and stress response, with the long-term goal to identify novel diagnostic markers or therapeutic targets in the treatment of disease.

**DREAM Scholar Training Plan**

DREAM scholars will interact with Dr. Robert Tams (Postdoctoral fellow), and with graduate and undergraduate students in the lab. Since an important aspect of development as an independent scientist is communication, we place particular emphasis on weekly presentation and discussion of published articles and scientific findings from the laboratory. The DREAM scholar will have the opportunity to attend the weekly departmental seminars in the Department of Pharmacology, and to travel to one international conference (such as the annual meeting organized by the American Society of Cell Biology).

The DREAM scholar will work within the scope of the following projects currently active in the lab:

**Proposed research projects**

**Project 1:** Characterize key NDR substrates with a role in cell shape emergence.

**Project 2:** Establish if human NDR kinase regulates specific mRNA binding proteins with a role in cell growth.
Project 3: Establish if and how yeast and human NDR kinase responds to specific environmental signals to promote cell resilience.
**Villarino, Alejandro**

**Title: Cellular and molecular characterization of oncogenic STAT5 mutations**

**Project Description**

Cytokines propagate inter- and intra-cellular signaling networks that protect against cancer, infection and tissue damage. However, they also pose latent danger. Failure to control cytokine responses fuels pathology in most, if not all, disease settings. Operating downstream of more than 50 cytokines, Signal Transducer and Activator of Transcription (STAT) family transcription factors underlie each of these properties. It has long been known that STATs are hyper-active in cancer cells and can drive oncogenesis. Our laboratory seeks to understand these activities at cellular, molecular, and genomic levels, this informing the development and/or implementation of drugs that modulate the JAK-STAT pathway. To that end, we have designed a 1-year DREAM program project to discover cell intrinsic mechanisms for STAT-driven transformation of immune cells. The work will center on STAT5 as it has been strongly linked to oncogenesis. STAT5 is particularly relevant for leukemias and lymphomas, so the work will further focus on immune cells, specifically T cells.

The proposed project will leverage both in vitro and in vivo systems to interrogate oncogenic STAT mutations (Figure 1). For in vitro modeling, STAT5-deficient primary T cells will be transduced with retroviral vectors expressing either wild type or mutant versions of STAT5, the latter on somatic mutations identified in human leukemia and lymphoma patients (Figure 1). High Dimensional Flow Cytometry (hd-FC) will then be used to measure cellular responses, population-level ‘bulk’ RNA-seq to compare transcriptomes and Seahorse XF to measure effects on metabolism, specialty glycolysis and oxidative phosphorylation. The goal is to identify unique and common features of STAT5-activating mutations that are amenable to therapeutic intervention.

A gain-of-function approach will also be used for in vivo modeling. STAT5 deficient hematopoietic stem cells will be transduced with wild type or mutant STAT5, then adoptively transferred to lymphopenic hosts. These will be monitored for lymphoma/leukemia development, and, at various times post-engraftment, donor cells will be inspected by hd-FC and single-cell RNA-seq (scRNA-seq). Crucially, each STAT5 construct will include a unique DNA barcode that allows us to compare transcriptomes cross individual mutations. It is also important to note that all tools (transgenic mice, retroviral transduction), experimental models (in vitro culture, adoptive transfer) and analysis platforms (hd-FC, RNA-seq, Seahorse XF) necessary for the proposed research are presently available in our laboratory. Thus, we are poised to welcome a DREAM scholar who wants to shed light how STATs promote blood cancers.

**Training Plan:**

Mentorship for the DREAM scholar will have three major components. First, weekly one-on-one meetings with their research mentor will provide frequent opportunities to gauge and guide progress, both in terms of research output and intellectual development. Second, they will participate in weekly laboratory meetings held in conjunction with the laboratory of Erietta Stelekati, a group whose expertise in T cell biology will benefit the proposed research. These joint laboratory meetings provide a rigorous, yet supportive venue to learn research fundamentals, like experimental troubleshooting and data interpretation, and to receive constructive feedback on one’s work. Third, attendance at weekly seminars hosted by the department Microbiology and Immunology and the Sylvester Comprehensive Cancer Center will expose them to contemporary research methods and ideas, while providing a broader sense of immunology and cancer biology.

Along with intellectual mentorship, the DREAM scholar will receive practical training in experimental
design and execution, data generation and data analysis. All training will be conducted under direct care and supervision of their research mentor.

Specifically, the DREAM scholar will learn to:

1. Isolate and culture primary immune cells
2. Produce and apply retroviral gene expression vectors
3. Perform and analyze high dimensional flow cytometry
4. Assay immune cell metabolism by Seahorse XF analyzer
5. Generate and analyze RNA sequencing data
Yosipovitch, Gil

Title: Pathogenic role of IL-13 in prurigo nodularis (PN) associated disease severity

Project Description
The DREAM Scholar will undertake a hands-on research project focused on analyzing data from the largest itch blood, skin, and data bank center in the United States. The results of this work will provide evidence for explorations of epidemiology and genetic aspects of chronic pruritic diseases that are under-investigated. Further research in this area has the potential to reveal useful insight into specific genetic and molecular targets of itch pathways that function aberrantly in pathological conditions. More specifically these targets may be useful in developing new anti-pruritic treatments. Additionally, the student will assist in subject recruitment, study procedures (skin biopsy, blood draws, patient survey administration), and data entry for the Skin, Blood, and Data Bank of Patients with Chronic Itch.

A primary study to which the DREAM Scholar will contribute is titled, "Pathogenic role of IL-13 in prurigo nodularis (PN) associated disease severity - Itch Blood Bank Study". This study will analyze blood from 30-40 PN patients using:

1. IL-13 Simoa ultra-sensitive immunoassay using the Quanterix platform to measure circulating IL-13 levels.
2. Periostin immunoassay, since IL-13 is known to induce periostin, an extracellular matrix protein involved in tissue remodeling and fibrosis.
3. O-link Inflammation panel, which is a multiplex immunoassay for 92 inflammation related protein biomarkers. This assay will allow a broad survey of serum biomarkers elevated in PN compared to healthy controls.

The aim of this specific project is to understand if elevated levels of IL-13 and/or its downstream mediators are associated with PN.

DREAM Scholar Training Plan:
Dr. Yosipovitch (PI) will work closely with the DREAM Scholar throughout the research year to ensure that the scholar receives a strong foundation in basic and translational science, as well as specific skills in research management, documentation practices and research ethics. The scholar and PI will maintain weekly contact throughout the period to monitor progress and ensure that the following key learning goals are met:

1. Achieve foundational CITI/lab training for skin biopsy, blood draws, and patient survey administration.
2. Shadow in the Itch Clinic and Eczema School
3. Understand how to conduct a clinical trial (may complete a Clinical Research Professional course and/or certification)
4. Understand how to write an IRB and research proposal
5. Master SAS for data/statistical analysis

In terms of project monitoring, the scholar will attend weekly research lab meetings on Mondays from 11 am-12 pm in addition to weekly meetings with research mentor. During these meetings, Dr. Yosipovitch will provide constructive feedback to the student about their progress in relation to their understanding and execution of the research methodology, the integrity of their work, and their ability to communicate key findings and insight with colleagues. This detailed feedback will be provided in the spirit of preparing the scholar for a fruitful career as a physician-scientist.
Zhai, Rong Grace

Title: DREAM to fly: Drosophila modeling of neurological diseases

*Description of DREAM project*

Research in the Zhai lab is focused on understanding the genetic and molecular mechanisms of neural degeneration and protection in the context of both common and rare neurological disorders. We use a ‘Drosophila - mammalian tissue culture two-model’ systems, to identify genetic components in Drosophila and characterize the cellular mechanisms in mammalian cells. We have three projects for DREAM scholars.

Project 1. Mechanisms of NMNAT-mediated neuroprotection. Neurodegeneration occurs in numerous neurological diseases and conditions including stroke. Although the precise cause is often unknown, many neurodegenerative conditions share common features such as protein aggregation and age dependence. We were the first to identify NMNAT as a neuronal maintenance factor in Drosophila retina, mutations in which were later identified in human to cause Leber congenital amaurosis, an early onset retinal degeneration. Our studies in Drosophila have uncovered protective effects of NMNAT against activity-induced neurodegeneration, injury-induced axonal degeneration, spinocerebellar ataxia 1 (SCA1)-induced neurodegeneration, Tauopathy, and Huntington’s disease, suggesting a general neuroprotective function of NMNAT. We are currently investigating the role of sleep, stress, and environmental toxins in the process of neurodegeneration, and screening for small molecules that can enhance NMNAT-mediated neuroprotective activity.

Project 2. Functional analysis of neurological phenotypes in Drosophila models of rare and common neurological diseases. My lab is dedicated to taking full advantage of the Drosophila genetic model systems to understand human (rare) genetic diseases. In collaboration with NIH Undiagnosed Disease Program (UDP), we have carried out a pilot functional screen in Drosophila of the mutant variants identified in UDP, and facilitated the confirmation of 11 disease-causing genes, 4 out of which are new diseases. For common neurological diseases, we recently established a model of chemotherapy induced peripheral neuropathy (CIPN) and characterized the mechanisms of paclitaxel induced sensory disfunction. Recently, we established collaboration with European Rare Disease Mechanisms and Models Consortium (Solve-RD) to provide functional and mechanistic analysis for newly discovered diseases. Currently, we focus on modeling peripheral neuropathies, including Charcot-Marie-Tooth (CMT) disease and Hereditary Spastic Paraplegia (HSP).

Project 3. Mechanisms of mitochondria function and polyamine metabolism in rare neurological diseases. We are interested in understanding the role of metabolic pathways in the pathogenesis of several neurological diseases in vivo using Drosophila models. We established a model for Snyder-Robinson Syndrome (SRS), an X-linked intellectual disability syndrome caused by loss-of-function mutations in spermine synthase (SMS), a polyamine biosynthesis enzyme. We carried out more in-depth functional analysis and discovered an important mechanism underlying the neurotoxicity of polyamine oxidation. Specifically, we found that SMS deficiency leads to excessive spermidine catabolism, which generates toxic metabolites that cause lysosomal defects and oxidative stress that compromise autophagy-lysosome flux and mitochondrial function in the Drosophila nervous system and SRS patient cells. Currently we explore mechanistically the mitochondria toxicities in SRS and other polyamine-associated neurological disorders.
• DREAM Scholar training plan

I have an extensive training track record. At the University of Miami, I have mentored 11 graduate students (8 have completed PhD, 3 current), 7 postdocs (4 have completed, 3 current), and 1 junior faculty member (current). These trainees have received 6 training fellowships (1 AHA predoc fellowship, 1 NIH K99/R00, 1 NIH K01, and 3 private foundation predoc fellowships). I also serve as a faculty mentor for two junior faculty members.

• Graduate Advising: 8 have completed PhD, 3 current
  o Predoctoral Fellowships: 1 AHA, 3 private foundation fellowships

• Postdoctoral advising: 4 have completed, 3 current
  o Postdoctoral Fellowships: 1 NIH K99/R00

• Junior faculty mentoring: 2 current
  o Career Awards: 1 NIH K01

DREAM scholars will receive intense training in the area of Drosophila genetics and human disease modeling. Specifically, the training will include the following aspects.

1. Training on the study of neurodegeneration and in Drosophila biology and genetics. DREAM scholars will build a strong knowledge base on the principles of neurodegeneration and neuroprotection; and acquire new research skills and techniques in a Drosophila modeling of neurological diseases.

2. Training in scientific writing, presentation and dissemination of research findings. DREAM scholars will attend and present in at least one conference or symposium. Scholars will author at least one manuscript that summarizes the research results generated from the DREAM project.

3. Training in physician scientist track. DREAM scholars will be encouraged to participate in physician scientist training activities organized by the DREAM and MDPHD program, including clinical grand rounds and relevant clinical case reviews.
Title: The role of protein arginylation in human diseases

Research in My Laboratory

The main research interest of my laboratory is N-terminal arginylation, a poorly understood posttranslational modification mediated by arginyltransferase1 (ATE1). This modification adds one extra arginine to the protein, resulting in changes in the primary sequence and surface charge.

We are among the few research groups (4 in the USA) with demonstrated expertise on arginylation. We aim to understand its molecular mechanism and also aim to generate novel research tools for mechanistic investigations. We have achieved substantial breakthroughs by revealing that acutely increased arginylation during injury causes cell death and that downregulated arginylation in cancer leads to stress resistance, metabolic reprogramming, and mutagenesis. We have also developed several novel techniques that are now being used in many labs. For these reasons, my lab is considered as a pioneer in arginylation studies.

The research being conducted in my lab is highly multidisciplinary. The test models include mammalian cells, human tissue samples, live animals (mouse and rat), and yeasts (S. cerevisiae and S. Pombe). We employ many experimental techniques including biochemical analyses for nucleic acids and proteins, molecular cloning, enzyme reactions, Mass Spectrometry, high-precision optical imaging, and bioinformatic analysis.

The current focus of our research is on the role of arginylation in cancer, spinal cord injury, and aging-related abnormalities. Since arginylation is a less explored direction, there are many unaddressed questions that are “low hanging fruits” that are ready to be harvested. We have several exciting projects that are ideal for the DREAM scholar to perform for a period of one year. These include:

1. Determining the role of protein arginylation in spinal cord injury and test if the inhibition of arginylation can effectively reduce neuronal cell death in injury. The test models will include primary neuronal cells and live animals (mouse and rats). The main techniques will include biochemical assays, genetic knockout and/or knockdown, animal surgery and physiology, and tissue immunohistology.

2. Testing the potential efficacy of metabolic therapy for ATE1-dysregulated cancer (including prostate and breast cancer). The main employed techniques is similar to project 1.

3. Revealing how a small portion of ATE1 is imported into mitochondria and if its function in mitochondria is different than in cytosol. Mammalian cells and/or yeast cells will be used as the main test models. Molecular cloning, biochemical assays, and optical imaging (including confocal microscopy) are the expected techniques.

4. Developing small molecules to inhibit or activate ATE1 for the treatments of diseases. The test models will include culture mammalian cells. The main techniques are biochemical assays, optical imaging, molecular design and bioinformatics.
Training Plan for the DREAM Scholar

I will pay special attention to train DREAM scholars in these two areas: the ability of critical thinking, and the ability to perform independent research to test the hypothesis. Based on these principles, I have successfully trained 3 postdoctoral researchers (postdocs) and 1 graduate student. Among them, 2 of the postdocs already obtained faculty positions.

My lab currently contains one senior postdoc and one postdoctoral visiting scholar. We are also expecting 1-2 PhD students in 2021, in addition to at least one undergrad student as in past years. The scholar will be assigned 1-2 projects based on his/her research interest and experience. All projects are independent but are also related to the projects of other existing staffs in the lab. As such, the scholar will be able to enjoy a substantial amount of intellectual interactions with everyone in the lab.

To develop the ability of the scholar in hypothesis-testing, the scholar will be directly supervised by me. We will have daily meetings and briefings for updates and troubleshooting. The scholar will also be paired with the senior postdoc to learn basic experimental techniques.

To develop the ability of the scholar in data analysis and presentation, they are expected to attend multiple meetings, where they will have the chance to present their studies and obtain feedbacks. These include:

- Weekly lab meeting for everyone to present their research progress to the whole group.
- Monthly meeting of the RNA club (including more than 10 labs in UM with common interest in stress response) at the fourth Wednesday of each month.
- Annual academic conferences taking place in UM community. These may include the Zubrod Symposium, the Eastern-Atlantic Student Research Forum, and the Miami Winter Symposium.
- Annual academic conference by the choice of the scholar. We routinely attend the annual conference of ASBMB/EB, ASCB, and AACR. The scholar may also suggest something else that fits his/her interest and career goal. The cost will be paid by the lab.

Furthermore, to translate the fundamental discoveries in our group into multiple types of human diseases including cancer, spinal cord injury, and aging-related abnormalities, we have ongoing collaborations with a handful of other researchers in the UM community. These include Drs. Kerry Burnstein, Fulvia Verde, Antonio Barrientos, Flavia Fontenasi, Stephen Lee, Damien Pearce, Olesandr Kryvenko, Merce Jorda, Mark Gonzalgo, Damien Pearce, Theodore Lampidis, and Xi (Steven) Chen. These researchers are actively contributing their various expertise to our projects in stress response, cell morphology, cancer biology, metabolism, or bioinformatics. Depending on the nature of the assigned project, the DREAM scholar is expected to frequent interactions with some of these researchers. For this reason, a co-mentoring plan can also be arranged based on the needs and the career goal of the scholar.