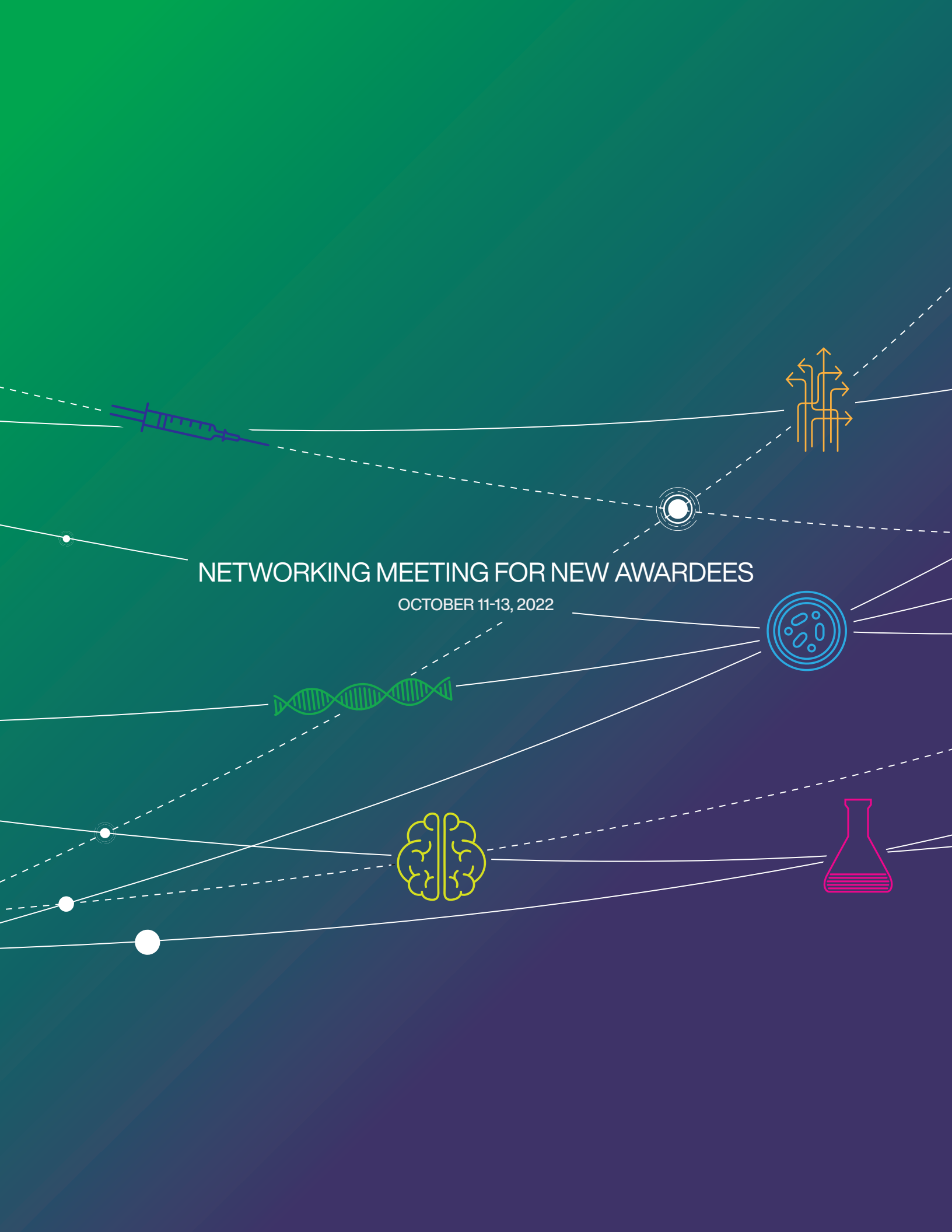
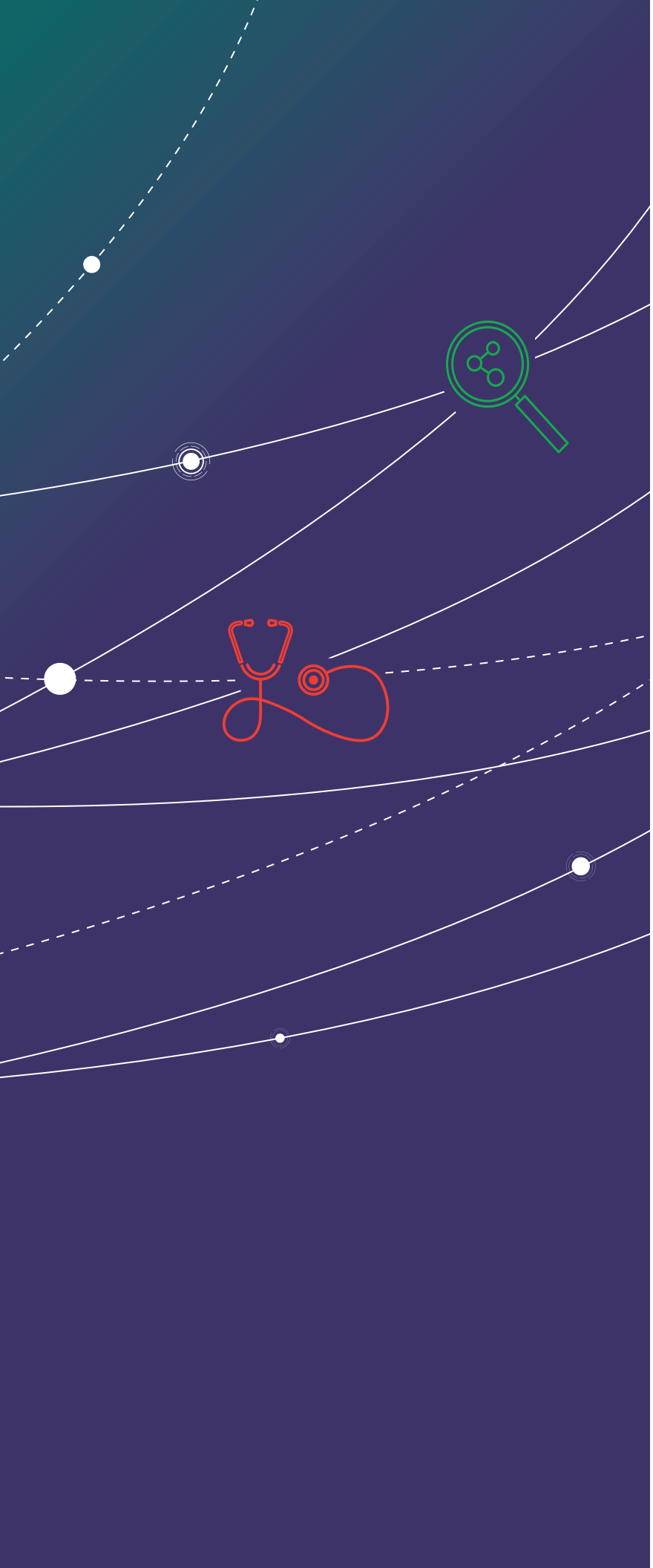
NETWORKING MEETING FOR NEW AWARDEES

BURROUGHS WELLCOME FUND



NETWORKING MEETING FOR NEW AWARDEES

OCTOBER 11-13, 2022



Contents

Tuesday Reception Site:
Burroughs Wellcome Fund
21 T. W. Alexander Dr.
Research Triangle Park, NC 27709
919-991-5100
www.bwfund.org

Meeting & Hotel Site:
Sheraton Chapel Hill
1 Europa Drive
Chapel Hill, NC 27515
www.Marriott.com/RDUSC

Participating Programs
Career Awards at the Scientific Interface (CASI)
Career Awards for Medical Sciences (CAMS)
Graduate Diversity Enrichment Group (GDEP)
Investigators in the Pathogenesis of Infectious Disease (PATH)
Next Gen Pregnancy Initiative (NGP)

Agenda

Monday, October 10, 2022

10:00 am – 5:00 pm **Registration** | Location: Hotel Lobby
Upon arrival at the hotel please check in at the BWF Registration Desk to pick up your meeting information packet. Your nametag, meeting agenda, poster session assignments, departure transportation schedule and reimbursement form will be in the packet. Please review all the material provided.

5:00 – 7:00 pm **Diversity Enrichment Networking Social** | Location: Founders Ballroom, 2nd Floor
PDEP AND GDEP Awardees and Mentors only

Tuesday, October 11, 2022

10:00 am – 5:00 pm **Registration** | Location: Hotel Lobby
Upon arrival at the hotel please check in at the BWF Registration Desk to pick up your meeting information packet. Your nametag, meeting agenda, poster session assignments, departure transportation schedule and reimbursement form will be in the packet. Please review all the material provided.

1:00 – 4:00 pm **Workshop: Cultural Identity and the Power of Authenticity**
Location: Carolina Room, Lobby Level | Facilitator – George Langford, PhD
PDEP AND GDEP Awardees and Mentors only

4:00 pm **Networking Meeting** | Location: Hotel entrance
(Transportation departs from hotel to BWF for all meeting attendees)

4:30 pm **Welcome and Introduction to the Burroughs Wellcome Fund**
Location: Burroughs Wellcome Fund – Multipurpose Room
Lou Muglia, MD, PhD (BWF President & CEO)

5:00 pm **Welcome Reception** | Location: Burroughs Wellcome Fund – Courtyard and Formal Loggia

7:00 pm **Transportation to hotel**

Wednesday, October 12, 2022 | Location: Sheraton Chapel Hill Hotel

10:00 am – 5:00 pm **BWF Registration/Information Desk** | Blue Hill Ballroom Foyer, Lobby Level

7:00 am **Breakfast** | Location: Founders Ballroom, 2nd Floor

7:00 – 8:30 am **Poster Set-Up** | Location: Blue Hill Ballroom C & D, Lobby Level

8:00 – 12:00 pm **PDEP Mentors Workshop (PDEP Mentors ONLY)** | Location: Carolina Room

8:30 am **Wake Up to the Beat – Communication and Mindfulness**
Location: Blue Hill Ballroom A & B, Lobby Level | Presenter: Bill Schiedt, Sewa Beats

9:30 am **BREAK**

10:00 am **New Awardee Introduction Blitz** | Location: Blue Hill Ballroom A & B, Lobby Level
CAMS, CASI, Next Gen, PATH and PDEP Awardees please sit in assigned seats in Blue Hill Ballroom for the Introduction Blitz. Seating in the front of the ballroom will have your name placed on a seat in alphabetical order for this session only.

12:00 pm **LUNCH** | Location: Founders Ballroom, 2nd Floor

1:00 pm **Poster Session #1** | Location: Blue Hill Ballroom C & D, Lobby Level

2:00 pm **Poster Session #2** | Location: Blue Hill Ballroom C & D, Lobby Level

Wednesday, October 12, 2022 Continued | Location: Sheraton Chapel Hill Hotel

3:00 pm	**BREAK**
3:15 pm	**Diversity Presentation** | Location: Blue Hill Ballroom A & B, Lobby Level Presenters: Sherilynn Black, PhD, George Langford, PhD, Alfred Mays
4:30 pm	**BREAK**
5:00 – 5:45 pm	**Reception** | Location: Founders Ballroom, 2nd Floor
5:45 – 7:15 pm	**Dinner** | Location: Founders Ballroom, 2nd Floor
7:30 – 10:00 pm	**After Dinner Hospitality Room** | Location: Carolina Room, Lobby Level

Thursday, October 13, 2022

8:00 am – 4:00 pm	**BWF Registration/Information Desk (luggage storage will be available)** Location: Blue Hill Ballroom Foyer, Lobby Level
8:00 am	**Breakfast** | Location: Founders Ballroom, 2nd Floor
9:00 am	**Revisit Posters** | Location: Blue Hill Ballroom C & D, Lobby Level
10:00 am	**Science Communication Workshop** | Location: Blue Hill Ballroom A & B, Lobby Level Presenters: Shahir Rizk, PhD, Maggie Fink
12:00 pm	**Lunch and Poster Breakdown** | Location: Founders Ballroom, 2nd Floor
1:30 pm	**Award Recipient Meetings with Program Staff** **CAMS/Next Gen | Location: Carolina Room, Lobby Level** Program Officer Paige Cooper, PhD Program Associate Kendra Tucker Program Assistant Daniel Baroff **CASI | Location: Blue Hill Ballroom D, Lobby Level** Program Officer Tammy Collins, PhD Sr. Program Associate Melanie Scott Program Assistant Daniel Baroff **PATH | Location: Boardroom, Lobby Level** Sr. Program Officer Victoria McGovern, PhD Program Associate Darcy Lewandowski Program Assistant Samantha Moore **PDEP/GDEP | Location: Blue Hill Ballroom A & B, Lobby Level** Sr. Program Officer Alfred Mays Sr. Program Associate Tiffanie Taylor Program Assistant Samantha Moore
2:45 pm	**Wrap Up Session with Individual Programs and Lou Muglia**
3:30 pm	**Adjournment and Transportation to Airport** *The transportation schedule will be included in your information packet that you will pick up at check in.*

SPEAKER BIOS

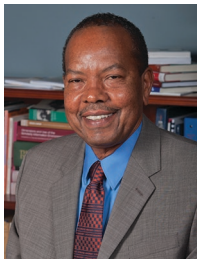
Sherilynn Black, PhD

ASSOCIATE VICE PROVOST FOR FACULTY ADVANCEMENT
DUKE UNIVERSITY

Sherilynn Black, PhD is the Associate Vice Provost for Faculty Advancement at Duke University. She creates strategic initiatives and implements practices that support faculty development and advancement in many areas, including mentoring, support for pre-tenure and mid-career faculty, and career pathways and professional development for non-tenure system faculty. She also leads initiatives to increase diversity among the faculty ranks and further develop an inclusive climate within academic units. Dr. Black is an Assistant Professor of the Practice of Medical Education. Her research focuses on understanding effective ways to optimize interactions between faculty and trainees in mentoring relationships, and also on developing institutional models to increase effectiveness of interventions designed to promote diversity in academia. Dr. Black previously served as the founding Director of the Office of Biomedical Graduate Diversity for the Duke University School of Medicine and provided intellectual and strategic leadership for all diversity initiatives for trainees and faculty in the basic science departments and programs. She was also a Principal Investigator of the Duke Initiative for Maximizing Student Development (IMSD) Program referred to as the Duke Biosciences Collaborative for Research Engagement (BioCoRE), which provided extensive mentoring and scientific engagement opportunities for diverse undergraduate/graduate students and faculty in the biomedical sciences. Dr. Black holds several national appointments relating to faculty development and advancement, including serving on advisory boards, developing strategic initiatives, and holding committee appointments with the National Institutes of Health, Howard Hughes Medical Institute, The Burroughs Wellcome Fund, the American Association of Medical Colleges, the National Academies of Sciences, Engineering and Medicine, the National Labs, and the Society for Neuroscience. She has won a number of distinctions for her work, including the Samuel Debois Cook Society award and the Deans Award for Inclusive Excellence in Graduate Education. Dr. Black earned her Bachelor of Science in Psychology and Biology with highest honors at the University of North Carolina at Chapel Hill and was a Morehead-Cain Scholar. She earned her PhD in Neurobiology at Duke University.

George Langford, PhD

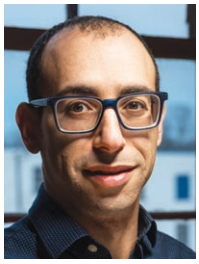
DEAN EMERITUS, COLLEGE OF ARTS AND SCIENCES
SYRACUSE UNIVERSITY



George M. Langford is Distinguished Professor of Neuroscience and Professor of Biology at Syracuse University and served as the dean of the College of Arts and Sciences from 2008-2014. His primary area of study is the actin cytoskeleton and the mechanisms of transport of organelles and vesicles in nerve cells. He served as dean of the College of Natural Sciences and Mathematics at the University of Massachusetts-Amherst, the inaugural Ernest Everett Just Professor of Natural Sciences at Dartmouth College and professor of Physiology, the School of Medicine at the University of North Carolina Chapel Hill. He was appointed in 1998 by President Clinton to a six-year term on the National Science Board, the governing board of the National Science foundation. He was awarded an honorary Doctor of Humane Letter by Beloit College in 2001 and elected a Fellow of the American Association for the Advancement of Science (AAAS) in 2013 and a Fellow of the American Society for Cell Biology (ASCB) in 2017. A longstanding advocate for supporting underrepresented minority students in the sciences, Professor Langford served as chair of the Minority Affairs Committee of ASCB and the first recipient of the ASCB EE Just Lectureship Award for his seminal work on the actin cytoskeleton and molecular motors. He recently served on the Science Education Advisory Board of the Howard Hughes Medical Institute and was former chair of the Board of Directors of the Burroughs Wellcome Fund. He is Program Director of the Syracuse University CHANcE Project funded by the HHMI Inclusive Excellence Initiative.

Shahir Rizk, PhD

ASSOCIATE PROFESSOR OF CHEMISTRY AND BIOCHEMISTRY
INDIANA UNIVERSITY SOUTH BEND



Shahir Rizk is an Egyptian-American biochemist, poet, and illustrator. He received a PhD in biochemistry from Duke University and worked as a faculty member at the University of Chicago and the University of Notre Dame. He is currently an associate professor of chemistry and biochemistry at his alma mater Indiana University South Bend. Shahir's research in the field of protein engineering has been published in several top international journals including the journals Nature, The Proceedings of the National Academy of Sciences, and Protein Science.

Shahir has received national awards for his research including the NIH Ruth Kirschstein National Research Service Award, and his research has been funded by the National Science Foundation. Shahir is a co-inventor on two United States Patent applications for work related to protein engineering and drug delivery. In 2019, Shahir received the prestigious Cottrell Scholars Award, recognizing only two dozen teacher-scholars annually from all US Higher Education Institutions. The award notes his outstanding research and his excellence as a science communicator. He has also received the Indiana University Trustees Teaching Award in 2018 and 2022. Shahir is the co-founder of Ultreia, Inc, a non-profit that promotes arts and art education in the Northern Indiana Region.

During his time as president of the board, he led the Ultreia:STEAM initiative, which hosted public events and workshops featuring speakers whose work overlaps art and science. He has also served on the Board of the South Bend Lyric Opera. For his community involvement, Shahir was selected as one of the Michiana Area forty under 40. Shahir's poetry has appeared in The Acorn, Modern Haiku, and Twyckenham Notes.

Maggie Fink

PHD CANDIDATE
UNIVERSITY OF NOTRE DAME

Maggie Fink, is a PhD candidate at the University of Notre Dame in the Department of Civil and Environmental Engineering and Earth sciences. Maggie is a 2021 NSF graduate research fellow and co-inventor with extensive experience in bacterial interactions in the environment. Both Shahir and Maggie have broad experience in science outreach within and outside their respective institutions. Both are illustrators and published poets and have combined their artwork and scientific experience to reach a wide range of audiences through public talks and workshops as well as social media blogs and online platforms.

Bill Scheidt

MANAGING PARTNER
SEWA BEATS

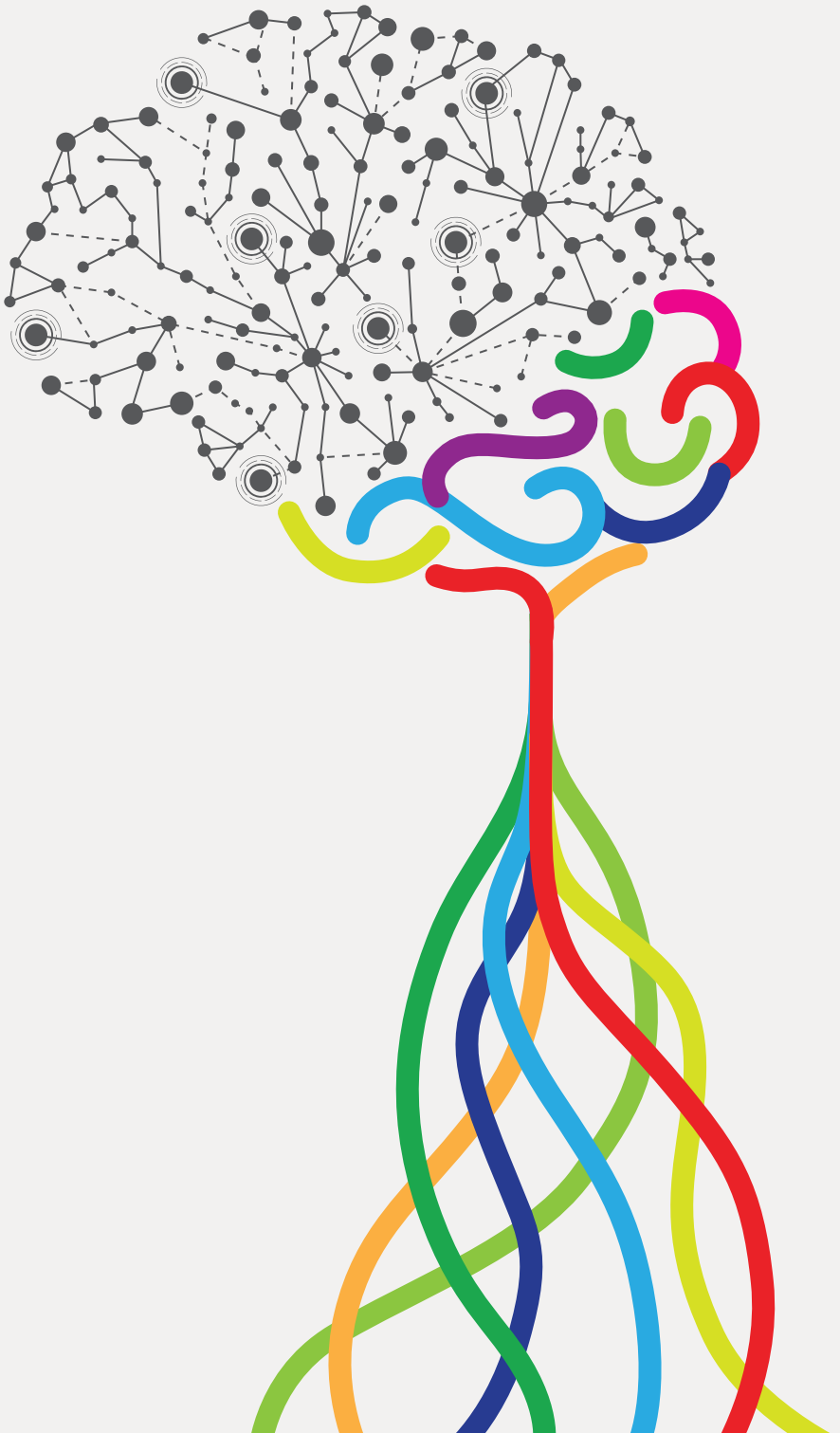
Before becoming the Managing Partner of Sewa Beats, Bill spent a total of one year and a half living, working, and studying music in Africa. His first trip to Africa was as the leader of an ecology research project he designed to study a population of giraffe in a national park. It was then that he first fell in love with Africa, its music, and its people.

Regularly returning to study music, Bill learned Swahili, volunteered to teach English in a rural school, and worked on local community outreach initiatives. He later went on to become an instructor at the world's first international academy of West African drumming, and a close personal student of legendary Master Drummer Mamady Keita.

With the help of Bill's directorship, Sewa Beats has delivered corporate programs in 19 countries, 7 languages, and reached more than 300,000 participants around the world. Sewa Beats' clients include organizations such as BMW, Pfizer, Wells Fargo, Hewlett Packard, and Capital One.

Today, Bill is based in North Carolina, taking advantage of living between the mountains and the ocean to pursue his love of outdoor sports. When he's not mountain biking or hiking, he can be found spending quiet time with family. For him, Sewa Beats is a way of paying forward the many gifts that have come out of his time in Africa and are an expression of his commitment to making a difference in the world.

ATTENDEE ABSTRACTS



Salvador Almagro-Moreno, PhD

UNIVERSITY OF CENTRAL FLORIDA
INVESTIGATOR IN THE PATHOGENESIS OF INFECTIOUS DISEASE

The Moreno Lab: Emergence and Evolution of Bacterial Pathogens

The Moreno Lab focuses on the emergence and evolution of bacterial pathogens. Our major research interests include elucidating the molecular strategies that bacterial pathogens develop for **host colonization, virulence regulation and dispersal from the host**. Furthermore, we are interested in the connection that ecosystems and manmade environmental perturbations (e.g. climate change, pollution) have in their pathogenic potential and transmission.

Our research program focuses on several **pathogenic members of the Vibrionaceae**, a family of aquatic bacteria, as model systems. Our investigations have an emphasis on the intestinal pathogen *Vibrio cholerae*, which represents a paradigm of infectious disease agents, and *Vibrio vulnificus*, a poorly understood emergent zoonotic pathogen source of a fulminant septicemia.

Our research approach strives to be holistic and multidisciplinary; what we call "From Bays to Bases." It encompasses a mix of **molecular biology, genomics, ecology and pathogenesis**. We believe that by understanding pathogen evolution and ecology, we will ultimately gain the knowledge that will allow us to forecast the traits of emergent virulent strains, predict the sources of outbreaks, and to design reliable therapeutic treatments against bacterial threats.

David Archer, PhD

EMORY UNIVERSITY
NEXT GEN PREGNANCY INITIATIVE

Sickle cell disease (SCD) is a group of inherited red blood cell disorders for which the most common variant, sickle cell anemia, is caused by homozygous inheritance of the hemoglobin S mutation on the beta-globin gene. This mutation results in the sickling of red blood cells due to hemoglobin polymerization under conditions of low oxygen saturation and acidosis. Common complications in SCD include both acute and chronic occurrences of hemolytic anemia, organ damage, endothelial dysfunction, reduced vascular perfusion, and vaso-occlusive crises. These drawbacks delay childhood development and sexual maturity and tend to become exacerbated during pregnancy.

Pregnancy in SCD is associated with increased risk of complications including preterm delivery, deep vein thrombosis, intrauterine growth restriction, preeclampsia, and intrauterine death. Additionally, individuals with SCD have higher cesarean and maternal death rates. The mechanistic drivers of poor pregnancy outcomes specific to SCD are not well defined; however, similar hypertensive complications in non-SCD pregnancy are often attributed to dysregulation of angiogenic growth factors, endothelial dysfunction, and impaired vaso-regulation ultimately leading to renal dysfunction. Further, placental ischemia and oxidative stress are attributed to reduced trophoblast invasion and impaired uterine spiral artery remodeling.

We believe the underlying drivers of these complications during pregnancy to be heavily exacerbated in SCD, a disease hallmarked by an internal milieu of ischemia, inflammation, and baseline vasculopathy. The objectives of this study are to determine the role of inflammation in poor pregnancy outcomes in a sickle cell mouse model that recapitulates issues seen in humans. We will use targeted knockout mice to determine outcomes and to investigate transcriptional programs as potential mechanisms of action and therapeutic targets which may improve pregnancy outcomes in SCD.

Hector Arciniega, PhD

HARVARD MEDICAL SCHOOL
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

The central aim of my research is to understand better the cognitive and neural consequences of repetitive head impacts in former American football players. This work is important as repetitive head impacts have been linked to the development of chronic traumatic encephalopathy (CTE), which is a neurodegenerative disease characterized by the widespread accumulation of hyperphosphorylated tau (p-tau) and specific regional brain atrophy. The main predictor of CTE is exposure to repetitive head impacts, as commonly seen in American football players and other collision sports (e.g., boxing, soccer, hockey). Importantly, there is no current *in vivo* diagnosis of CTE. Thus, studying groups at higher risk of developing this disease can help us characterize possible biomarkers for the diagnosis of CTE and understand better the consequences of repetitive head impacts. A promising approach for diagnosing CTE *in vivo* is to compare known neuropathological changes at post-mortem to *in vivo* neuroanatomical structures, as seen on structural magnetic resonance imaging (MRI). In my current research, I use data from the NIH/NINDS funded Diagnostic, Imaging, And Network for the Objective Study and Evaluation of CTE (DIAGNOSE-CTE) Research Project to evaluate neuropsychological assessments, neuropsychiatric measures, structural magnetic MRI, diffusion MRI, and resting state functional MRI to understand better the long-term consequences of repetitive head impacts and to attempt to identify possible neuroimaging biomarker(s) of CTE.

Sima Asadi, PhD

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAREER AWARD AT THE SCIENTIFIC INTERFACE

Pathogen-laden Respiratory Droplet Formation via Mucosalivary Fluid Fragmentation

Sima Asadi, PhD, Patrick S. Doyle

The alarming frequency of epidemics and pandemics of infectious diseases in the past two decades urges a comprehensive research on the airborne route of transmission. Pathogen-laden respiratory droplets (PRDs) generated during respiratory activities are believed to be the main vehicles by which the pathogens are spread through the air. However, the underlying physics of PRD formation and the relative contribution of each respiratory activity to this process remain poorly understood. My recent work showed voice loudness and pitch intensify PRD emission in a coupled manner. I also found a small fraction of individuals behaves as “superemitters” by consistently releasing up to an order of magnitude more PRDs than others during speaking and coughing. Understanding the physiological factors that contribute to the heterogeneity of these individuals in PRD emission will help elucidate the existence of “superspreaders” who play a significant role in the explosive growth of the number of cases during the outbreaks.

In the first part of this project, I will investigate the physics of PRD formation throughout the human respiratory tract. I am currently designing experimental devices that simulate PRD formation in trachea, larynx, and bronchiolar airways as a result of Kelvin-Helmholtz instabilities in the mucus-air interface and also mucosalivary fluid film burst. I will use these devices to investigate: i) how airflow dynamics, vocal folds vibration, and the interaction between speech organs affect the size distribution of PRDs and ii) how PRD formation depends on the mucosalivary fluid rheology which is mainly determined by its mucin composition and the viral/bacterial infection. In the second part of the project, I will perform PRD emission measurements with human subjects to first, decouple the effect of vocalization loudness and pitch on PRD emission, and second, find a correlation between the PRD emission rate and rheological properties of the subjects’ mucosalivary fluid samples. The results of this research are expected to elucidate the relative contribution of different respiratory activities to disease transmission, and explain the existence of superspreaders in terms of their mucosalivary fluid rheology and PRD emission ability.

Danielle Atibalentja, MD, PhD

STANFORD UNIVERSITY
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

Mechanisms of Regulation of B-cell immune responses by Oncogenic MYC

Danielle F Atibalentja[1], Stephanie C Casey[2], Dean W Felsher[1]

1 Division of Oncology, Department of Medicine, Stanford Medicine, Stanford CA, USA.
2 Amgen, South San Francisco, CA, USA.

The MYC oncogene is an important driver of tumor development in many human cancers including some hematological malignancies. Despite its important role in cancer, the development of MYC targeting drugs has proved challenging due to its complex biology and there are currently no FDA approved drugs directly targeting oncogenic MYC.

In lymphoma mice (huMYC T-ALL) where the human MYC gene is expressed under the control of a tetracycline-regulated promoter, MYC inactivation leads to apoptosis and rapid tumor regression. Moreover, our group has previously shown that oncogenic MYC actively suppresses the immune system. MYC Inactivation in huMYC T-ALL mice restored type I IFN (IFN) secretion and maturation of natural killer (NK) cells and led to CD4+T-cell activation. CD4+ T-cells in particular were shown to be critical in the establishment of long-term tumor control. Together, these data pointed to a key role of MYC as a regulator of immune responses during tumorigenesis. Understanding how oncogenic MYC promotes cancer immune evasion is of great interest and an essential step to restoring normal immune function through MYC targeting.

Our work to date has focused on understanding how oncogenic MYC alters B-cell function during lymphomagenesis. This interest stems from preliminary data indicating that MYC inactivation in huMYC- T-ALL mice results in increased serum IgG antibody levels. These antibodies bound to tumor cells *in vitro* and mediated antibody-dependent cellular cytotoxicity. Immunodeficient mice adoptively transferred with tumor-experienced B-cells from mice that successfully cleared tumor after MYC inactivation, exhibited delayed kinetics of tumor recurrence and reduced tumor growth compared to mice that received naïve B-cells or no immune cells. Interestingly, there was no increase in B-cell tumor infiltration in mice transplanted with a huMYC T-ALL-derived cell line before and after MYC inactivation. However, we noted significant disorganization of the splenic architecture in tumor-bearing mice that was reversed following MYC inactivation. These data are strongly suggestive that tumor MYC suppresses normal B-cell responses and inactivation of MYC likely restores normal B-cell function. The underlying mechanism behind these observations remains to be determined.

In light of preliminary evidence that MYC inactivation likely induces immunogenic cell death, and, published data showing that 1) MYC suppresses transcription of genes that lead to tumor type I IFN secretion, 2) STING (stimulator of IFN genes) may regulate some types of antibody responses, we **hypothesized** that tumor-derived DNA released from lymphoma cells during MYC inactivation activates the STING-cGAS-Type I IFN axis leading to restored B-cell activation and antibody production. My project goals are thus to: 1) determine whether MYC inactivation induces immunogenic cell death in mice leading to B-cell activation and antibody production (AIM1), 2) examine the immunophenotypic changes of B-cells following MYC inactivation, and 3) investigate whether MYC inactivation induces cGAS-STING and the consequent effects on B-cell activation and antibody responses (AIM 3).

Results from this study will have important implications for how MYC and other cancer causing genes suppress the immune system and may identify new therapeutic targets to restore immune responses against cancer.

Heather Beasley, PhD, MS

VANDERBILT UNIVERSITY
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

TMEM135 is a Novel Regulator of Age-associated Heart Decline

Heather K. Beasley, Antentor Hinton Jr.

The aging process is well defined as a time-dependent accumulation of cellular damage. It has been demonstrated that mitochondrial dysfunction is strongly associated with the aging process; however, the molecular mechanisms that underlie the pathogenesis of age-dependent diseases are still poorly understood. Moreover, mitochondrial proteins are heavily involved in the aging process leading us to investigate novel proteins in this space. Transmembrane protein 135 (TMEM135) is an understudied protein thought to regulate the mitochondrial dynamics affecting fusion and fission. TMEM135 also plays a role in regulating lipid droplet formation and tethering. Moreover, TMEM135 was identified as a novel factor upregulated in cardiac dysfunction that is associated with VLCAD (very long-chain acyl-CoA dehydrogenase) deficiency. TMEM135 is highly expressed in mitochondria and fat-loaded tissues, and interestingly, cardiac function significantly declines due to lipotoxicities. Therefore, we were interested in understanding if TMEM135 may have a role in heart-related phenotypes and cardiac decline often associated with aging. Lipid/lipoprotein abnormalities, collectively termed as dyslipidemia, are prevalent in cardiac abnormalities. We, therefore, hypothesized that overexpression of TMEM135 may lead to pathological ventricular remodeling and may provide insights into mitochondrial remodeling in the heart. To evaluate this hypothesis, we examined the structural changes in mitochondria of human hearts from heart failure patients using Serial Block Facing Scanning Electron Microscopy and 3D Reconstruction using Amira software. We also used Echocardiogram and Immunohistochemistry staining of TMEM135 in human heart failure patients compared to control. We found that TMEM135 expression is higher in patients with end-stage failing hearts in comparison to the control hearts. Moreover, there are significant structural changes in the mitochondria, which were quantified by measuring the volume, area, and perimeter of the mitochondria. Furthermore, we observed changes in the frequency of nanotunnels, a proposed compensatory mechanism during stress conditions. We sought to investigate if the effects we observe correlate to cardiac-related phenotypes in individuals of both European and African ancestry utilizing BioVU, the Vanderbilt University Medical Center (VUMC) biorepository linked to de-identified electronic health records (EHRs). We applied a statistical framework to calculate predicted gene expression for TMEM135 in 72,353 individuals of European descent and 17,868 individuals of African ancestry in BioVU. We find that TMEM135 is significantly associated with osteochondropathies in patients of European descent (P=1018E-05, OR=7.074) and Myocardial infarction (P=0.001, OR=4.092) in patients of African ancestry. Both heart failure and rare osteochondropathies are prevalent in the aging population, providing evidence that TMEM135 may be a viable biomarker in heart failure (HF).

Maigen Bethea, PhD

UNIVERSITY OF COLORADO
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

Assessing the Role of Gastrointestinal Distention in the Metabolic Success of Vertical Sleeve Gastrectomy

Maigen M. Bethea[1], Marwa Mommandi[1], Danielle Leander[1], Silvania da Silva Texeira[1], Michelle Mangette[1], Jasmine Hendrix[1], and Darleen A. Sandoval[1]

1 Department of Pediatrics, Nutrition Section, University of Colorado Anschutz Medical Campus, Aurora, CO USA

Bariatric surgeries that alter gut anatomy, like vertical sleeve gastrectomy (VSG) are currently the most effective, but most drastic, treatments for obesity, yet the mechanism(s) by which bariatric surgery modulates these metabolic processes is largely unknown. The resulting sustained weight loss has been associated with changes in feeding behavior. We have evidence that the ability of VSG to reduce weight and alter feeding patterns is in part due to alterations in the signals in the gut-brain-axis. Specifically, we demonstrate that the nucleus of the solitary tract (NTS), a brain region critical for integrating peripheral signals, is more highly activated by a meal after VSG. Additional studies from our lab demonstrated accelerated gastric emptying rate in rat and mouse models of VSG, likely due to increased gastric pressure, thus exaggerated intestinal distention. Furthermore, emerging data demonstrates that intestinal distention has a critical role in the regulation of feeding. Therefore, we hypothesized that intestinal stretch is critical for VSG-induced reductions in food intake. Using non-nutritive substances such as methylcellulose and mannitol to differentiate stomach versus intestinal stretch respectively, we demonstrate that high fat diet feeding ablates intestinal stretch induced reductions in food intake while weight loss via dietary intervention, restores this response. More importantly, VSG robustly restores intestinal stretch induced food intake reduction. Taken together, our data reveal for the first time that intestinal distention is critical for VSG-induced reductions in food intake.

Lawrence Brown, MD, MPH, MHS

JOHNS HOPKINS UNIVERSITY
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

Among the 12,000 deceased organ donors yearly in the US, there are racial disparities that have persisted over decades, with the Black population most recently donating at 69% of the White population. Relatively lower organ donation rates among racial minorities not only contribute to the organ shortage but also contribute to racial disparities in waitlisted candidate's access to transplantation, with some racial minorities having longer wait times owing to difficult matching.

Historically, efforts to address racial disparities in deceased organ donation have examined inpatient medical facility deaths, using inpatient death counts to estimate the potential organ donor pool, to benchmark successful organ recovery, and to target interventions. While only individuals who die in an inpatient medical facility can have their organs recovered for transplantation, the focus on this highly selected population is limiting. Structural racism, a determinant of racial disparities in health, affects healthcare resource availability, with Black individuals being 40% less likely than White individuals to have a usual source of healthcare in racially segregated neighborhoods. To date, healthcare resource availability has not been examined as a potential mediator of racial and geographic disparities in deceased organ donation.

To better understand the impact of structural racism on deceased donor rates, we will perform novel linkages with three nationally representative datasets (Scientific Registry of Transplant Recipients, CDC WONDER, and National Health and Nutrition Examination Survey) to study the following aims: (1) To examine county-level risk factors for inpatient and outpatient death under medical conditions consistent with organ donation; (2) To examine the relationship between structural racism and the potential organ donor rate; and (3) To examine whether healthcare access mediates the relationship between structural racism and the potential organ donor rate.

We hypothesize that structural racism affects inpatient facility death distribution, and subsequent organ donation rates, through its differential effects on healthcare access according to race and across geographies. If the proposed aims are achieved, we will directly inform national healthcare access and organ allocation policy, and population-level structural interventions to eliminate racial disparities in transplantation.

Diego Calderon, PhD

UNIVERSITY OF WASHINGTON
CAREER AWARD AT THE SCIENTIFIC INTERFACE

Application of multiplex reporter assays towards understanding trans-acting gene regulation

Diego Calderon, Chase C. Suiter, Tony Li, Cole Trapnell, Jay Shendure

Genome-wide association studies (GWAS) have demonstrated that the dysregulation of gene expression has a significant impact on one's risk of developing disease, which emphasizes the critical importance of elucidating gene-regulatory relationships that underlie complex traits. Gene regulation can be partitioned into contributions attributable to proximal or cis-acting elements (e.g., enhancers) and trans-acting factors (e.g., transcription factors). Genomic assays and analysis techniques have revolutionized how we understand the cis-acting component of gene regulation. However, because of the sheer number of interaction tests, the lack of efficient perturbation methods to establish causality, and the complexity of the various gene regulatory processes, *high-throughput methods have largely ignored contributions from trans-acting factors. As a result, there remain many disease-critical questions related to the effects of trans-acting factors for which the current toolbox of genomic assays are unable to address.* What are the upstream gene pathways involved in activating disease-associated enhancers? How do cells control which cancer-associated proteins remain stable while others are quickly degraded? Which splice factors determine differential inclusion of disease-relevant exons? To establish a framework for addressing these and related questions, **the overarching goal of this proposal is to pioneer the application of a new class of multiplex reporter assays that I recently developed towards understanding trans-acting contributions to gene regulation.**

At the beginning of my postdoctoral fellowship with Jay Shendure and Cole Trapnell, I developed a new method for testing protein-enhancer regulatory interactions called *trans*MPRA (*trans* Massively Parallel Reporter Assay) that combines the power of massively parallel reporter assays (MPRAs) with perturbations of CRISPR screens. In brief, transMPRA identifies causal *trans*-acting regulatory interactions by testing whether a specific gene perturbation induces differential enhancer-based reporter activity. I will optimize and scale my newly developed assay towards achieving its full potential of genome-wide screens and refine the computational tools for processing *trans*MPRA data to increase the power of current and future studies. In parallel, I am working towards generalizing my newly established experimental design to uncover *trans*-acting contributions to other disease-relevant regulatory processes. Specifically, I will characterize gene regulators of protein degradation and differential exon splicing.

Overall, this proposal will establish massively parallel reporter assays paired with gene perturbations as a generalizable platform for elucidating the *trans*-acting contribution to gene regulation. The anticipated results will have a broad impact on our understanding of the *trans*-acting regulatory determinants of gene expression, protein degradation and splicing.

Jasmin Camacho, PhD

STOWERS INSTITUTE FOR MEDICAL RESEARCH
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

The insatiable sweet tooth: adaptations to increased sugar consumption in mammals

Derived features that have evolved multiple times in related organisms in similar environments is known as parallel evolution and provides insight into how traits become adapted by natural selection. Nectarivory, a diet of simple sugars in liquid form, is a parallel trait in two groups of neotropical leaf-nosed bats (Phyllostomidae). The frequent and excess consumption of simple sugars is a rare trait, as most mammals on high sugar diets suffer long-term damage to organs. Despite consuming excessive quantities, often 1.5x their body weight in nectar each night, bats avoid glucotoxicity and enhance DNA repair. Therefore, how sugar is metabolized is important for understanding the development of their adaptive physiology. To investigate the metabolic changes driving adaptations to sugar consumption, wild nectar bats were caught and fed a stable-isotope glucose solution. Following sugar exposure, their metabolites were measured by nonlethal blood sampling. After feeding on glucose, nectar bats experienced high postprandial blood sugar levels, more than any other mammal previously studied. The high levels were not rapidly cleared from the blood, raising the question as to how they avoid glucotoxicity. To understand the molecular basis underlying elevated blood glucose level, we compared the genome between three independent trait gains of nectar feeding in bats and their relatives. We found parallel and divergent amino acid substitutions in gene sets functionally enriched for DNA damage response, immunity, and aging. While the genomic changes have yet to be functionally validated, molecular changes correlate to highly conserved coding regions among vertebrates, which in turn suggest functional changes needed to thrive on an extreme sugar diet.

Kate Cavanaugh, PhD

UNIVERSITY OF CALIFORNIA-SAN FRANCISCO
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

Probing the role of mechanotransduction in embryo dysfunction of aged mothers

Kate Cavanaugh[1], Sneha Rao[1], Bill Bement[2], Diana Laird[1], Orion Weiner[1]

1 University of California, San Francisco
2 University of Wisconsin, Madison

Infertility represents a significant societal burden, as nearly 60% of human pregnancies fail before the embryo implants into the uterus. Implantation failure is further exacerbated as mothers reach ages above 35 years. Since global trends indicate an increasing average maternal age of childbirth, the reproductive effects of maternal aging on embryogenesis pose a pressing and impactful scientific question. Embryos of advanced maternal age display poor developmental health with decreased placental structures owing to impaired implantation. However, there is little characterization of the developmental events culminating in embryo implantation failure in aged mothers. Implantation efficacy is determined much earlier in development with the formation of the placental precursor tissue, the Trophectoderm lineage. Driving this lineage fate commitment is the formation of the Apical Domain, a protein-rich structure emerging at the 8-cell stage that is both necessary and sufficient to transcriptionally differentiate and spatially segregate Trophectoderm fates. Mechanical forces are a key integrator of these domain-induced fate decisions, as they activate the force-sensitive transcription factor, YAP, to guide specification of placenta. In mice and humans, embryos from aged mothers show defects in placental structures, reduced trophectoderm cell counts, and abnormal YAP subcellular localization. These age-related defects are consistent with misregulation of domain-mediated YAP dynamics early at the 8-cell stage, yet this mechanism has not been explored. I will therefore probe the role of maternal aging on embryogenesis by examining upstream mechanical inputs driving force-sensitive YAP activity. My central hypothesis is that, in embryos of aged mothers, the loss of mechanical forces hinders domain-mediated YAP signaling for defective placental lineage commitment (Aim 1). I will then attempt to restore YAP dynamics to rejuvenate embryos from aged mothers using precision optogenetic tools (Aim 2). This proposal will therefore address the cell biological mechanisms underlying proper lineage determination and age-related changes thereof, building experimental frameworks enabling me to achieve my long-term goal of studying the generation of embryonic form.

Alice Cheng, MD, PhD

STANFORD UNIVERSITY
CAREER AWARD FOR MEDICAL SCIENTISTS

Engineering a complex synthetic microbiota for modulation of host bile acids

Alice G Cheng[1], Marissa Jasper[2], Alejandra Dimas[2], Advait Patil[2], Michael Fischbach[2]

1 Department of Gastroenterology and Hepatology, Stanford School of Medicine,
2 Department of Bioengineering, Stanford University

We constructed and optimized a defined consortia of 119 human gut bacterial strains (hCom2) that largely recapitulates the phylogenetic diversity, ecologic stability, metabolic and immune function of native human microbiota (1). We then engineer hCom2 to rationally modulate circulating levels of secondary bile acids in the murine host. Specifically, we find that hCom2 containing Bacteroides with engineered 7a and 7b HSDH genes successfully converts host primary bile acids into target secondary bile acids ursodeoxycholic acid and ursocholic acid *in vitro* and *in vivo*. This engineered community may have implications for study and treatment of diseases impacted by circulating bile acids such gallstone disease and Nonalcoholic steatohepatitis, both widely prevalent and costly conditions (2, 3). Furthermore, our work demonstrates that hCom2 is a valid model microbiota that can be used for mechanistic interrogation of microbiome-associated disease.

1. A. G. Cheng *et al.*, Design, construction, and *in vivo* augmentation of a complex gut microbiome. *Cell*, S0092-8674(0022)00990-00994 (2022).
2. Q. Wang *et al.*, Alteration of gut microbiota in association with cholesterol gallstone formation in mice. *BMC Gastroenterol* **17**, 74 (2017).
3. J. P. Arab, S. J. Karpen, P. A. Dawson, M. Arrese, M. Trauner, Bile acids and nonalcoholic fatty liver disease: Molecular insights and therapeutic perspectives. *Hepatology* **65**, 350-362 (2017).

Rose Creed, PhD

UNIVERSITY OF CALIFORNIA-SAN FRANCISCO
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

Assessing eye movement and basal ganglia activity in a mouse model of progressive supranuclear palsy

Rose B. Creed, Alexandra Nelson

Progressive Supranuclear Palsy (PSP) is a neurodegenerative disease that affects movement, behavior, and cognition. Due to an overlap in symptoms with Parkinson's disease, PSP is considered an atypical parkinsonian disorder, but PSP patients have distinct clinical and pathological features. Clinically, PSP patients have early gait abnormalities, frequent falls, gaze palsy (slowed saccadic eye movements), and tend not to respond to dopamine replacement therapy. Pathologically, aggregated Tau protein (rather than alpha synuclein) accumulates in the brain of PSP patients. As in other neurodegenerative disorders, a combination of cellular dysfunction and cell loss is believed to drive disease symptoms. However, a lack of animal models for PSP has hindered investigation of the causal links between neuropathology, cellular and circuit dysfunction, and symptoms. Here we have utilized the Thy1-hTau.P301S mouse model of tauopathy to determine whether Tau pathology (1) is sufficient to recapitulate key PSP phenotypes in mice and (2) results in aberrant neural activity in motor control nuclei. We find Tau transgenic mice have impaired motor performance in both the open field and accelerating rotarod test. We also find that Tau transgenic mice have tau pathology in several basal ganglia nuclei. The basal ganglia are a group of subcortical nuclei involved in motor and cognitive control, which were recently identified as an initial site of Tau pathology in PSP patients. Lastly, we use head-fixed and freely moving measurements of eye movements to detect whether tau transgenic mice have decreased evoked and spontaneous saccade velocity. Overall these findings highlight the utility of tau transgenic mice to modelling PSP and will provide a platform to investigate the changes in neural structure and function that drive the movement abnormalities seen in disease.

Theodore Drivas, MD, PhD

UNIVERSITY OF PENNSYLVANIA
CAREER AWARD FOR MEDICAL SCIENTISTS

Diabetes, obesity, kidney failure, hepatic fibrosis – each of these diseases remains a major public health burden despite billions of dollars spent on their treatment and research every year. For patients with rare genetic disorders of the primary cilium, termed ciliopathies, the dysfunction of this single organelle can produce all of these diseases in a single person. By studying the primary cilium, can we discover new pathogenic mechanisms and identify novel therapeutic targets for common diseases of huge public health burden?

The primary cilium is a non-motile projection of the cell surface that acts as an antenna for the reception of extracellular signals. Numerous signaling pathways, including insulin, TGFbeta, and PDGF, require ciliary localization of their receptors for appropriate downstream signaling. The pathologies seen in the ciliopathies can be attributed to deficits in these, and other, signaling pathways; however, despite a recent revolution in our understanding of the cilium's role in syndromic disease, and the many links between ciliary signaling and common disease pathways, we do not know what role the cilium might play in common disease pathogenesis.

My preliminary data indicate that common variants in ciliary genes have significant effects on common complex disease phenotypes in the general population, and show that individuals with chronic diseases develop secondary perturbations in ciliary gene expression. To further explore this novel area of investigation, I propose to: (i) identify common and rare genetic variants in ciliary genes that increase risk for common complex disease in the general population using bioinformatic and genomic approaches in large patient biobanks; (ii) differentiate the ciliary genes required for signaling though the TGFbeta, PDGF, and insulin signaling pathways in cell models using molecular signaling assays and RNAseq; and (iii) compare the impact of different chronic disease states on ciliary gene expression and cilium structure in different tissues in mouse models of chronic diseases using confocal microscopy and RNAseq. The completion of the proposed work will immediately generate a number of testable, conceptually novel hypotheses that will advance our knowledge of cilium biology, establish a platform to evaluate the roles of ciliary genes in numerous other signaling pathways, and identify novel therapeutic targets for diseases of immense public health burden.

Aileen Fernandez, PhD

YALE UNIVERSITY
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

Immune checkpoint inhibitors (ICI) are a class of immunotherapy that enhance a patient's anti-cancer immune response, but only a small percentage of patients who are treated respond. This means patients who do not respond undergo costly and side effect-inducing treatment for no benefit indicating a need for improved selection criteria. Current predictive biomarkers include immunohistochemical detection of PD-L1 but are insufficient for determining who will respond or, more importantly in the adjuvant setting, who will not respond.

Black Americans (BA) have an increased incidence rate of non-small cell lung cancer (NSCLC), a cancer type that responds to ICI treatment, and decreased overall survival compared to White Americans (WA). This disparity is also seen in response to ICIs and is partly due to social determinants of health and a decreased likelihood of undergoing surgery when access to healthcare is equal. However, studies show that there are also key biological differences between the transcriptomes and tumor microenvironment (TME) of BA and WA patients.

Spatial information refers to the architecture of tissues and how proteins relate to one another and the TME. Our previous work showed that PD-L1 protein expression in macrophages, but not in tumor cells, was higher in NSCLC tissues with associated longer overall survival (OS) after ICI therapy. In a separate NSCLC, ICI-treated, cohort, we analyzed the tumor-specific regions of the tissue using a closed-system RT-qPCR and showed that target immune gene mRNA (CD274 (PD-L1) and PDCD1LG2 (PD-L2)) were associated with both improved long-term benefit at 24 months and overall survival. Importantly, patients with low PD-L1 were **unlikely to benefit** (92% negative predictive value).

Taken together there are several questions I propose to address for this three-year project: (1) can spatial information be harnessed to create an improved gene signature that determines which patients should not receive ICIs? (2) Is the tumor or the surrounding TME driving the response to ICIs? (3) Can we further identify specific differences in immune profiles that may account for racial disparities, and differences by ancestry, in NSCLC response? I propose to assess patients with NSCLC treated with ICIs and stratify them as responders, resistors and responders who later recur. I will harness spatial information to (1) determine mRNA and molecular pathway differences based on response and (2) analyze the TME of patients. I hypothesize that patients with improved response to ICIs will have a more robust immune infiltrate. Furthermore, I will stratify cases based on race and ethnicity, as well as ancestry, to determine response and further identify genomic differences. I hypothesize that BA who do not respond to ICIs will have an increased pro-tumorigenic TME.

Ultimately, the goal is for this work to undergo pilot validation of the resistance signature using a closed-system RT-qPCR assay. The use of this assay which is simple and operator-independent could impact patients around the world. This assay will be essential for improving the quality of life for patients by avoiding costly treatments that their tumors have a high probability of not responding to.

William Freed-Pastor, MD, PhD

HARVARD MEDICAL SCHOOL

CAREER AWARD FOR MEDICAL SCIENTISTS

Pancreatic adenocarcinoma (PDAC) carries a dismal prognosis and remains a critical unmet public health need. The recent recognition that a subset of pancreas cancer harbors potential neoantigens has intensified interest in defining the molecular and cellular mechanisms of immune evasion in PDAC to guide effective therapeutic strategies that leverage the adaptive immune system in this disease. Defective localization (exclusion) of tumor-reactive T cells is a well-recognized phenomenon in pancreatic cancer. We hypothesize that in order to overcome the profoundly immunosuppressive tumor microenvironment in PDAC, effective-immune based strategies will need to simultaneously boost an anti-tumor immune response, prevent T cell exhaustion, and overcome T cell exclusion. Our studies to date support this hypothesis. Using neoantigen-expressing preclinical models of PDAC to evaluate tumor-specific immune responses, we recently demonstrated that neoantigen-specific $CD8^+$ tumor-infiltrating lymphocytes (TILs) adopt multiple states of dysfunction. This work identified a particular reliance on the CD155/TIGIT axis in the promotion and maintenance of immune evasion in pancreatic cancer and uncovered a novel combination immunotherapy (TIGIT/PD-1 co-blockade plus CD40 agonism) that elicits profound anti-tumor responses in preclinical models (**Freed-Pastor et al. Cancer Cell, 2021**). These insights led directly to clinical evaluation of this combination immunotherapy as part of an upcoming multicenter Phase Ib/II clinical trial (**co-PI: Freed-Pastor/Cleary**). In this CAMS proposal, we will leverage sophisticated preclinical models, advances in spatial transcriptomic profiling, and *in vivo* CRISPR-based gene modulation to uncover and functionally interrogate mechanisms of T cell exclusion and immune escape in PDAC. These insights will be directly evaluated for their ability to augment emerging immunotherapies. Collectively, these studies hold tremendous promise for accelerating effective immune-based therapies for PDAC.

Diego Gelsinger, PhD

COLUMBIA UNIVERSITY
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

Versatile technology for universal engineering of microbial isolates and communities

Diego Rivera Gelsinger, Carlotta Ronda, Harris Wang, Samuel Sternberg

The advent of deep sequencing has shed light on the vast microbial diversity in nature, dramatically changing our understanding of the crucial role that microbial communities play in ecological settings and human physiology. Despite advances in culturomics, in nature, microbes live in open, dynamic, and complex habitats that are difficult to recapitulate in a laboratory setting. Knowledge of microbial gene functions comes from manipulating the DNA of isolated species from their natural communities, yet less than 1% of microbes are culturable and even fewer are genetically tractable. To better understand the intricate network among these microbes and how these communities affect their surrounding environment, it is necessary to be able to genetically manipulate them in their natural setting. Canonical CRISPR-Cas systems, such as Cas9, have revolutionized our ability to genetically engineer genomes but these methods perform poorly for large DNA insertions. Importantly, no tools exist to genetically manipulate bacterial within complex microbial communities *in vivo*, while maintaining individual strain- and gene-level precision. My central vision is to genetically manipulate microbial communities *in vivo* to dissect the interplay between the mammalian gut microbiome and its host environment. To address these critical limitations, I propose a novel framework that will enable *in vivo* precision microbiome engineering by leveraging recent advances in targeted DNA integration using CRISPR-associated transposons (CASTs), combined with highly mobile vectors that effectively shuttle payloads between diverse microbes. To this end, I have optimized delivery and activity of CRISPR-transposons in non-model isolates to develop a suite of highly mobile and hyperactive gene editing systems (**Aim 1**); developed CAST systems into a technology for in situ editing of moderately complex gut consortia (**Aim 2**); and future work will apply this technology to stably introduce novel genetic functions with high temporal persistence *in vivo* in the gut microbiome of mice (**Aim 3**). By demonstrating the broad-host-range capabilities of this approach, I will advance a universal tool for genetic manipulations of microbiomes across diverse ecological environments.

Alexander Gitlin, MD, PhD

MEMORIAL SLOAN KETTERING CANCER CENTER
CAREER AWARD FOR MEDICAL SCIENTISTS

Rare monogenic immune disorders have illuminated key aspects of inflammation, but many of the underlying mechanisms remain poorly understood. For example, autoimmune lymphoproliferative syndrome (ALPS), a disorder in which T cells fail to undergo apoptosis, is most often caused by genetic defects in the death receptor FAS or its ligand FASL. However, mutations in caspase-8 or its adaptor FADD – which mediate cell death downstream of FAS – cause a combination of ALPS plus severe immunodeficiency. Since immunodeficiency is not generally observed in patients with FAS or FASL mutations, I hypothesized that FADD-caspase-8 must have an apoptosis-independent function downstream of an immune receptor other than FAS. Indeed, I recently discovered that activation of multiple immune receptors elicits the caspase-8-mediated cleavage of Nedd4-binding protein 1 (N4BP1), a novel cytokine suppressor. This represents a critical point of regulation during inflammation. Notably, deletion of N4BP1 does not ordinarily affect the TRIF-dependent subset of toll-like receptors (TLRs) that activate caspase-8 (e.g., TLR3 and TLR4). However, the impaired cytokine production of caspase-8-deficient macrophages stimulated with a TLR4 agonist is restored to normal by co-deletion of N4BP1. In contrast, N4BP1 deletion leads to exorbitant cytokine responses by the TRIF-independent TLRs (e.g., TLR1/2, TLR7 and TLR9) that do not directly activate caspase-8. Thus, N4BP1 cleavage by caspase-8 inactivates the anti-inflammatory activity of intact, un-cleaved N4BP1. These findings offer a novel mechanistic explanation for immunodeficiency caused by FADD-caspase-8 mutations, whereby the inability to cleave N4BP1 results in its aberrant persistence and constriction of cytokine responses. Like TLR3 and TLR4 agonists, tumor necrosis factor (TNF) also leads to caspase-8 cleavage of N4BP1, endowing TNF with the ability to inactivate N4BP1 and thereby license cytokine production by the TRIF-independent TLRs. This latter finding highlights a key point of molecular crosstalk between the TNF and TLR systems that converges on caspase-8 cleavage of N4BP1. Moving forward, I aim to dissect the molecular mechanism by which N4BP1 acts to suppress inflammation and perform global proteomic studies of caspase substrates to find additional molecules that, like N4BP1, control the nature and magnitude of inflammatory responses.

Gregory Handy, PhD

UNIVERSITY OF CHICAGO
CAREER AWARDS AT THE SCIENTIFIC INTERFACE

Investigating the ability of astrocytes to drive neural network synchrony

Recent experimental works have implicated astrocytes as a significant cell type underlying several neuronal processes in the mammalian brain, from encoding sensory information to neurological disorders. Despite this progress, it is still unclear how astrocytes are communicating with and driving their neuronal neighbors. While previous computational modeling works have helped propose mechanisms responsible for driving these interactions, they have primarily focused on interactions at the synaptic level, with microscale models of calcium dynamics and neurotransmitter diffusion. Since it is computationally infeasible to include the intricate microscale details in a network-scale model, little computational work has been done to understand how astrocytes may be influencing spiking patterns and synchronization of large networks.

We overcome this issue by first developing an "effective" astrocyte that can be easily implemented to already established network frameworks. We do this by showing that the astrocyte proximity to a synapse makes synaptic transmission faster, weaker, and less reliable. Thus, our effective astrocytes can be incorporated by considering heterogeneous synaptic time constants, which are parametrized only by the degree of astrocytic proximity at that synapse. We then apply our framework to large networks of exponential integrate-and-fire neurons with various spatial structures. Depending on key parameters, such as the number of synapses ensheathed and the strength of this ensheathment, we show that astrocytes can push the network to a synchronous state and exhibit spatially correlated patterns.

Sophie Helaine, PhD

HARVARD MEDICAL SCHOOL
INVESTIGATORS IN THE PATHOGENESIS OF INFECTIOUS DISEASE

Bacterial persistence, characterized by chronic and relapsing infections, is a major threat to human health as these infections cause considerable morbidity and frequently require multiple courses of antibiotics. Such long-lasting infections are caused by a variety of bacterial pathogens including *Mycobacterium tuberculosis*, *Salmonella*, *Pseudomonas*, *Staphylococcus aureus* and pathogenic *Escherichia coli*. During infection, *Salmonella* specifically responds to engulfment by host macrophages by forming high proportions of antibiotic persisters. These persisters escape the combined action of the antibiotic and host immune killing mechanisms for prolonged periods of time by adopting a non-growing state. The molecular mechanisms that govern persister survival and resumption of growth, potentially initiating infection relapse, are not understood. We are notably focusing on how these growth arrested bacteria control their cell cycle and experience dramatic changes to their chromosome. We hope to leverage this knowledge to resensitize these cells to antibiotics, limiting the risk of relapse.

Jacqueline Ho, MD, MSc

CHILDREN'S HOSPITAL OF PITTSBURGH
NEXT GEN PREGNANCY INITIATIVE

In Utero Exposure to Maternal Diabetes Reprograms Nephron Formation and Predisposes to Hypertension and Chronic Kidney Disease

Débora Malta Cerqueira, Takuto Chiba, Ariane Bruder do Nascimento, Andrew Scott Clugston, Maliha Tayeb, Andrew J. Bodnar, Dennis Kostka, Thiago Bruder do Nascimento, Sunder Sims-Lucas, Jacqueline Ho

Background: The prevalence of diabetes has markedly increased among pregnant women worldwide and infants who are exposed to maternal diabetes *in utero* are at increased risk of congenital anomalies of the kidney and urinary tract (CAKUT). These anomalies can result in a reduction in the number of nephrons formed during kidney development, which is linked to hypertension and chronic kidney disease (CKD). However, it remains unclear how exposure to maternal diabetes *in utero* reprograms the developing kidney, predisposing to hypertension and CKD later in life.

Methods: We used the *Ins2*$^{+/C96Y}$ mouse as a genetic model of maternal type 1 diabetes. Diabetic *Ins2*$^{+/C96Y}$ females were bred with wildtype *C57BL/6J* males, and the wildtype offspring (DM_Exp) were compared to wildtype offspring from *C57BL/6J* dams (=Control). Nephron numbers were estimated using the gold-standard physical dissector/fractionator method. scRNA-seq was performed on postnatal day 2 (P2) kidneys. Renal ischemia reperfusion injury was performed in male 3-month-old mice, and renal function was examined by BUN and sCr levels. Radio-telemetry was utilized to measure continuous blood pressures in male 6-month-old mice.

Results: Adult DM_Exp mice exhibited a nephron deficit of approximately 20% with no associated growth restriction. The expression of the nephron progenitor markers, *Six2* and *Cited1*, was increased in DM_Exp kidneys, while the number of developing nephrons was significantly reduced at postnatal day 2 (P2). This was accompanied by reduced levels of the *miR-200* family and increased expression of their target genes, *Zeb1/2*. Moreover, increased *DNMT3a* expression was observed in DM_Exp kidneys. scRNA-seq indicated that the majority of significantly differentially expressed genes occur in the distal tubules and many of them encode solute transporters. Finally, adult DM_Exp mice exhibited increased susceptibility to acute kidney injury and salt-sensitive hypertension.

Conclusion: Together, these data suggest that the diabetic intrauterine environment reprograms nephron formation and function via epigenetic mechanisms, predisposing to hypertension and CKD later in life.

Gil Hoftman, MD, PhD

UNIVERSITY OF CALIFORNIA-LOS ANGELES
CAREER AWARD FOR MEDICAL SCIENTISTS

Schizophrenia affects ~1% of US adults, causes years of disability and death ~15 years prematurely, and urgently requires novel interventions. Early interventions improve clinical outcomes, but cognitive impairments are persistently disabling and remain undertreated. Since schizophrenia is a disorder of cognitive neurodevelopment, using neuroimaging and molecular measures to characterize cortical circuitry during adolescence may reveal pathophysiological mechanisms of cognitive dysfunction and underlying progression to overt illness onset in individuals at clinical high-risk (CHR) for psychosis.

With access to collected and available structural MRI and neurocognitive data from a unique and large prospective longitudinal cohort of youth at CHR (North American Prodromal Longitudinal Study [NAPLS2] cohort, N=757), stratified by those who convert to psychosis over follow-up, non-converters, and healthy controls, I am utilizing a novel neocortex-wide neuroimaging network analysis to identify patterns that distinguish CHR youth who will develop psychosis. Advances in imaging analysis allow for the construction of morphometric similarity networks (MSNs), which are inter-regional correlation measures of multiple standardized MRI indices that quantify the kinship between cortical areas and 1) can be used to construct whole-brain anatomical networks for individual subjects, 2) reflect cortical cytoarchitecture, and 3) are linked with spatial expression patterns of brain-expressed genes. MSN topology has been linked to both cognition and expression of genes implicated in nervous system development and shown to be globally reduced in chronic schizophrenia. Furthermore, imaging transcriptomics methods provide the opportunity to bridge molecular findings in postmortem tissue – using publicly available resources including the Allen Human Brain Atlas, a brain-wide transcriptomic atlas from human postmortem adult brains – with *in vivo* MRI data.

Using detailed neurocognitive data from NAPLS2, I will utilize a data-driven multidimensional linkage of cognitive measures and MSNs. I am focusing on working memory as the most salient cognitive link, given that there are prominent working memory deficits in schizophrenia, working memory undergoes protracted development along with the refinement of higher order cortical regions, and individuals who develop schizophrenia show a lag in typical developmental gains in working memory performance prior to illness onset that often occurs in late adolescence. Working memory depends upon widely distributed glutamate/GABA circuitry, and molecular components of these circuits are altered in postmortem brains of subjects with schizophrenia. Therefore, I aim to identify MSNs in the NAPLS2 cohort at baseline and longitudinally during adolescent maturation, and to integrate MSN patterns with gene expression patterns in these transcriptomic datasets to discover molecular and developmental mechanisms contributing to psychosis risk. Future studies will include developmental transcriptomic data, examine a genetic high-risk cohort, and use non-human primate brain imaging and tissue to better understand the relationship between MRI and molecular measures within individuals and throughout development.

William Hwang, MD, PhD

HARVARD MEDICAL SCHOOL
CAREER AWARD FOR MEDICAL SCIENTISTS

Dissecting mechanisms of perineural invasion and tumor-nerve tropism by spatial transcriptomics and neuronal kinetics

William L. Hwang, Jennifer Su, Carina Shiau, Jimmy A. Guo, Jaimie L. Barth, Hannah I. Hoffman, Prajan Divakar, Jason W. Reeves, Eric Miller, Grissel Cervantes-Jaramillo, William Freed-Pastor, Vanessa Funes, Jennifer Y. Wo, Theodore S. Hong, Andrew J. Aguirre, David T. Ting, Lei Zheng, Mari Mino-Kenudson, Tyler Jacks

Tumor-nerve interactions play important roles in cancer development, treatment-resistance, and metastasis but the molecular mechanisms are poorly understood. Pancreatic ductal adenocarcinoma (PDAC) features an exceptionally high frequency of perineural invasion (PNI), a histopathologic manifestation of tumor-nerve crosstalk whereby cancer cells recruit, migrate towards, and envelop or invade peripheral nerves. Prior work on molecular mediators of PNI was limited by a lack of cell-type specificity, spatial context, and/or fragmented focus on individual pathways.

We comprehensively identified cell-type specific genes spatially linked to PNI in patient tumors by performing whole transcriptome digital spatial profiling (NanoString GeoMx) on twelve custom tissue microarrays (n=288 cores) derived from intratumorally-matched malignant regions with and without PNI in primary resected PDAC specimens (n=31 patients). We then dissected the functional roles of these genes through live imaging of dorsal root ganglia (DRG) sensory neurons incubated in conditioned media (CM) from murine cancer cell organoids ($Kras^{G12D/+}$;$Trp53^{FL/F}$L;R26-dCas9-VPR) overexpressing candidate genes via CRISPR activation (CRISPRa).

We examined associations between PNI and expression of malignant subtypes previously identified from single-nucleus RNA-seq of resected primary PDAC specimens. Malignant cells engaged in PNI were enriched in the mesenchymal, basaloid and neural-like progenitor (NRP) subtypes and depleted in the classical subtype. To test these associations functionally, we generated isogenic murine organoid lines overexpressing subtype-specific transcription factors and collected CM. DRG sensory neurons demonstrated enhanced and suppressed growth kinetics when grown in NRP and classical CM, respectively; mesenchymal and basal-like CM did not appear to influence growth kinetics. In a complementary manner, syngeneic orthotopic transplants of NRP organoids formed tumors with greater nerve-specific immunohistochemistry staining compared to tumors derived from control organoids. These results suggest that while mesenchymal, basaloid, and NRP cells likely all play a role in perineural invasion, NRP cells may have an additional role in tumor-nerve tropism.

We anticipate that this study will provide a high-resolution understanding of critical intercellular interactions in the PDAC tumor microenvironment that facilitate tumor-nerve interactions and guide novel therapeutic strategies.

Malina Ivey, PhD

UNIVERSITY OF CINCINNATI
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

Cardiac fibroblast deactivation: the Holy Grail or another obstacle to overcome?

Malina J. Ivey[1], Shannon M. Jones[1], Perwez Alam[1], Bruce Aronow[2], Jeffery D. Molkentin[2], Onur Kanisicak[1]

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Objective: Cardiac fibrosis is a major component of heart disease and is a hallmark of decreased cardiac function. Additionally, 1 in 4 people who suffer from a heart attack will have another, leading to a need to determine if there are consequences of repeated fibroblast activation. Recently generated mouse models have allowed for our lab to perform the first study of cardiac fibroblasts during *in vivo* cardiac fibrosis resolution.

Methods and Results: Our preliminary data demonstrates that the activated fibroblast lineage is maintained in the heart after fibrosis resolution, and we have interrogated the fate and altered function of these previously activated cardiac fibroblasts during deactivation and healing. Interestingly, transcriptome analysis on these retained cardiac fibroblasts showed many fibroblast-specific genes had returned to quiescent levels. However, these deactivating fibroblasts also acquired a unique gene expression profile with an up-regulation in genes involved in extracellular matrix degradation, proliferation, and myofibroblast dedifferentiation leading us to a variety of potential therapeutic targets. Of particular interest is *Runx1*, a transcription factor with a well-defined role during development, which is not expressed in mature cardiac fibroblasts until after injury. As reported in the literature, *Runx1* is turned on in activated fibroblasts, but never returns to baseline levels. To further investigate the role of *Runx1* in the fibroblast activation continuum, we have generated fibroblast specific *Runx1* conditional knockout mice to study the role of this transcription factor during activation, deactivation, and reactivation.

Conclusion(s): These genetic changes in previously activated fibroblasts, including a constant expression of *Runx1*, indicate that deactivated fibroblasts are altered from their previous quiescent state and our preliminary data further demonstrates that these altered fibroblasts become hyperactive upon subsequent insult and these changes result in severe pathological consequences.

Chinyere Agbaegbu Iweka, PhD

STANFORD UNIVERSITY
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

In the United States, a stroke occurs every 40 seconds and a resulting death every 3.5 minutes. With the aging population increasing, stroke incidence is expected to dramatically increase. The estimated cost for stroke including treatment and rehabilitation was $53 billion between 2017 and 2018 and is projected to be $1.5 trillion by 2050. Thrombolytic therapy and an embolectomy are the only effective interventions for stroke with a narrow window of 4.5-16 hours, benefiting <10% of stroke patients. **Therefore, there is a critical need to understand the stroke process and identify effective therapies that will reduce stroke severity and improve outcome.**

NIH-funded studies have highlighted a significant racial disparity in stroke where higher stroke incidence and severity is observed in African Americans compared to American Whites. This disparity is in part due to an unprecedented increase in shift-work and nocturnal activity from increasing socioeconomic pressures. Nearly 20% of the workforce nationwide is comprised of shift-workers who are more commonly minorities and individuals with lower education. Both human and animal studies provide remarkable evidence that disruption of circadian rhythmicity alters homeostasis and normal molecular response mechanisms, and is associated with increased risk for cardiovascular and metabolic diseases such as stroke and diabetes.

Stroke triggers a multiphasic and amplified innate immune response where peripheral myeloid cells infiltrate the ischemic brain and worsen injury. Innate immune responses are bioenergetically expensive and recent studies highlight a fundamental role for cellular metabolism in regulating immune responses. Both immune cell function and metabolism are tightly controlled by the circadian clock. Disruption of circadian rhythmicity in innate immune cells impairs immune cell response by negatively impacting metabolism.

My long-term goal is to understand how immune cell metabolism and function are impaired as a result of circadian disruption and to examine the effect on stroke outcome. Studies from my mentor's lab showed that blockade of components of the innate immune response dramatically improves stroke outcome. Additionally, enhancing the levels of nicotinamide adenine dinucleotide (NAD^+), a key metabolic factor that is tightly regulated by the circadian clock, restores healthy immune responses in aged myeloid cells.

To determine circadian regulation of immune responses and assess the metabolic status of blood monocytes before they traverse into the brain post-stroke, I induced stroke in young and aged mice by performing a distal middle cerebral artery occlusion (dMCAo). I determined that blood monocyte metabolic response to stroke is significantly different between young and aged mice. Blood monocytes from young mice do not initially exhibit metabolic shifts in response to stroke, but a decrease in metabolism is observed by 24 hours, that resolves by 72 hours post stroke. In aged mice, the initial response is a dramatic increase in metabolism that is depleted by 24 hours, and these cells remain metabolically exhausted by 72 hours post stroke. These strokes were induced at zeitgebers (ZT) 2–4, during the peak expression of circadian core clock protein, BMAL1, and subsequent strokes will be induced at ZT12-14 during the trough of BMAL1 expression.

Using orthogonal methods to disrupt the circadian clock, genetic ablation of the core clock gene, Bmal1, and chronic jet-lag, my future studies will evaluate how circadian rhythm disruption impacts the immune cell metabolic response to stroke in young and aged mice, and will determine what metabolic mechanisms change with aging. I will also investigate whether restoring metabolism by increasing levels of circadian regulated energy co-factor, NAD^+, will improve immune cell metabolic response to stroke and overall stroke outcome.

This research proposal is highly significant because it will allow us to better understand the potentially harmful effects of shift-work and jet-lag as they relate to stroke, and it will address a critical public health challenge – to design workplace initiatives that will alleviate the effects of shift-work on cardiovascular health and reduce health disparities in the workforce.

Zachary Jones, PhD

ST. JUDE CHILDREN'S RESEARCH HOSPITAL
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

Functional labeling of behavioral circuits in the mouse locus coeruleus

Despite its small size, the locus coeruleus (LC) is the main source of norepinephrine in the brain and plays an important neuromodulatory role through its numerous and far-reaching projections. In addition to regulating diverse behaviors such as attention, arousal, motivation, and stress responses, the LC is implicated in various neurological and neuropsychiatric disorders such as Alzheimer's disease, ADHD, PTSD, and addiction. The precise nature of the LC's involvement in these behaviors and disorders is poorly understood, largely because the LC's small size and deep location make it difficult to target *in vivo*. To overcome these challenges, my research uses novel intersectional and activity-dependent genetic tools to examine the role of the LC in alcohol use disorder (AUD). Ongoing experiments utilize the "drinking in the dark" paradigm to model binge-like ethanol intake in mice, while future experiments will seek to delineate the molecular identity and connectivity of LC norepinephrine neurons active during binge drinking and alcohol seeking. Greater efficacy in treating and preventing AUD will require a more complete understanding of the neurobiological mechanisms underlying alcohol abuse. This research will provide new insights into the underappreciated roles of norepinephrine and the LC in alcohol-motivated behaviors.

Demetrice 'Dee' Jordan, PhD

HARVARD MEDICAL SCHOOL
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

A Spatial Risk Assessment of COVID-19 Seroprevalence in Ifanadiana District, Madagascar in 2021

Background: The COVID-19 pandemic is an inherently geographic, health, and place-based phenomenon. The role geographic equity plays in the spread of the coronavirus infection is poorly understood throughout the world. Geographical input and spatial analyses can strengthen public health knowledge of COVID-19 diffusion dynamics and hotspots of exposure risk through detailed site-specific population, ecological, and environmental indicators. Testing, surveillance, and epidemiological approaches help inform these blind spots to an extent, but are constrained by inadequate infrastructure, health system access, testing capacity, and uncertainty. Granular information obtained through seroprevalence studies coupled with spatial analysis using Geographic Information Systems (GIS) can help illuminate factors that worsen disease spread and identify areas of increased risk to better understand the disease burden in populations where adequate testing practices are unlikely. Accounting for geography can have a significant impact on the public health response COVID-19 and improve how we respond by improving what we know.

Study Aims: The aim of this study is to critically evaluate the spatial risks associated with COVID-19 infections in the Ifanandiana district of Madagascar in order to answer the following questions: Where is the risk of COVID-19 infection the greatest and what drivers contribute to risk across the district's landscape? How does infection risk vary across geographic scale (i.e., administrative units)? What surveillance indicators and household factors are the most effective at nowcasting and forecasting outbreaks?

Data and Methods: Leveraging geolocated bi-annually collected longitudinal cohort household survey data of general population health dynamics including COVID-19 seroprevalence, a spatial distribution model of infection risk will be developed. The collected data includes a representative sample of 1,600 households or 8,000 people in ninety geographic clusters. The presence/absence of COVID-19 infections will be analyzed using GIS. The aggregated testing data, demographic information, ecological and environmental factors will be examined to determine trends of potential new outbreaks across space and time using retrospective case data.

Steven Z. Josefowicz, PhD

WEILL CORNELL MEDICINE
INVESTIGATOR IN THE PATHOGENESIS OF INFECTIOUS DISEASE

Epigenetic regulation of immunity: molecular mechanisms of inflammatory priming and altered hematopoiesis

Studies of acute SARS-CoV-2 infection describe a highly inflammatory and protracted course of infection. Recent advances have established broad relevance of innate immune memory and a persistent influence of inflammation on hematopoietic development, though molecular and cellular features of these phenotypes are poorly described in humans. We have revealed durable alterations of innate immune and hematopoietic progenitor cells post-COVID-19, with distinct molecular programs across disease severities. Enabled by approaches to study hematopoiesis from peripheral blood, we reveal epigenetic programming in progenitors that persists and is conveyed, for months to a year, to short-lived progeny monocytes. We developed an approach we call PBMC Progenitor Input Enrichment or PBMC-PIE that enables complete interrogation of hematopoiesis and hematopoietic stem and progenitor cells (HSPC) from peripheral blood. Using this approach paired with combined snRNA/ATACseq we established that these rare circulating HSPC reflect the diverse range of HSPC subsets found in bone marrow and demonstrate that this approach can also be used to study concepts of central trained immunity – epigenetic memory of infection and inflammation within HSPC populations. We find that epigenetic changes in HSPC are associated with increased myeloid cell differentiation and inflammatory programs. We now seek to identify if these changes indicate a risk of “long COVID” and an altered response to vaccination, or changes in immunity to common seasonal viruses. We also apply our unique approaches to study changes in children’s immune systems following COVID-19 and MIS-C. Finally, we use animal models to understand how changes we observe post-COVID-19 alter immunity. For example, the dynamic and regulatory histone variant H3.3 has been the subject of the lab’s mechanistic studies for years. We discovered that signals of pathogen sensing and inflammation are transduced directly to H3.3 in chromatin, resulting in H3.3 phosphorylation at target genes, and are critical for augmented transcription of inflammatory genes. Remarkably, we also discovered that repression of the H3.3 gene itself is a prominent feature of post-COVID-19 HSPC. Here, we also pursue a mechanistic understanding of the role of H3.3 in the response to infection, including its positive and negative regulation or dosage, and its specific residues and their modifications. Our studies provide insights into post-infectious progenitor and innate immune alterations likely to be broadly relevant.

Lisa Joss-Moore, PhD

UNIVERSITY OF UTAH
NEXT GEN PREGNANCY INITIATIVE

Placental-Fetal Lipid Regulation and Dynamics in Pathologic Pregnancies

The placenta represents an essential regulatory organ in delivering critical bioactive long-chain polyunsaturated fatty acids (LCPUFA) from the mother to the fetus. In pathologic pregnancies, this transfer can be disrupted by placental accumulation of LCPUFA. The important implication of placental accumulation of LCPUFA is that these lipids are no longer available to the fetus during a critical developmental window. Deficits in fetal LCPUFA hinder the development of multiple organs, including the lung and brain. Despite the importance of placental fatty acid partitioning, mechanisms driving placental LCPUFA accumulation and how placental accumulation affects fetal acquisition are not well understood. We recently described a novel epigenetic mediator of placental fatty acid metabolism that is conserved between rat and human systems and that is upregulated in hypoxic placenta in a sex-divergent manner causing increased placental fatty acid accumulation. We are currently interrogating the molecular and functional roles of the epigenetic mediator in human placental cells and in our rat model of uteroplacental insufficiency with hypoxia through parallel *in vitro* and *in vivo* studies. These studies demonstrate that placental hypoxia activates the pathway that causes LCPUFA to be accumulated in the placenta. Our corresponding work indicates that when these LCPUFA remain in the placenta at birth, the fetus has reduced circulating LCPUFA, as well as a reduction in select LCPUFA in the lung and brain. As we continue to determine the mechanisms by which hypoxia increases activation of the epigenetic pathway driving placental LCPUFA accumulation, we are developing strategies to overcome pathway activation, thus normalizing fetal LCPUFA acquisition. Our ongoing work is also identifying other conditions of pregnancy that result in pathway activation. In the long-term, optimal management of placental lipid metabolism in pathologic pregnancies has the potential to ameliorate developmental impacts associated with reduced fetal LCPUFA acquisition, thus improving pregnancy outcomes.

Kellie Ann Jurado, PhD

UNIVERSITY OF PENNSYLVANIA
NEXT GEN PREGNANCY INITIATIVE

Early-life immune exposures can profoundly impact lifelong health. A greater understanding of fetal immunity has the potential to help us understand health and disease during gestation, as a neonate, and every stage of life afterward. There are gaps in knowledge regarding cell types that are unique to the fetus, including the nucleated red blood cell. Fascinatingly, unlike adult counterparts, circulating fetal red blood cells are nucleated and possess the capacity to modify gene expression in response to the environment. Red blood cells have classically been disregarded as immunologically inactive due to an inability to respond to external ques. We discovered that fetal nucleated red blood cells are immunologically active. Here, we propose to assess the immune functionality of nucleated red blood cells during gestation. Our work is poised to describe an unexpected cellular orchestrator of immune programming in utero.

Maya Kotas, MD, PhD

UNIVERSITY OF CALIFORNIA-SAN FRANCISCO
CAREER AWARD FOR MEDICAL SCIENTISTS

Tuft cells and the orchestration of airway mucociliary defense

The airway employs a highly developed defense system to protect the lung from transmitted particulates, toxins and microbes. Many potential threats are trapped by the mucus layer, neutralized there by antimicrobial peptides and immunoglobulins, and swept out along the mucociliary escalator—a process that is modulated through immune, epithelial, and neuronal communication. Because failures of mucociliary defense manifest as bronchitis, asthma, pneumonia, pneumoconiosis, and other disease, it is essential to understand the cells and molecules that coordinate this function. We recently discovered that tuft cells (rare sensory epithelial cells) increased during type 2 airway inflammation, and augmented production of prostaglandin E2 (PGE2). PGE2 activated CFTR and accelerated mucociliary transit, suggesting tuft cells as mucosal sensors that help to direct airway mucociliary defense. I seek to uncover how other tuft cell-derived molecules work alongside PGE2 to coordinate epithelial behavior and recruit immune help during airway challenges; to identify the ligands and pathways that stimulate tuft cell development and activation during allergic inflammation; and to probe the consequences of chronic airway epithelial activation.

Freeman Lan, PhD

UNIVERSITY OF WISCONSIN-MADISON
CAREER AWARD AT THE SCIENTIFIC INTERFACE

Understanding complex microbial systems using ultrahigh-throughput experimentation

Background: The diversity of microbes is vast and rapidly evolving. The traditional approaches of strain isolation and characterization is limited by low throughput and high labor costs, making it unsuitable to address the enormous diversity of natural microbial populations and complex microbial communities. To overcome these limitations, I focus on developing ultrahigh-throughput approaches to studying microbial populations and systems by using a combination of ultrahigh-throughput droplet microfluidics, computational modeling, and machine learning.

Methods and results: So far, I have developed a robust and generalizable method for ultrahigh-throughput single-cell targeted sequencing of bacterial populations. This method allowed me to rapidly uncover the phase-variation (an ubiquitous bacterial survival strategy) dynamics of polysaccharide capsules of the human symbiont B. fragilis, a feat that would have required significantly more work if only traditional methods were used. I have further used this method to characterize mobile genes in microbial populations showing that they are in constant flux and respond to environmental cues.

Discussion: This method is robust, easy to use, and generalizable, democratizing single cell targeted sequencing of microbes for all researchers. Out of its many potential applications, I am currently pursuing its use in tracking host-phage interactions, evolutionary trajectories, and microbe-microbe interactions at ultrahigh-throughput.

Future work: I will further develop this method to enable simultaneous single cell genotyping and phenotyping. This type of data should allow us to rapidly elucidate the gene regulatory networks underlying phase-variation of bacterial cell surface markers such as polysaccharide capsules. This cutting-edge approach using ultrahigh-throughput experimentation to gain mechanistic insights into a complex system is a powerful new way of studying microbes.

Christopher LaRock, PhD

EMORY UNIVERSITY
INVESTIGATOR IN THE PATHOGENESIS OF INFECTIOUS DISEASE

The first barrier to infection is the skin, where the bacterium Group A Streptococcus (GAS) can live asymptomatically, cause mild self-limiting infections, or go on to deadly invasive diseases like necrotizing fasciitis. Skin keratinocytes can restrict pathogens that enter them through autophagy. However, hypervirulent strains of GAS escape autophagy with the secreted protease virulence factor SpeB. In response to SpeB, keratinocytes can induce a novel pathway of cell death of GSDMA (gasdermin A) -dependent cell death. In our model, GSDMA serves as a cell-autonomous sensor of pathogenicity to deprive invasive pathogens of the intracellular niche, a mammalian twist on the "guard hypothesis." We further propose that GSDMA activation requires coordination of virulence factors, such as adhesins for invasion and pore-forming toxins for vacuole disruption, for cytosolic SpeB delivery. Integrating several virulence requirements licenses keratinocytes against proven threats while safeguarding against aberrant activation by the non-invasive GAS and microbiota they must tolerate. Our studies examine how GSDMA acts as an immune sensor of invasive skin infection, giving insight into gasdermin regulation and pathogen detection and new therapeutic strategies for invasive infections.

Lakeisha Lewter, PhD

UNIVERSITY OF TEXAS-DALLAS
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

The role of amygdala calcitonin gene-related peptide receptors (CGRP-Rs) on the development of bladder pain

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Chronic pain affects hundreds of millions of people worldwide. Most research focuses on somatic pain. However, pain from internal organs is also a serious health issue and is understudied. Visceral pain (e.g. bladder pain) is difficult to localize, therefore difficult to treat. Within the brain, the amygdala is a region that has received increasing attention as a significant contributor to the pathology of chronic pain. Findings from both human and rodent studies have revealed left versus right brain differences in the amygdala in pain modulation. The amygdala in the right hemisphere of the brain has been shown to increase pain outside of the body and in internal organs, including the bladder. In contrast, the left amygdala has been shown to reduce bladder pain. Recent evidence has shown that amygdala activity is not only asymmetric, but also changes with time once pain is induced. However, it is unknown whether time-dependent activation of the amygdala contributes to the development of chronic bladder pain. We seek to study the hemispherical and temporal changes of the amygdala in the context of bladder pain and identify cell-types that might be responsible for contributing to these changes. One interesting target that has been shown to produce asymmetric functions within the brain is the neuropeptide, calcitonin gene-related peptide (CGRP). In this study, we used a CGRP antagonist – $CGRP_{8-37}$, to study the role of amygdala CGRP receptors (CGRP-Rs) on bladder pain-related changes over time. The effects of $CGRP_{8-37}$ were examined using a mouse model of bladder pain (100 mg/kg cyclophosphamide, 3 days). Two pain assays, abdominal von Frey and the voiding spot assay were conducted (2-21 days post-injury) in mice that received direct amygdala injections (right central amygdala) of $CGRP_{8-37}$ (1 uL of 100uM) or saline. Preliminary data indicate that animals that received saline displayed a decrease in 50% withdrawal threshold (increase in bladder pain) in the abdominal von Frey assay once treated with cyclophosphamide. Animals that received a direct injection of CGRP8-37 displayed an increase in 50% withdrawal threshold (less bladder pain) compared to saline treated animals. In the voiding assay, $CGRP_{8-37}$ led to changes in voiding frequency. Collectively, these data support the study of cell-specific manipulation of the right amygdala to produce pain relief. Focusing on the contributions of CGRP receptors in visceral pain modulation will provide insight into the underlying mechanisms contributing to bladder pain. These data, in turn, will lead to the development and advancement of effective central nervous system targeted therapies for chronic bladder pain.

Maijia Liao, PhD

YALE UNIVERSITY
CAREER AWARD AT THE SCIENTIFIC INTERFACE

Dendrites, which serve as the antennae of neurons, are often highly branched so they can receive a large number of synaptic inputs, thereby supporting the high connectivity in the nervous system. The ability of dendrites to transmit electrical signals and transport nutrients depends on the diameters of their neuronal processes. During my postdoctoral research, I pioneered in developing a novel technique with computer algorithms that enables large-scale super-resolution measurements of diameters in living dendrites for the first time. I have made breakthroughs in discovering the key biophysical principles underlying the systematic narrowing and branching patterns of developing dendrites. In parallel, through adopting advanced microscopy techniques, image analysis, molecular biology, and neurobiology, I have made significant progress in dissecting the molecular determinants of the neuronal design rules. These progresses open the door for quantitative understandings of the molecular building blocks of neurons.

The **long-term goal** of my research is to establish a mechanistic understanding of structure-function relations in nerve cells. The key step to attain this goal is to find principles governing overall morphology, to dissect the roles of the cytoskeleton and transport machinery, and to characterize how molecular perturbations lead to altered neuronal morphologies. I will employ multidisciplinary approaches to discover the neuronal design rules and dissect the molecular determinants of these rules.

Vincent Lynch, PhD

UNIVERSITY OF NEW YORK-BUFFALO
NEXT GEN PREGNANCY INITIATIVE

Evolutionary changes in the anatomy and physiology of the female reproductive system contributed to the origin of pregnancy in early mammals and influences the ways in which dysfunction contributes to reproductive trait diseases and adverse pregnancy outcomes. Evolutionary changes in the uterus and placenta also contributes to uniquely human pregnancy traits such as the spontaneous differentiation of uterine cells to hormone signals associated with pregnancy, menstruation, deeply invasive placentas, and an unknown signal that initiates labor and delivery. Humans have also evolved longer pregnancy and labor compared to other primates and appear particularly susceptible to complications of pregnancy such as infertility, pre-eclampsia, and preterm birth. Here, we argue that changes in the uterus during pregnancy are associated with these human-specific traits as well as adverse pregnancy outcomes. We propose to compare active genes in the uterus during pregnancy between species to identify genes that are uniquely expressed in the human uterus during pregnancy with a suite of functional studies to determine the functions of these genes. We suggest that explicit evolutionary studies of anatomical systems complement traditional methods for characterizing the genetic bases of disease and can provide unique insights into the causes of adverse pregnancy outcomes. We anticipate our results will advance the emerging synthesis of evolution and medicine ('evolutionary medicine') and be a starting point for more sophisticated studies of the maternal-fetal interface. Furthermore, the gene expression changes we identified may contribute to the development of diagnostics and interventions for adverse pregnancy outcomes

Monica Mainigi, MD

UNIVERSITY OF PENNSYLVANIA
NEXT GEN PREGNANCY INITIATIVE

Despite advances in obstetric care, hypertensive disorders of pregnancy remain among the leading causes of morbidity and mortality. However, the pathophysiology of these disorders remains poorly understood. A dramatic increase in pregnancies conceived by assisted reproductive technologies (ART) has occurred in parallel, unveiling higher rates of perinatal complications that differ by fertility treatment methods. Programmed frozen-thawed embryo-transfer (pFET) cycles, which utilize exogenous estrogen and progesterone in the absence of a corpus luteum (CL), significantly increase the rate of preeclampsia (PE). This unexpected finding prompted speculation that the CL and its products play a protective role against PE. The CL is the primary source not only of progesterone, but of 17ß-estradiol and multiple estrogen metabolites (E_xM) which have both pro- and anti-angiogenic actions on endothelial cells (ECs). Alterations in maternal serum E_xM have been associated with PE in mid/late gestation. Our preliminary data suggest that E_xM levels early in gestation differ during ART cycles and are significantly different in cycles without a CL. We hypothesize that the increased risk of PE seen following pFET is due to an *imbalance* of angiogenic and anti-angiogenic E_xM, which leads to uterine endothelial cell dysfunction, inadequate trophoblast invasion and disordered spiral artery remodeling. In the first aim of our proposal, we will use maternal serum from early pregnancy to compare the E_xM milieu between three peri-implantation environments that differ by number of corpora lutea and estrogen/ progesterone exposure and examine the association with PE. In the following two aims we will investigate how E_xM influence uterine EC function and utilize our novel microengineered "implantation-on-a-chip" device, seeded with primary human cells, to examine how E_xM alter EC regulation of trophoblast invasion. We believe that the proposed studies will help us elucidate the role of E_xM in abnormal placentation and identify new biomarkers and pathways responsible for E_xM mediated changes in ECs and extravillous trophoblasts. These findings have the potential to help us identify modifiable pre-conception and perinatal factors and reduce the risks of certain disorders of placentation.

Christopher Medina, PhD

EMORY UNIVERSITY
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

Phosphatidylserine as a nonclassical inhibitory molecule on exhausted CD8 T cells

Christopher B. Medina[1,2], E. Sobierajska[3], M. Gong[5], S. Im[1], V.A. Master[3,4], S.S. Ramalingam[4], R. S. Lui[5], Brekken[6,7], H.T. Kissick[1,2,3], and R. Ahmed[1,2]

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CD8 T cells eliminate infected and malignant cells. However, during chronic infection and cancer, CD8 T cells are constantly stimulated, leading to exhaustion and loss of killing potential. Inhibitory receptors on CD8 T cells such as PD1 and Tim3 contribute to this dysfunctional state, and as a result, have become immunotherapeutic prospects to reinvigorate exhausted CD8 T cells in cancer. Nevertheless, some patients remain unresponsive, highlighting the need to identify novel inhibitory molecules. We asked if phosphatidylserine (PS), a lipid metabolite, functions as a metabolic inhibitory checkpoint on exhausted CD8 T cells. PS localizes to the inner plasma membrane but is best known to be externalized during apoptosis where it can exert immunosuppressive actions. Less understood is the exposure of PS on live cells *in vivo*. Using an LCMV chronic infection model and three different mouse tumor models we find that antigen specific exhausted CD8 T cells expose PS *in vivo*, independent of cell death. Transcriptomics and metabolomics suggest an upregulated PS metabolic circuit within exhausted CD8 T cells potentially contributes to its exposure. Therapeutically, blocking exposed PS *in vivo* with αPS antibodies during chronic infection reinvigorated the CD8 T cell response and worked synergistically with current cancer treatments such as αPDL1. RNA-seq of exhausted CD8 T cells isolated from αPS treated mice suggest that blocking exposed PS induced an increased proliferative state within these cells. Lastly, CD8 T cells from human renal cell carcinoma and non-small cell lung carcinoma also expose PS and upregulate a PS metabolic circuit, highlighting the translational potential of targeting exposed PS. Overall, we demonstrate that CD8 T cells externalize PS as a potential 'non-classical' inhibitory molecule in mice and humans and begin to uncover an interesting aspect of exhausted CD8 T cell biology.

Vineet Menachery, PhD

UNIVERSITY OF TEXAS MEDICAL BRANCH
INVESTIGATOR AT THE PATHOGENESIS OF INFECTIOUS DISEASE

The focus of the Menachery laboratory has been on two related research areas: 1) emergence and infection by novel coronaviruses and 2) the role of host factors/comorbidities in coronavirus infection and disease outcomes. The emergence of SARS-CoV, MERS-CoV, and more recently, SARS-CoV-2, underscores the continued threat of cross-species transmission events leading to damaging viral outbreaks in humans. With this in mind, our experimental platforms use robust reverse genetic systems, novel *in vivo* models, and knowledge of the CoV life cycle to prepare for epidemic and future emergent coronaviruses. Notably, viral capacity is also dependent on host aspects including age, host genetics, and immune status. As such, my other research focus considers the impact of these comorbidities on host factors and infection outcomes. Taking advantage of unique and diverse animal models, my research program uses coronavirus infection to probe the role of age, genetic diversity, and immune status on infection. We leverage this knowledge to improve vaccine and drugs approaches. We seek to disrupt critical disease pathways, limit pathogenesis, and possibly stem disease outbreaks. Together, these research areas have the potential to produce critical insights with implications for improving global public health and provide treatment for human disease.

Leenoy Meshulam, PhD

UNIVERSITY OF WASHINGTON
CAREER AWARD AT THE SCIENTIFIC INTERFACE

Emerging simplicity in the nervous systems of mouse and octopus

For an animal to perform any function, millions of neurons in its nervous system furiously interact with each other. Be it a simple behavior or a highly complex computation, all functions involve the concerted activity of many individual units. My work seeks theoretical approaches that can simplify the rich dynamics of the coordinated activity of thousands of individual cells. Here, I focus on two seemingly very different nervous systems: mouse brain neural activity patterns, and octopus skin cells activity patterns. I draw on concepts from statistical physics such as the renormalization group (RG), to capture the collective nature of activity. My approach uncovers hallmarks of striking simplicity despite the complexity of both systems. In the mouse, I uncover scaling behavior and hallmarks of an RG fixed point. In the octopus, camouflage skin pattern activity is reliably confined to a (quasi-) defined dynamical space. Together, these results demonstrate the benefits of comparison across animals to achieve a multi-scale understanding of the nervous system. Such understanding illustrates how macroscale properties, such as memory or camouflage, emerge from microscale level activity of individual cells.

Juan Osorio, MD

MEMORIAL SLOAN-KETTERING CANCER CENTER
CAREER AWARD FOR MEDICAL SCIENTISTS

Engagement of Fc gamma receptors modulates the antitumor activity of antibodies blocking the innate immune checkpoint CD47

Juan C. Osorio, M.D.[1,2], David A. Knorr, M.D. Ph.D.[1,2], Jeffrey V. Ravetch, M.D. Ph.D.[2]

1 Memorial Sloan Kettering Cancer Center
2 The Rockefeller University

Background: Antibodies blocking immune checkpoints primarily expressed on T cells have revolutionized cancer therapeutics. Despite these advances, many patients fail to respond to these therapies, highlighting the need to investigate novel targets for cancer immunotherapy. Blocking the "don't eat me" signal CD47 has recently become a promising strategy to enhance antitumor immunity. Anti-CD47 antibodies enable phagocytosis and elimination of tumor cells by myeloid cells and lead to effective antitumor responses in preclinical studies and most recently in clinical trials. Since interactions between the antibody fragment crystallizable (Fc) domain and Fc gamma receptors (FcγRs) could regulate the activity of myeloid cells in the tumor microenvironment, the goal of this study is to elucidate whether the Fc domain of anti-CD47 antibodies contribute to their antitumor activity.

Methods: We modified the Fc domain of an antibody blocking mouse CD47 (MIAP301) to generate three antibodies with varying affinity to FcγRs: 1) mIgG1 D265A which lacks binding to any FcγR; 2) mIgG1 MIAP301 binding preferentially to the inhibitory Fc receptor IIB (FcγRIIB); and 3) mIgG2a MIAP301 binding preferentially to activating FcγRs. A second antibody blocking human CD47 (Hu5F9) was also modified to generate three Fc chimeric variants (mIgG1 D265A Hu5F9; mIgG1 Hu5F9 and mIgG2a Hu5F9). *In vitro* phagocytosis of CD47-expressing tumor cells (MC38 and B16) by macrophages was assessed in co-culture experiments after treatment with MIAP301 or Hu5F9 Fc variants. *In vivo* antitumor activity of MIAP301 and Hu5F9 Fc variants was determined using B16 and MC38 tumors implanted in immunocompetent C57BL/6 mice and hCD47/hSIRPα knock-in (KI) mice. Depletion studies and multiparameter flow cytometry were used to evaluate the contribution of tumor infiltrating myeloid cells of established MC38 tumors after treatment with MIAP301 Fc variants.

Results: mIgG2a MIAP301 significantly increased phagocytosis of MC38 and B16 when compared to the other two Fc variants (mIgG1 and mIgG1 D265A) or isotype control (**Figure 1A**). Similar results were found using the mIgG2a Hu5F9 antibody (**Figure 1B**). mIgG2a MIAP301 significantly reduced tumor burden when compared to isotype or other Fc variants in mice bearing subcutaneous MC38 tumors (**Figure 2A**), this activity was abrogated in mice lacking Fc gamma receptors (**Figure 2B**). In the B16 lung metastases mouse model, both mIgG2a MIAP301 and mIgG2a Hu5F9 led to a significant decrease in lung metastases when compared to the other Fc variants or isotype control **(Figure 3A-B**). Treatment with mIgG2a MIAP301 resulted in overall increase in tumor infiltrating macrophages ($CD11b^+F4/80^+$), conventional dendritic cells 2 ($CD11c^+MHCII^+$ $SIRPa^+$) and reduction in immunosuppressive myeloid and T cells (Data not shown).

Conclusion: Engagement of activating FcγRs by anti-CD47 antibodies augments phagocytosis of tumor cells by macrophages, enhances in vivo antitumor activity and alters the composition of myeloid and T cells within the tumor microenvironment. Our findings indicate that optimal engineering of the Fc domain of antibodies blocking human CD47 could enhance the antitumor activity of these therapies, which could expand the therapeutic use of these antibodies in patients.

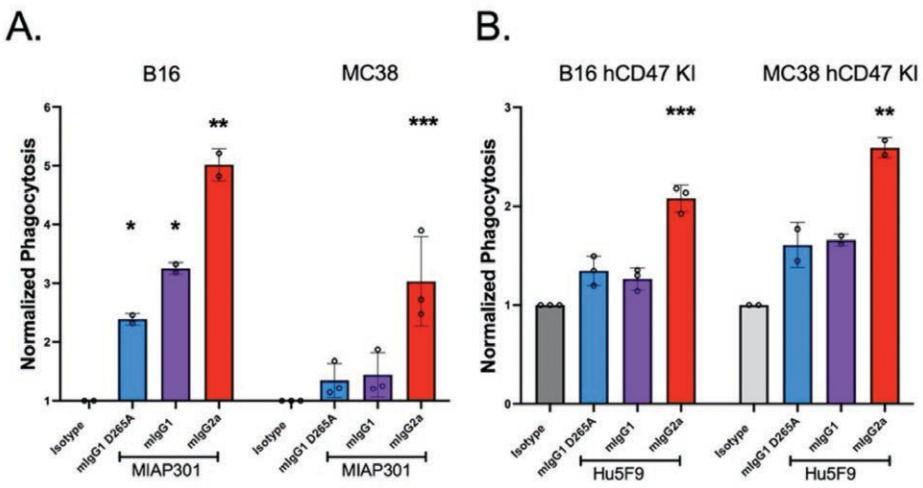

Figure 1. A) Phagocytosis of CFSE-labeled MC38 and B16 tumor cells by bone marrow derived macrophages (BMDM) from C57BL/6 mice was assessed after 2 hours of treatment with MIAP301 Fc antibody variants. **B)** Phagocytosis of CFSE-labeled MC38 hCD47KI and B16 hCD47KI tumor cells by BMDM from hCD47/hSIRPα KI mice was assessed after 2 hours of treatment with Hu5F9 Fc antibody variants.

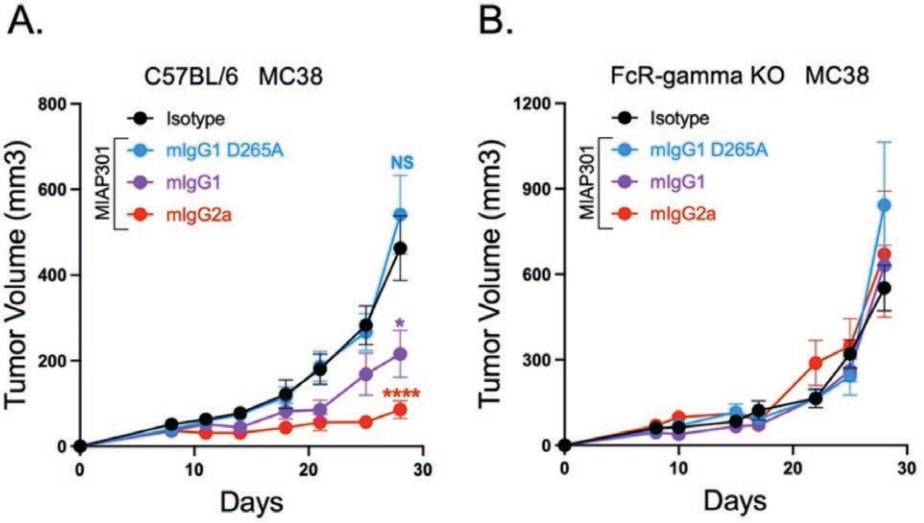

Figure 2. Tumor growth of MC38 tumors in **A)** WT mice or **B)** Mice that lack Fc gamma Receptors, treated with MIAP301 Fc variants or isotype (50ug intratumorally on days 8,10,14 and 18)

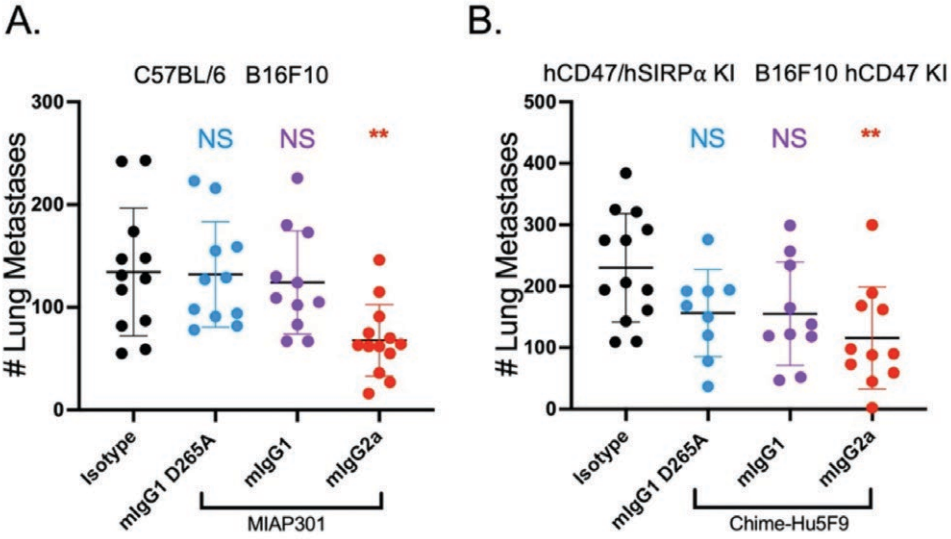

Figure 3. A) Number of lung metastases of C57BL/6 mice inoculated IV with B16 tumor cells, treated with MIAP301 Fc variants or isotype control (20 mg/Kg IP, days (d.) 1,4,7 and 11). **B)** Number of lung metastases of hCD47/hSIRPα KI mice inoculated IV with B16 thCD47KI tumor cells, treated with Hu5F9 Fc variants or isotype control (20 mg/Kg IP, days (d.) 1,4,7 and 11).

Kartik Pattabiraman, MD, PhD

YALE UNIVERSITY
CAREER AWARDS FOR MEDICAL SCIENTISTS

While schizophrenia (SCZ) has been traditionally described as a disorder manifesting during adolescence and early adulthood, disruption of early neurodevelopmental events is implicated in SCZ. Understanding how in utero disruption of brain development leads to complex symptoms of schizophrenia decades later is essential for identifying early interventions to possibly prevent the symptoms of SCZ. Recent studies have identified a convergence of SCZ associated genes in the frontal cortex during mid-fetal development, a crucial developmental period for the formation of neuronal circuits. Using BrainSpan database, we identified an enrichment of genes involved in axon development, synaptogenesis and retinoic acid (RA) signaling in the human and macaque mid-fetal frontal cortex and mouse medial frontal cortex at postnatal day 0. Cross-species analysis of expression of RA synthesizing and degrading enzymes identified human and primate-specific expression patterns in the prefrontal cortex (PFC). CRISPR/Cas9 based gene editing in mice revealed that RA signaling is required for intra-PFC synaptogenesis and the development of reciprocal PFC-MD long-range connectivity, which is disrupted in SCZ. These findings reveal a critical role for RA signaling in the specification and development of PFC and, potentially, its evolutionary expansion. Furthermore, we also identified a possible mechanistic link between retinoic acid dysregulation, cognitive dysfunction and neuropsychiatric disorders.

Samantha Petti, PhD

HARVARD UNIVERSITY
CAREER AWARD AT THE SCIENTIFIC INTERFACE

Multiple Sequence Alignments (MSAs) of homologous sequences contain information on structural and functional constraints and their evolutionary histories. Despite their importance for many downstream tasks, such as structure prediction, MSA generation is often treated as a separate pre-processing step, without any guidance from the application it will be used for. Here, we implement a smooth and differentiable version of the Smith-Waterman pairwise alignment algorithm that enables jointly learning an MSA and a downstream machine learning system in an end-to-end fashion. To demonstrate its utility, we introduce SMURF (Smooth Markov Unaligned Random Field), a new method that jointly learns an alignment and the parameters of a Markov Random Field for unsupervised contact prediction. We find that SMURF learns MSAs that mildly improve contact prediction on a diverse set of protein and RNA families. As a proof of concept, we demonstrate that by connecting our differentiable alignment module to AlphaFold and maximizing predicted confidence, we can learn MSAs that improve structure predictions over the initial MSAs. Interestingly, the alignments that improve AlphaFold predictions are self-inconsistent and can be viewed as adversarial. This work highlights the potential of differentiable dynamic programming to improve neural network pipelines that rely on an alignment and the potential dangers of relying on black-box methods for optimizing predictions of protein sequences.

Boyang Qin, PhD

PRINCETON UNIVERSITY
CAREER AWARD AT THE SCIENTIFIC INTERFACE

Bacterial biofilms are surface-attached communities of cells that represent a basic form of multi-cellular organization. The biofilm lifestyle confers survival advantages to constituent cells, including a 1000-fold increase in resistance to antibiotics compared to isogenic free-living cells. Biofilms act as reservoirs of toxigenic bacteria in chronic infections. Cells readily disperse from biofilms to stake out new territory and repeat the cycle of infection. We know little about the single cell events that enable biofilm formation and dispersal. For example, does gene expression heterogeneity exist between cells or cell lineages during biofilm development? If so, does it drive different cell fates? How do gene expression patterns and signal transductions dictate biofilm morphogenic steps? How do biofilms develop its macroscopic properties? To begin unraveling these mysteries, I developed dual-view light-sheet microscopy and intracellular labeling technology to track individual cell trajectories and lineages in *Vibrio cholerae* biofilms. *V. cholerae* is a deadly global pathogen, and biofilm formation and dispersal are key to disease transmission. I find that biofilm cells flow collectively like a “fountain” and they leapfrog over one another during biofilm formation. My work showed that this cooperative behavior enables the biofilm community to expand into new territory. Moreover, by eliminating a single gene, called *rbmA* which encodes an extracellular matrix protein, I could disrupt cooperation and force biofilm cells to move erratically as individuals rather than as a coordinated group. Many questions remain unanswered. Does gene expression heterogeneity drive distinct cell fates, the onset of dispersal, and/or macroscopic community patterning? The insights we obtain will deliver a deeper understanding of the multicellular biofilm lifestyle and promote new strategies to curb biofilms in disease.

Elze Rackaityte, PhD

UNIVERSITY OF CALIFORNIA-SAN FRANCISCO
NEXT GEN PREGNANCY INITIATIVE

Antibody Surveillance of Human Development for Preterm Birth Diagnostics and Prevention

Preterm birth is the leading cause of infant death worldwide. Maternal immune dysregulation is associated with preterm birth pointing to a breakdown of tolerance in this disease. I hypothesize that maternal immune system catalogues fetal proteins during pregnancy via production of low-affinity antibodies which disarm broader antigenic responses to the fetus. When anti-fetal responses are not suppressed, higher affinity antibodies are generated and contribute to inflammation associated with preterm birth. Identification of these antibodies may be leveraged for early pregnancy risk stratification, non-invasive tracking of fetal developmental hallmarks, as well as understanding the mechanisms of preterm labor progression.

To test this hypothesis, I will investigate maternal immune surveillance of the fetus in three pregnancy cohorts. (1) I established a longitudinal cohort of pregnant women who are undergoing frozen embryo transfer. Leveraging the exact time of implantation and a baseline pre-pregnancy blood draw, I will measure antibody and immune cell perturbations in response to becoming pregnant. (2) I will test the predictive ability of serum antibody antigen profiles in a large California-wide first trimester serum cohort (n=1000) to develop a serum diagnostic for preterm birth. (3) Using paired placenta and serum in a case-control cohort of preterm premature rupture of membranes pregnancies (n=28 cases, n=41 controls), I will investigate whether pathogenic antibodies target the placenta and inhibit placental enzymes.

An unbiased human proteome-wide phage display immunoprecipitation and sequencing (PhIPseq) approach will be used to profile the antigenic landscape of antibodies during pregnancy and preterm birth. Discriminatory antigens will be identified and validated by probing tissues with high target expression with patient sera and determining immunoprecipitated targets using mass spectrometry and immunofluorescence. Cell-based over-expression of target peptides and immunoprecipitation will be used to narrow down to the antibody-binding epitopes. B cells from patients will be stimulated with identified peptides and expanded *in vitro*. Antibodies purified from differentiated B cells will be bound to target proteins and the structural conformation changes will be interrogated using cryogenic electron microscopy.

Long-term, mechanisms of antibody targeting will be used to develop serological diagnostics of pregnancy and fetal health. Antibody targets in preterm pregnancies will be utilized to prioritize investigation of the biochemical functions of these proteins in the placenta and reproduction. Beyond the discovery of novel biomarkers associated with disease, this work will advance our understanding of antigen-specific immune suppression via antibodies, which could be applied to limit inflammation in organ transplantation and autoimmune disease.

Michael Reese, PhD

UNIVERSITY OF TEXAS, SOUTHWESTERN MEDICAL CENTER
INVESTIGATORS AT THE PATHOGENESIS OF INFECTIOUS DISEASE

Evolution of cell signaling at the Toxoplasma host-pathogen interface

The Reese Lab at UT Southwestern Pharmacology uses a variety of techniques from molecular genetics and fluorescence microscopy to biochemistry and molecular evolution to X-ray crystallography and cryo-EM to interrogate the biology of cellular signaling that occurs on both sides of the *Toxoplasma* host-pathogen interface. A few of the questions we are working on now include: (1) How do divergent parasite kinases regulate the biogenesis of the vacuole in which the parasite replicates? (2) What are the critical control points in the parasite lytic cycle? What can this tell us about the architecture of parasite signaling networks and its evolution? Can we leverage this knowledge to identify small molecules that target these processes? (3) How does the parasite invasion machinery assemble and function to drive parasite infection? (4) What are the functions of the many unannotated apicomplexan proteins? Because the parasite is genetically divergent from typical model organisms, the majority of *Toxoplasma* genes are refractory to bioinformatic functional predictions (even AlphaFold gets it wrong!). We are working to use structural biology to help probe the biochemical functions of these molecules.

Anny Reyes, PhD

UNIVERSITY OF CALIFORNIA-SAN DIEGO
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

Cognitive phenotypes in Epilepsy: Moving Towards Precision Neuropsychology and Culturally-Informed Clinical Practices

Temporal lobe epilepsy (TLE) is characterized by debilitating and progressive cognitive impairment, but there is significant variability in the nature and severity of impairment observed across patients. Cognitive phenotyping is a promising approach for understanding the heterogeneity within TLE as it considers an individual's pattern of cognitive impairment and groups patients based on this pattern. This is a paradigm shift from the traditional approach (i.e., lesion model) which focused on the associations between cognitive deficits and the type of epilepsy and etiology (e.g., memory impairment in TLE). In a series of studies (Reyes et al., 20219, 2020, 2022), I demonstrated that cognitive phenotypes in TLE are stable across samples, methods employed, and has proven useful for establishing links between distinct neural abnormalities and patterns of cognitive impairment that is otherwise obscured by the lesion-based model. The cognitive phenotyping literature has gained considerable attraction in epilepsy research and up to date, 18 studies have been published. Importantly, this approach has informed the development of the first expert consensus-based classification system for guiding cognitive diagnostics in epilepsy research, the International Classification of Cognitive Disorders in Epilepsy (IC-CoDE). The IC-CoDE was found to be stable and reproducible across six independent epilepsy cohorts of adults with TLE (McDonald, Busch, Reyes, et al., 2022). Currently, our group is examining the cross-culture application of the IC-CoDE in several culturally and linguistically international samples in order to determine its generalizability and international applicability, which will facilitate global research efforts in epilepsy. In a Spanish-speaking sample (Reyes et al., under review), we demonstrated that the pattern of test impairment and the distribution of IC-CoDE-derived phenotypes are similar to previous published IC-CoDE findings. We also show that important demographic factors (i.e., education and sex) are important to consider when applying the IC-CoDE to culturally and linguistically diverse samples. Future work in this area will focus on applying the IC-CoDE to large linguistically diverse samples and examine cultural factors that impact the classification system and explore social determinants of health that may moderate patient diagnostic classification in order to address the existing health disparities in epilepsy care and research.

Carolyn Sangokoya, MD, PHD

UNIVERSITY OF CALIFORNIA-SAN FRANCISCO
CAREER AWARD FOR MEDICAL SCIENTISTS

Illuminating Post-transcriptional Control of Stem Cell Fate and Function

Overview: Post-transcriptional regulation by RNA-binding proteins (RBPs) orchestrates diverse molecular and cellular mechanisms that pattern early mammalian development. The RBPs IRP (iron regulatory proteins) and Argonaute-2 (Ago2) coordinate cellular iron and miRNA-mediated regulation, mechanisms essential for proper execution of early development. Cellular iron regulation is critical for gut, brain, and liver development, yet the roles of IRP-targets in the earliest cell fate decisions from pluripotency transition to trilineage specification are not well known. Since iron is so essential, we don't yet know the full complement of IRP roles outside of iron metabolism, specifically within these early cell fate decisions. New tools including stem-cell-based models and genomic-engineering approaches now allow the opportunity for functional dissection of the IRP-target network within this early developmental window – without removing essential machinery – and enable a roadmap for functional rewiring in engineering stem/progenitor cell-based regenerative therapies.

My postdoctoral work focused on a dual miRNA and IRP target, Profilin-2, a cytoskeletal protein, and defined an axis of post-transcriptional control, endocytosis, and signal transduction that is essential for stem cell biology and for the initial stem cell fate decision to differentiate. In this work I used these gene-editing approaches to dissect the functional role of the Profilin-2 miR-290 target site. **My current work** and subsequent follow-up study suggests that deletion of the Profilin-2 IRP target site is sufficient to induce cell fate defects during trilineage differentiation. **In summary** I've found that an IRP target RNA can drive cell fate and cellular functions outside of iron homeostasis and coordinate with miRNA-mediated regulation to orchestrate early development.

A central hypothesis for my independent research program *is that the IRP RNA-binding proteins dynamically interact with a network of targets, including Profilin-2, and regulate cell fate and function during early mammalian development as well as in regenerative contexts.* Mapping functional IRP/iron-dependent RNA regulatory networks in pluripotent states of early development is an integral step towards mirroring similar networks in the regenerative context, and using these networks to re-engineer and re-wire cells in the future. My lab will 1) dissect and understand how the circuits between iron homeostasis and key cell functions (including endocytosis and signal transduction) intersect to drive cell fate and function 2) use in vitro and in vivo models to illuminate IRP regulation of cell fate and iron utilization in early development and 3) model cellular iron dynamics to understand the role of IRP/iron-dependent RNA regulatory

networks during human hepatocyte maturation and function. Success in these areas will pave the way to investigate these networks in other cell types where successful iron regulation is critical to organ function, including those in the liver, gut, brain, nervous, and cardiovascular systems.

Significance: The Sangokoya Lab will integrate functional genomics and multimodal transcriptomic approaches to study regulatory networks underlying cell fate decisions in development and disease. A comprehensive understanding of the dynamic relationships of IRP and its targets as pluripotency transitions through early cell fate decisions will reveal new regulatory and metabolic wiring of cell fate and function in early development. The results of the proposed studies will enhance the fields of stem cell biology and regenerative medicine by identifying and dissecting functional IRP targets *in the short term* and IRP/microRNA dually-regulated targets *in the long term* – targets that can offer new molecular tools for *our ultimate goals of re-wiring cellular plasticity and regenerative capacity – initially for liver cell-based therapies and then for other cell types.*

Next big questions: My strategy is to use RBP/RNA regulation and iron homeostasis/metabolism as lenses to explore cell fate decisions within the temporal, spatial, and functional box of stem cell to early trilineage specification stage of development. My vision is built on a simple thesis that iron pressure – using IRPs as a broad transcriptomic lever – can shift cell fates. The next big question is whether oxygen and nitric oxide-sensing pressures (also known to drive IRPs in other cellular contexts) also act within this early developmental window in vivo and if so, which target networks do these metabolic pressures use to shift cell fates? Building on the answers to our simpler questions, we can tackle the ways multiple pressures work together and iteratively build better tools to study these networks in specific cellular contexts. I am most interested in translating these findings to build sensitive RNA-based tools to characterize iron, lipid, and oxygen pressures in human liver tissue in health and disease. As a pathologist, such tools can provide snapshots of spatial metabolic expression for our patients.

Cristina Santarossa, PhD

NEW YORK UNIVERSITY SCHOOL OF MEDICINE
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

Elucidating bacterial lipid transport mechanisms by the envelope spanning LetAB complex

Cristina Santarossa[1], Minkyung Baek[2], David Baker[2], Gira Bhabha[1], Damian Ekiert[1]

1 Department of Cell Biology, New York University School of Medicine, New York, NY, USA
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Gram-negative bacteria are surrounded by an outer membrane (OM) that shields against environmental stressors and contributes to antibiotic resistance. The OM is an asymmetric bilayer composed of phospholipids (PL) and lipopolysaccharides (LPS). Trafficking lipids and other hydrophobic molecules between the two membranes, across the hydrophilic periplasm poses a significant challenge. Bacteria have evolved various mechanisms to achieve this. The MCE system, Let (Lipophilic Envelope-spanning Tunnel), is one system that plays a role in maintaining OM integrity. LetB is a homo-hexameric protein that forms a hydrophobic tunnel long enough to span the periplasm, allowing the sheltered movement of substrates directly between the inner and outer membranes. LetB functions together with its binding partner, LetA, but how these proteins come together to extract/insert lipids from/into the membrane remains unclear. LetA has an unknown structure and function and belongs to an unstudied family of proteins called the PqiA-domain proteins. Using cryo-EM coupled with RoseTTAFold, we have obtained a ~3.5 Å structure of the LetAB complex, which reveals that LetA has eight transmembrane helices along with two cytoplasmic zinc finger domains, and appears to adopt a novel transporter fold. The structure also shows an outward-open cavity that faces the tunnel of LetB, forming a continuous pathway between the two proteins. Along with biochemical and cell-based data, we will discuss insights that the structure provides into the function of LetA.

Jay Sarthy, MD, PhD

FRED HUTCHINSON CANCER RESEARCH CENTER
CAREER AWARD FOR MEDICAL SCIENTISTS

An emerging body of literature has shown that nucleosomes, the fundamental subunit of chromatin, are destabilized in a broad array of common cancers. This destabilization was previously thought to require cancer-specific mutations in histone-encoding genes, called "oncohistones." We identified a new mechanism that allows cancers to gain unstable nucleosomes, through upregulation of the nucleosome-poisoning histone H2A variant H2A.B. This variant is normally expressed in testis, where it contributes to the unique chromatin environment in sperm. We compared the amino acid sequences of H2A.B and H2A and identified oncohistone features in wildtype H2A.B sequence, suggesting that this is a "readymade" oncohistone sitting in our genomes. Consistent with this hypothesis, we identified H2A.B expression in 50% of diffuse large B-cell lymphomas and 5-10% of many other common malignancies but not in normal tissue outside of testis. We also found unique patterns of alternative splicing in H2A.B-expressing cancers, and these changes were previously reported in the context of nucleosome destabilization. Finally, we performed knockdown studies and found that H2A.B reduction impairs cancer cell growth, results that are supported by large-scale CRISPR studies. However, the contributions of H2A.B, and more broadly nucleosome instability, to oncogenesis have yet to be elucidated. This proposal will apply innovative chromatin profiling methods developed in our lab to investigate the effects of H2A.B on the transcriptomes and epigenomes of cancer cells. We will also determine whether a histone-targeting, minimally cardiotoxic anthracycline has efficacy in H2A.B-positive cancers. Finally, we will investigate how two other candidate oncohistone variants, H4.7 and H2A.Z.2.2, perturb chromatin and characterize their expression in cancer. At the completion of the experiments outline here, we expect to identify how nucleosome instability acts as a cancer driver, establish a new treatment strategy in H2A.B-positive cancers, and broaden the scope of nucleosome instability in cancer by identifying alternative mechanisms to acquire this emerging cancer driver.

Liat Shenhav, PhD

ROCKEFELLER UNIVERSITY
CAREER AWARD AT THE SCIENTIFIC INTERFACE

The placental vasculature spans several scales, from 10cm-long arteries to micron-sized capillaries, forming a complex network essential for effective maternal-fetal exchange. Abnormal development of the vessels in the placenta was found to both cause and modulate pregnancy-related complications such as preeclampsia, a leading cause of maternal death. The initial vascular alterations leading to preeclampsia occur in the placenta in the first trimester. However, since the placenta is not yet amenable to high-resolution in vivo measurements, no diagnostic test reliably detects preeclampsia early in its development, as symptoms are not apparent until the 2nd half of pregnancy.

Importantly, women destined to develop preeclampsia have increased vascular reactivity well before they become symptomatic. *This observation could be key to novel diagnostics.* As a window to vascular reactivity, I will focus on the vasculature of the eye; recent advancements in ocular imaging now provide high-resolution, cheap and non-invasive imaging of the retina, making it an accessible and sensitive imaging target, especially compared to the placenta. Retinal vasculature has been shown to be altered after symptoms of preeclampsia have manifested, and to persist even after it is resolved. However, retinal changes in early pregnancy, prior to the patient becoming symptomatic, have not been rigorously evaluated.

To address this challenge and devise a precise, early prediction of preeclampsia, I will model the vasculature of the eye as well as the multiscale vasculature of the placenta. The vasculature of mammalian organs is a hierarchical and interconnected network of "pipes." Therefore, I will model it as an optimal transportation network, an archetypical complex structure by which various goods are distributed or collected. A universal characteristic of such networks is hierarchy: the presence of large channels spanning long distances and recursively smaller channels spanning shorter distances. Another important attribute is interconnectivity – the ability to transport goods in the presence of local breaks. As such, the analysis of these networks requires methods that can capture complex, nonlocal topology.

To this end, I will develop network analysis frameworks suitable to characterize the 2-D and 3-D multiscale vascular topology of mammalian organs. This approach will provide a nuanced description of the vasculature topology and architecture and will allow extraction of interpretable vascular features. Next, I will devise machine learning algorithms and harness the predictive power of the "proxy vasculature" – the retina – to reveal interpretable biomarkers of preeclampsia and potentially other pregnancy-related disorders. Finally, I will study the retinal vasculature in tandem with the placental one. I will capitalize on new technologies, enabling in vitro 3D visualization of vascular labeled structures, and map the fine scale organization of the placental vasculature. I will quantitatively characterize the organization of the 3-D placental vascular network and associate it to vascular features extracted from high-resolution images of the retina. This will allow me to go beyond biomarkers: quantify the impact of vascular topology on placental function and elucidate the interactions between the placental and retinal vasculature in health and disease.

Jian Shu, PhD

MASSACHUSETTS GENERAL HOSPITAL/HARVARD MEDICAL SCHOOL
NEXT GEN PREGNANCY INITIATIVE

Prediction of Preterm Birth through Single-Cell Genomics and Machine Learning

Healthy pregnancies are essential for the existence of humankind. High rates of pregnancy complications, such as preeclampsia, fetal growth restriction, and preterm birth jeopardize the health of the mother and fetus, and entail lifelong complications to the newborn. These complications cause extremely high societal and economic burdens to all humans regardless of ethnicity, sex, or age. While genetic testing and ultrasounds have provided guidance for pregnancy, no comprehensive characterizations or public datasets are available yet. Thus, the nine months of pregnancy remain a "black box." Yet, the mechanisms responsible for the onset of labor remain to be elucidated. Understanding human pregnancy is essential to tackle the challenge of preterm birth (PTB), which affects 15 million neonates every year. However, the cellular and molecular etiology remains largely unknown. These knowledge gaps are primarily due to a lack of tools to identify the specific cells that are causing the disease and which specific genes and pathways are triggering the malfunction within those cells at high resolution.

Bulk population analysis can only provide averaged measurements of diverse cell populations. Experimental and computational approaches based on single-cell sequencing offer complementary approaches with a broader molecular scope and thus a few pioneering studies have sought to uncover pregnancy at single-cell resolution. The limitation with these studies, however, is the relatively small number of cells analyzed or limited to a specific data modality. Another challenge is to reliably analyze the data.

In this proposal, we aim to overcome those challenges and apply novel experimental and computational single-cell/nucleus single-cell RNA-seq and machine learning technologies that we have developed (e.g., WADDINGTON-OT) to systematically dissect the molecular circuits and disease modifier pathways of in the maternal blood from healthy pregnancies and preterm birth patients. We hypothesize integrating single-cell/nucleus gene expression will allow us to reconstruct the complex gene regulator networks and intercellular communication networks of the blood cell lineages during pregnancy. We can delineate the cell-type-specific gene modules and circuits, regulatory networks, disease modifier pathways of preterm birth and develop novel single-cell biomarker panels to predict gestational age and preterm birth and identify candidate therapeutic targets.

Dominique Stephens, PhD

VANDERBILT UNIVERSITY/FISK UNIVERSITY
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

DUSP11 modulation of intracellular Immunogenicity

To properly function, the innate immune system must respond quickly to an invading pathogen but not be so sensitive to ignite an inflammatory response when no pathogen is present[1-2]. The immune system detects and fights off pathogens like bacteria and viruses through receptors called pathogen recognition receptors (PRR)[3-5]. I will use triphosphorylated RNA receptor RIG-I as a model to study how tuning of the immune response must allow effective antiviral defense while avoiding pathological activation by the abundant host triphosphorylated RNAs. Our recent evidence indicates that Dual-Specificity Phosphatase 11 (DUSP11) is a key mediator acting on 5' triphosphate RNA to balance affecting the sensitivity of the RIG-I response9. Despite the potential benefits, there remains a **critical need** to decipher what controls the sensitivity of the innate immune response and DUSP11 offers an opportunity to do so. To this end, I will determine how DUSP11's locale changes during virus infection using immunofluorescence high-resolution microscopy and subcellular fractionation immunoblot analysis. To reveal how DUSP11 controls the immunogenicity of intracellular and neighboring cells, RT-qPCR, and RNA seq will be utilized. By identifying specific DUSP11-mediated pathways disrupted during virus infection, this research has the potential to transform inflammation-based therapeutics. Understanding how DUSP11 modulates the immunogenicity within cells will lay the foundation for my **long-term research goal** of understanding globally what controls the sensitivity of the innate immune response.

Cynthia Tchio, PhD

HARVARD MEDICAL SCHOOL
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

A Novel Translational Approach to Orphan GPCRs Deorphanization: New Insights into GPR61 Function in Sleep and Cardiometabolic Traits

Cynthia Tchio[1,2,3,5], Badri Kameswara[1], Herman Taylor[1], Jonathan Williams[4], Richa Saxena[2,3,5]

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G-protein coupled receptors (GPCRs) are the largest class of membrane receptors. They are involved in various sleep and cardiometabolic disorders; however, 150 out of 900 GPCRs remain orphans (oGPCRs) with unknown endogenous ligands; thereby, limiting our understanding of their biological function. GPCRs are targeted by 36 % of FDA-approved drugs; thus, the understudied oGPCRs are druggable and have a high potential to impact human health once disease associations are made.

This study aimed to use a genomic approach from a large dataset to deorphanize oGPCRs whose genetic variations significantly impact sleep and cardiometabolic disorders. First, we used the UK Biobank study summary statistics to identify oGPCRs loci where multiple sleep and cardiometabolic traits colocalized at a false discovery rate < 5%. Next, in the metabolic disease knowledge portal, we performed PheWAS analyses of the variants to identify new phenotypic traits in other datasets of European ancestry. We then used GTex to identify quantitative trait loci to highlight variants that affect gene expression.

Our study identified variants in oGPCRs *GPR61*, *GPR146*, and *GPRC5B* that have a pleiotropic effect on sleep and cardiometabolic traits in the UK Biobank cohort. The variant rs12044778 is an intronic variant in *GPR61* associated with ease of waking up and morningness chronotype. We also found that rs12044778 is also significantly associated with BMI and HDL cholesterol. Moreover, GPR61 is expressed in suprachiasmatic nuclei (master clock) AVP and VIP neurons suggesting their functional involvement in sleep and circadian rhythmicity. The next phase of de-orphanization story is to identify potential ligands that bind and activate our orphan GPR61. Hence, we used the BLOSUM62 similarity matrices score to help us identify sequence similarity for regions that are key for ligand binding. We were able to validate a ligand that binds to GPR61 and recruit the intracellular binding of Beta arrestin2. Overall, our study provides new insight into the functions of oGPCRs genetic variants in sleep and cardiometabolic processes. Our study also provides a novel approach to using genomic data to increase our understanding of the implication of understudied orphan GPCRs in human health.

Christina Theodoris, MD, PhD

GLADSTONE INSTITUTES / UNIVERSITY OF CALIFORNIA-SAN FRANCISCO
CAREER AWARDS FOR MEDICAL SCIENTISTS

Mapping gene networks requires large amounts of transcriptomic data to learn the connections between genes, which impedes discoveries in settings with limited data, including rare diseases and diseases affecting clinically inaccessible tissues. Recently, transfer learning has revolutionized fields such as natural language understanding and computer vision by leveraging deep learning models pretrained on large-scale general datasets that can then be fine-tuned towards a vast array of downstream tasks with limited task-specific data. Here, we developed a context-aware, attention-based deep learning model, Geneformer, pretrained on a large-scale corpus of ~30 million single cell transcriptomes to enable context-specific predictions in settings with limited data in network biology. During pretraining, Geneformer gained a fundamental understanding of network dynamics, encoding network hierarchy in the model's attention weights in a completely self-supervised manner. Fine-tuning Geneformer towards a diverse panel of downstream tasks relevant to chromatin and network dynamics using limited task-specific data demonstrated that Geneformer consistently boosted predictive accuracy. Applied to disease modeling with limited patient data, Geneformer identified candidate therapeutic targets for cardiomyopathy. Overall, Geneformer represents an invaluable pretrained model from which fine-tuning towards a broad range of downstream applications can be pursued to accelerate discovery of key network regulators and candidate therapeutic targets.

Josephine Thinwa, MD, PhD

UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER-DALLAS
CAREER AWARD FOR MEDICAL SCIENTISTS

A novel role for the neurodevelopmental gene CDKL5 in autophagy and antiviral immunity

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Virophagy, the selective autophagosomal engulfment and lysosomal degradation of viral components, plays a crucial role in antiviral immunity. However, the mechanisms leading to viral antigen recognition and autophagy induction remain poorly understood. In this work, we report a novel role for Cyclin-dependent kinase-like 5 (CDKL5), known to function in neurodevelopment, as an essential regulator of autophagy during virus infection. Deletion of CDKL5 reduced virophagy of Sindbis virus (SINV), a neurotropic RNA virus, and increased intracellular accumulation of SINV capsid proteins and cellular cytotoxicity. The ability of CDKL5 to regulate autophagy and mitigate the intracellular accumulation of viral capsid depended on its kinase activity. Through direct phosphorylation of the selective autophagy receptor p62, CDKL5 promoted formation of p62 inclusion bodies that bound capsid leading to autophagic degradation. Loss of CDKL5 disrupted the interaction between SINV capsid and p62, and a phosphomimetic mutant of p62 rescued the interaction. Finally, CDKL5 knockout mice infected with neurotropic viruses demonstrated increased neuronal cell death and greater susceptibility to infection compared to wild type mice. Overall, these findings identify a cell-autonomous innate immune mechanism for activation of autophagy to clear toxic viral capsid aggregates during infection.

Andre Toussaint, PhD

COLUMBIA UNIVERSITY'S ZUCKERMAN INSTITUTE
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

Pain and opioid addiction are co-occurring disorders with a complicated relationship. Patients suffering from chronic, and sometimes acute pain, are typically prescribed opioids for the management of their pain state. However, repeated exposure of any opioid can lead to the development of tolerance, physical dependence, and opioid addiction. This has led to the current opioid epidemic that is driven in part by the unmet need in treating chronic pain. Although several factors contribute to pain sensitivity, evidence using preclinical mouse models shows that inter-individual genetic variation plays a critical role in determining pain responses as well as susceptibility to abuse opioids. The Abdus-Saboor lab recently identified a genetically diverse inbred mouse line, SJL/J, that displays a hypersensitive pain phenotype in response to innocuous and noxious stimuli, even at baseline conditions. Given the relationship between ongoing pain and opioid addiction, we hypothesize that a genetic predisposition to heightened pain will translate into increased self-administration of opioids for both reward and pain relief. My overarching goal as a postdoc is to establish a causal connection between pathological pain sensitivity and subsequent abuse of opioids and molecular mechanisms that underpin this connection. To investigate the relationship between a genetic predisposition to chronic pain and subsequent opioid addiction, I will (**Aim 1**) assess the propensity to self-administer opioids between SJL/J mice and the canonical wildtype strain, C5B7BL/6J which displays normal pain responsiveness will serve as a control. Recent evidence shows that rodents experiencing both inflammatory and neuropathic pain have reduced VTA-dopamine release into the NAc, which ultimately affects motivated responding to drug rewards. In **Aim 2**, I will use microendoscopy in freely behaving mice of both strains to measure baseline VTA dopamine activity as well as firing after administration of natural (sucrose) and drug (morphine) rewards. Together, using this unique approach incorporating behavioral pharmacology and calcium (Ca^{2+}) imaging, I will be able to establish a strategy to delineate the molecular mechanisms associated with pathological pain sensitivity and addiction susceptibility.

Adelaide Tovar, PhD

UNIVERSITY OF MICHIGAN
POSTDOCTORAL DIVERSITY ENRICHMENT PROGRAM

Using massively parallel reporter assays to dissect context-specific regulatory grammars in type 2 diabetes

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Genome-wide association studies have revealed that ~90% of disease-associated genetic variants are found in non-coding regions, including in type 2 diabetes (T2D), where they are expected to modify gene regulation and downstream disease mechanisms. The framework to translate the impact of non-coding variants on specific transcriptional processes is ill-defined, underscoring the need for a set of regulatory grammars to accelerate efforts to link genetic associations with specific pathogenic consequences. Here, we used a massively parallel reporter assay (MPRA) to screen enhancer activity across a panel of 197-bp fragments spanning over 10k T2D- and metabolic trait-associated variants. To measure enhancer activity across several promoter and enhancer contexts in a diabetes-relevant cell model, we cloned these fragments up- or downstream of a reporter gene driven by a synthetic housekeeping promoter (SCP1) or the cell-specific human insulin (*INS*) promoter, and delivered the library to a pancreatic beta cell line (832/13 rat insulinoma). Next, we examined enhancer activity bias across this library (FDR < 0.05) based on position and linked promoter. Two unique subsets of fragments emerged: one with positional bias (n = 702/11,656) and one with promoter bias (n = 698/11,656). The former set was evenly distributed across up- and downstream activity bias, while a majority of fragments in the latter set had higher enhancer activity when paired with the cell-specific *INS* promoter (n = 512/698). To identify sequence features associated with promoter preference, we used Lasso regression with 562 genomic annotations and discovered that fragments with *INS* promoter-biased activity are enriched for HNF1 motifs. HNF1 family members HNF1A and HNF1B are key regulators of glucose metabolism and exonic mutations cause maturity onset diabetes of the young (MODY), suggesting genetic convergence between rare coding variants that cause MODY and common T2D-associated regulatory variants. We designed a follow-up MPRA containing HNF1 motif-enriched fragments to observe consequences of mutating or deleting these motifs on promoter-biased activity, and results from this library will be presented. Together, our study suggests that cell-specific regulatory activity is partially influenced by enhancer-promoter compatibility, and indicates that MPRA design is critical to capture context-specific regulatory processes at disease-associated genetic signals.

Rebecca M. Voorhees, PhD

CALIFORNIA INSTITUTE OF TECHNOLOGY
INVESTIGATORS IN THE PATHOGENESIS OF INFECTIOUS DISEASE

Novel host factors for viral membrane protein biogenesis

Viruses are major human pathogens that impose an enormous medical and economic burden. As obligate intracellular parasites, viruses must exploit host cellularly machinery for synthesis of their own viral proteome. Successful viral infection relies on several integral membrane proteins, which are critical for all aspects of the viral life cycle including cell entry, viral assembly, and release. Due to their essential role in infection, both viral envelope proteins and viroporins are targets of many antiviral therapeutics. Given the global impact of viruses on human health, there is an urgent need to better understand the host factors required to produce viral membrane proteins in human cells.

The defining structural feature of an integral membrane protein is the presence of one or more transmembrane domains (TMDs) that must be inserted into the lipid bilayer. For most viral membrane proteins, this process occurs at the endoplasmic reticulum (ER). Analysis of the membrane proteins encoded by diverse viral families suggests that their TMDs can differ substantially in length and hydrophobicity. For example, many viroporins and envelope proteins contain charged or polar residues within their TMDs that are essential for function or oligomerization, but are thermodynamically unfavorable when exposed to the lipid bilayer. How these hydrophilic TMDs are inserted and temporarily stabilized within the membrane during biogenesis is not well understood.

A small number of ER-resident intramembrane chaperones have been identified, but are insufficient to accommodate the enormous topological and biophysical diversity of the viral membrane proteome. We therefore hypothesize that many viral membrane proteins must rely on a suite of novel host factors to ensure their efficient insertion, folding, and assembly in the human ER.

We have developed a flexible pipeline to identify these host biogenesis factors for representative viral membrane proteins using two complementary strategies: (i) a genome wide pooled CRISPR screening platform in human cells, and (ii) proteomic analysis of the interactome of nascent viral membrane proteins in the ER. We reason that factors that both affect viral protein biogenesis in cells and stably interact with a newly made viral protein, will be the strongest candidates for subsequent follow-up experiments. These identified candidates will be further analyzed using a combination of functional and structural strategies to dissect their role in viral membrane protein biogenesis at the molecular level.

In pilot experiments, we have applied this pipeline to an integral membrane protein from SARS-CoV-2, the viroporin, ORF3a. We chose ORF3a because it is a conserved, putative ion channel that has been shown to increase the infectivity and morbidity of betacoronaviruses. Using our genetic and proteomic screening pipeline, we identified the poorly characterized NOMO-NCLN-TMEM147 complex (the NOMO complex hereafter) as a novel host biogenesis factor for ORF3a; have shown that the NOMO complex is required for ORF3a biogenesis in human cells; reconstituted its function *in vitro*; and used cryoelectron microscopy to determine its structure. We will leverage this interdisciplinary approach to understand the role of the NOMO complex in the biogenesis of ORF3a and more generally, that of other viral membrane proteins. This work establishes a blueprint for dissecting the general principles that govern viral membrane protein biogenesis, revealing fundamental insights into how viruses exploit their human hosts during infection.

Chandrasekhar Yallampalli, PhD

BAYLOR COLLEGE OF MEDICINE
NEXT GEN PREGNANCY INITIATIVE

Transcriptome and proteome profiling to evaluate role of placenta specific complement activation in preeclampsia and fetal growth restriction

Manu Banadakoppa, PhD, Chandra Yallampalli, PhD

Complement (C) activation byproducts in the circulation are elevated with pregnancy and they are further elevated significantly in preeclampsia (PE). Placental deposition of C activation byproducts is also significantly elevated in PE. The semi-allogenic nature of placenta induces maternal C cascade activation. Maintaining robust regulation of C activation at maternal-fetal interface is critical for successful pregnancy. In mice, ablation of complement receptor 1 related protein y (Crry), a rodent specific regulator of C pathway, causes embryonic lethality due to C activation mediated feto-placental injury. The lethal phenotype of Crry knockout was rescued with concurrent maternal C effector protein (C3 or factor B or factor D) deficiencies providing a direct role for excess C activation in fetal demise. Recently we have shown that expression levels of C regulators on placentas are significantly reduced in idiopathic miscarriage suggesting a critical role for C system in successful pregnancy. It is highly possible that C activation may also play a role in the pathophysiology of PE and fetal growth restriction (FGR) since several recent epidemiological reports suggested an association of increased C activation with PE.

Products of C activation such as C3a, and C5a are increased in blood during early pregnancy (10-13 weeks of gestation) in women who later developed PE compared to normotensive women. We recently reported that C activation products are increased in amniotic fluid during early pregnancy in women who later developed PE compared to normotensive women. Genetic polymorphisms in C cascade genes show an association with PE suggesting a possible genetic susceptibility. Our recent study indicated a higher prevalence of combinations of single nucleotide polymorphisms (complotypes) of fetal and maternal C genes in PE women compared to normotensive pregnancies. All these associative studies strongly suggest an important role for elevated C activation in PE and FGR. Largely, extent of C activation in humans with a range of activation levels appears to be determined by genetic variations in C regulatory genes (Complotype). Our recent publication on “pregnancy complotype” suggested a similar phenomenon during human pregnancy leading us to postulate that a range of C activation may at least partly contribute to the range of symptoms observed in PE. Though these studies strongly suggested an association between C activation and PE/FGR, molecular mechanisms that follow placental C activation promoting PE pathology and FGR are unknown.

Strong correlation between FGR and PE, especially early onset PE suggests a common etiology. But it is difficult to discern cause and effect relationship in multifactorial syndromes such as PE and FGR. Regardless, PE and FGR have different clinical

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features and can occur independently of the other. Therefore, we hypothesize that PE and FGR share a common upstream molecular pathway and differ in downstream molecular mechanisms leading to pathological changes. Based on previously published studies on the role of C in human diseases in general, and preliminary data presented in our application, we propose that placental C activation is a common upstream pathway in PE and FGR, with diverse canonical downstream mechanisms such as signaling through C3a-C3aR and C5a-C5aR axis, activation of transcription factor STAT3 and activation of signal transducer ERK1/2. Placenta specific C activation will induce differential gene expression (DGE) in placenta and maternal vascular tissue promoting an interplay between them mediated by soluble factors in maternal circulation. To test our hypothesis, **we propose to apply multi-omics approach in a novel transgenic mouse model of inducible, conditional and placenta specific C activation to identify similarities and differences in molecular pathways of C activation promoting PE pathology and FGR.** We propose to perform these studies under 3 specific aims: 1) To examine if placenta specific C activation leads to DGE in placenta, maternal circulation, and maternal vascular tissue, 2) To test if signaling through C3a-C3aR and C5a-C5aR axis induces different patterns of DGE in placenta, maternal circulation, and maternal vascular tissue, 3) To evaluate if C activation is related to PE pathology and FGR through different downstream signaling pathways involving different DGE patterns in placenta, maternal circulation, and maternal vascular tissue.

Andrew Yang, PhD

UNIVERSITY OF CALIFORNIA-SAN FRANCISCO
CAREER AWARD AT THE SCIENTIFIC INTERFACE

Decoding the molecular logic of brain-body crosstalk

The blood-brain barrier (BBB) represents one of the largest challenges in neurology: its noted impermeability impedes the effective treatment of nearly all brain disorders and its dysfunction is a leading cause of death, from stroke to Alzheimer's disease. Our understanding of BBB impermeability comes from using a handful of standard tracers injected one at a time dating back over a century. Yet, recent studies suggest that brain function is surprisingly sensitive to circulatory factors, largely unknown, hinting at currently under-appreciated modes of communication across the BBB. In our BWF CASI project, we will develop new molecular tools to tag, track, and identify which of the thousands of native proteins and cells in our bodies can cross the BBB and how they do so. Our comprehensive approach is possible only with recent developments at the intersection of chemistry, biology, and engineering—and promises to greatly accelerate our ability to decipher the general principles by which endogenous proteins and cells access the brain. Upon completion, our project may transform our understanding of fundamental BBB biology and inform a new generation of drug delivery approaches to treat neurological disease.

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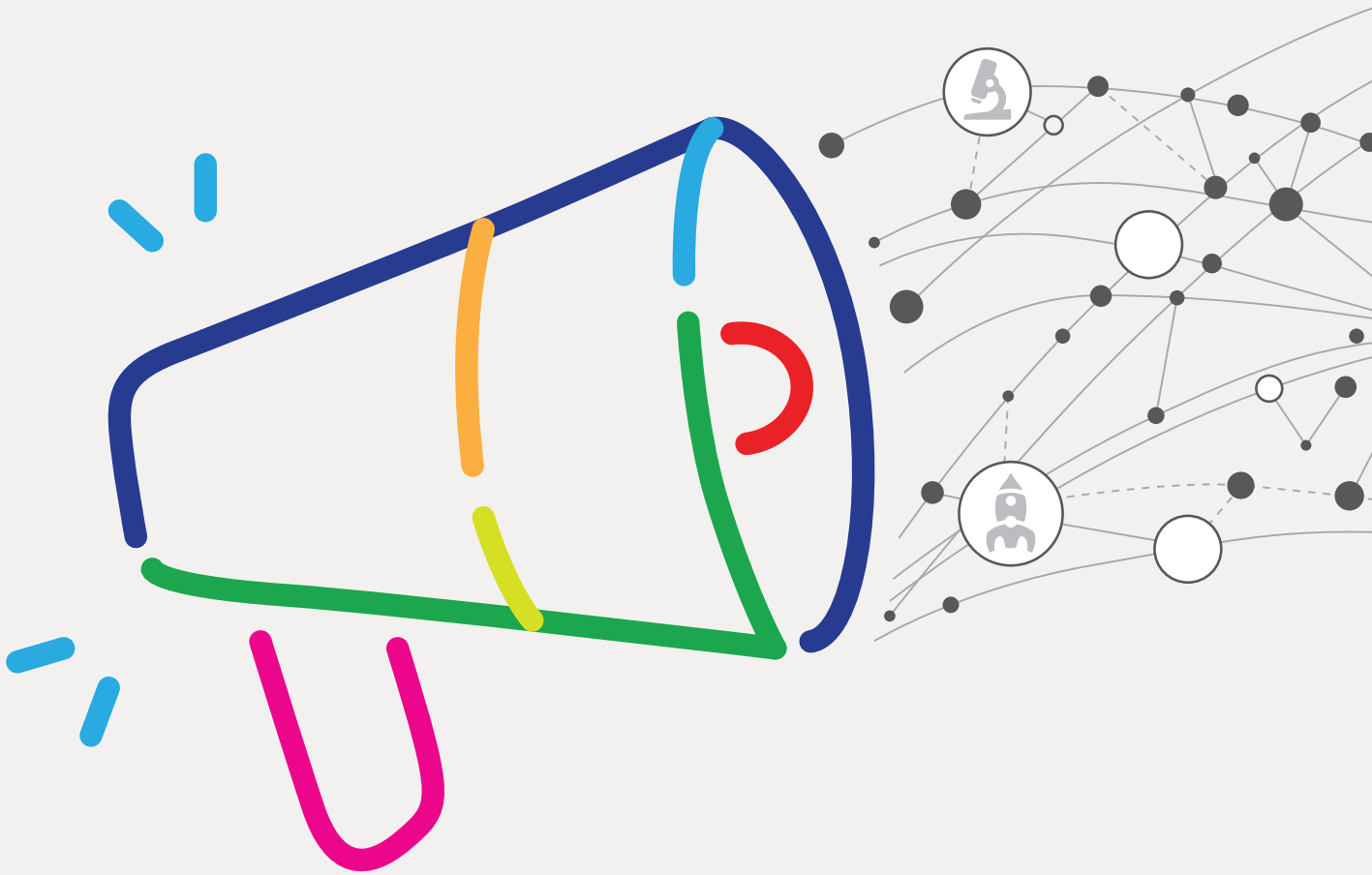

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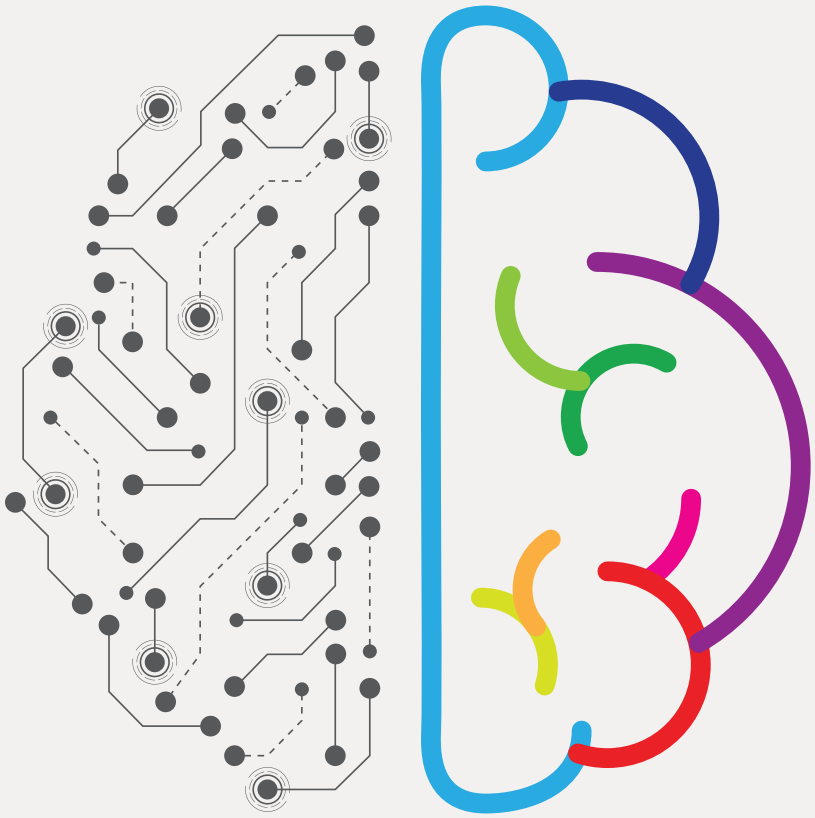

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