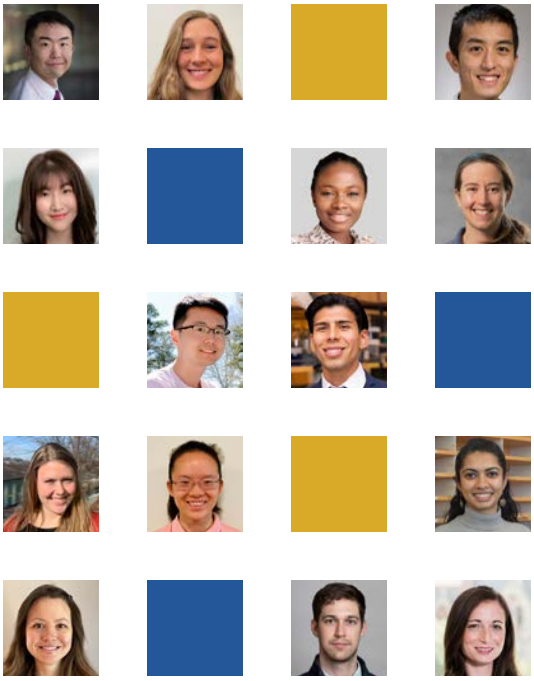
JANE COFFIN CHILDS

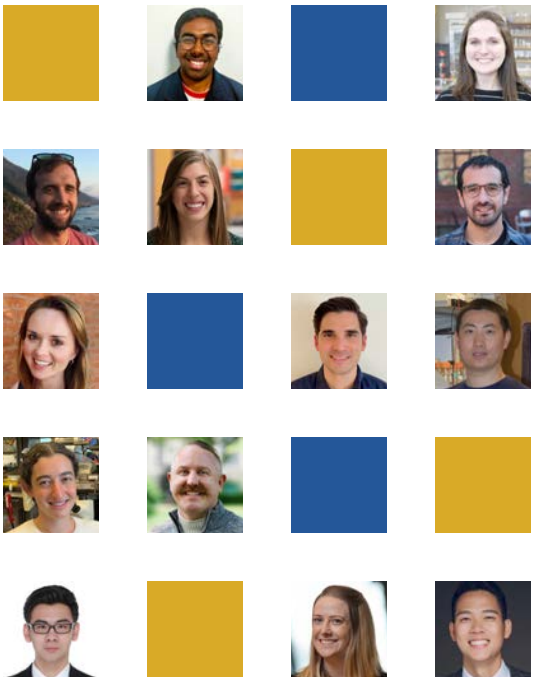
Fund for Medical Research



2023

JANE COFFIN CHILDS FELLOWS

FELLOW BIOGRAPHIES



GWENDOLYN BEACHAM, Ph.D.

LABORATORY OF DR. ELLIOTT HAGEDORN
DEPARTMENT OF MEDICINE
BOSTON UNIVERSITY

JANE COFFIN CHILDS FELLOW

The vascular system transports blood and immune cells throughout the body. Yet, how these cells selectively cross the endothelium and enter the appropriate cellular tissues is unclear. Dr. Gwendolyn Beacham will explore the fundamental mechanisms underlying this endothelial transmigration in Dr. Elliott Hagedorn's and Dr. Christopher Chen's labs at Boston University. Beacham predicts that endocytosis is important for this process and has identified candidate proteins by investigating blood stem cells. She will use zebrafish as a model system to validate her preliminary findings. Then, Beacham will use this understanding to engineer blood vessels with controllable endothelial transmigration in zebrafish and in human cell culture. This research may help improve the efficiencies of cancer therapies that rely on endothelial transmigration, such as bone marrow transplants and engineered CAR T-cells.

As a Ph.D. student in Dr. Gunther Hollopeter's lab at Cornell University, Beacham investigated clathrin-mediated endocytosis. In particular, she discovered that endocytosis is inactivated via phosphorylation of the clathrin Adaptor Protein 2. These findings revealed a novel regulatory mechanism for endocytosis and set up Dr. Beacham to explore how endocytosis contributes to endothelial transmigration.

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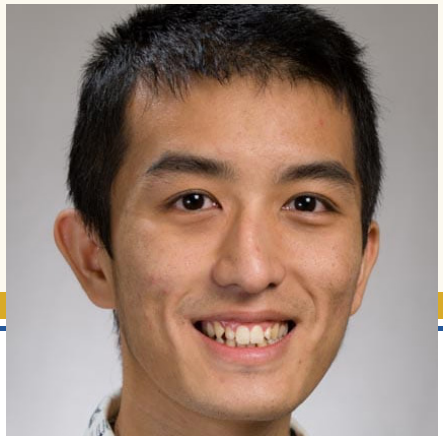


SIYU CHEN, Ph.D.

LABORATORY OF DR. ELIZABETH VILLA
DEPARTMENT OF MOLECULAR BIOLOGY
UNIVERSITY OF CALIFORNIA, SAN DIEGO

JANE COFFIN CHILDS-HHMI FELLOW

Mutations in LRRK2, a multi-domain kinase and GTPase, is the most frequent cause of familial Parkinson's disease. However, we currently lack the detailed understanding of LRRK2 function that could lead to therapeutics for Parkinson's. Dr. Siyu Chen will use cryo-EM and cryo-ET to study LRRK2 and its mutants in biochemical reconstitutions and in cells. Dr. Chen will conduct these experiments in Dr. Elizabeth Villa's lab at the University of California, San Diego. These experiments will directly visualize the molecular mechanisms of LRRK2 and interacting partners' function in the cell, and how pathogenic mutations disrupt these processes. Therefore, Dr. Chen's research may inform on novel therapies for Parkinson's disease.

As a graduate student in Dr. Yuan He's lab at Northwestern University, Chen studied DNA double-strand break repair. Specifically, Dr. Chen used Cryo-EM to solve two key intermediate states in the non-homologous end-joining pathway (NHEJ). These structures revealed novel interaction surfaces between NHEJ proteins and allowed Dr. Chen to propose a near complete reaction cycle for NHEJ. Dr. Chen will now apply his cryo-EM expertise to LRRK2 and will use cryo-ET to visualize LRRK2 in cells.

FELLOW

KATHERINE DEETS, Ph.D.

LABORATORY OF DR. NELS ELDE
DEPARTMENT OF HUMAN GENETICS
UNIVERSITY OF UTAH

JANE COFFIN CHILDS-HHMI FELLOW

A wide range of organisms – such as nematodes, sea anemones, and bacteria – possess immune defenses to protect themselves against infectious microbes and viruses. Yet studying the interactions between hosts and infectious microbes remains limited to a handful of species. Dr. Katherine Deets will expand this list by examining the interactions between Tetrahymena *thermophila* and viruses in Dr. Nels Elde's lab at the University of Utah. Dr. Deets is currently identifying novel viruses that infect Tetrahymena, and working to understand how *Tetrahymena* defend themselves against these viruses. This research will unlock a new experimental platform with powerful genetic tools for diversifying studies of the evolution of host-virus interactions.

As a graduate student, Deets investigated host-microbe interactions in the context of the mouse small intestine in Dr. Russell Vance's lab at the University of California, Berkeley. Dr. Deets discovered a novel mode of antigen presentation that only occurs following inflammasome activation. This finding revealed a new connection between innate and adaptive immunity in the intestine. Dr. Deets will use her experience in host-microbe interactions to expand our understanding of immune defense in diverse.

FELLOW

ROCKY DIEGMILLER, Ph.D.

LABORATORY OF DR. STEFANO DI TALIA
DEPARTMENT OF CELL BIOLOGY
DUKE UNIVERSITY

JANE COFFIN CHILDS FELLOW

Many animals, including zebrafish, have the ability to regenerate limbs, tails, or fins following amputation. The regeneration process is thought to faithfully reconstruct the appendage, yet it is unknown how spatial and temporal dynamics in gene expression and cell-signaling pathways control regrowth. Dr. Rocky Diegmiller will use quantitative imaging approaches to investigate morphological and patterning dynamics in regrowth of the paired zebrafish pectoral fin. Diegmiller will conduct these studies in Dr. Stefano Di Talia's and Dr. Kenneth Poss' labs at Duke University. Diegmiller will explore how gene expression patterns are re-formed following amputation, and throughout regeneration. These studies will reveal insights into the dynamics and robustness of regeneration, and will dissect how multiple signaling pathways are integrated to ensure faithful regeneration. Furthermore, these studies will generate quantitative tools for studying regeneration that can be applied to other systems.

As a graduate student, Diegmiller used mathematical models and imaging to investigate developmental biology in Dr. Stanislav Shvartsman's lab at Princeton University. Specifically, Dr. Diegmiller used the Drosophila germline cyst as a model system to investigate cell polarity and the emergence of symmetry breaking mechanisms in cell clusters. With his multidisciplinary background in developmental biology, Dr. Diegmiller hopes his research will also yield important connections and distinctions between developmental and regenerative pathways.

FELLOW

MARTIN DOUGLASS, Ph.D.

LABORATORY OF DR. ERIC SKAAR
DEPARTMENT OF PATHOLOGY, MICROBIOLOGY, AND IMMUNOLOGY
VANDERBILT UNIVERSITY MEDICAL CENTER

JANE COFFIN CHILDS FELLOW

Clostridioides difficile infection (CDI) is the leading cause of hospital-acquired and antibiotic-associated intestinal infections. However, we do not currently have a clear understanding of CDI pathogenesis, which impedes the development of additional therapeutic strategies. Dr. Martin Douglass will investigate how CDI overcomes the human microbiota and immune system in Dr. Eric Skaar's lab at Vanderbilt University Medical Center. Dr. Douglass will examine how CDI competes for nutrients with the microbiota and immune system. Furthermore, Dr. Douglass will identify which CD genes are required for host colonization and persistence. These studies may provide insight into novel therapeutic targets for treating CDI.

As a graduate student in Dr. M. Stephen Trent's lab at the University of Georgia, Douglass examined the outer membrane of Gram-negative bacteria. Dr. Douglass discovered novel proteins that are required for the transport of lipids to the outer membrane. These studies provide potential therapeutic targets for novel antibiotics and provide Douglass with a solid foundation for interrogating new targets in CDI.

FELLOW

LEAH ELIAS, Ph.D.

LABORATORY OF DR. SETH BLACKSHAW
DEPARTMENT OF NEUROSCIENCE
JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

JANE COFFIN CHILDS FELLOW

Sleep disorders are common and negatively impact our quality of life and biological health. Yet, how the brain encodes the need for restorative sleep is poorly understood. Dr. Leah Elias will investigate the cellular circuits and molecular signals that encode sleep pressure in Dr. Seth Blackshaw's lab at Johns Hopkins University School of Medicine. Using single nucleus RNA sequencing, Dr. Elias has identified a cluster of neurons that are activated by sleep deprivation. Furthermore, she has identified candidate genes that are differentially regulated in response to sleep deprivation. She will leverage these findings to mechanistically dissect sleep signals in the brain at the cellular and molecular levels. Dr. Elias' research has important implications for the basic biology of sleep and may reveal novel therapeutic targets for sleep and metabolic disorders.

As a PhD student in Dr. Ishmail Abdus-Saboor's lab at the University of Pennsylvania, Dr. Elias studied the neural circuitry controlling social touch. Specifically, she identified a new pathway that connects social touch in the skin to reward circuits in the brain. With this background in neural circuitry, Dr. Elias will now investigate how the need for sleep is encoded in the brain.

FELLOW

SHENG FENG, Ph.D.

LABORATORY OF DR. ERIC KOOL
DEPARTMENT OF CHEMISTRY
STANFORD UNIVERSITY

JANE COFFIN CHILDS-MERCK FELLOW

c-Myc is a transcription factor and an attractive therapeutic target as it drives the majority of human cancers. However, inhibiting c-Myc at the protein level is difficult, in part due to its intrinsically disordered structure. Dr. Sheng Feng aims to circumvent this problem by inhibiting c-Myc mRNA with small molecules. Dr Feng will use a fragment-based approach using an RNA-biased library that is functionalized to improve affinity for RNA. Dr. Feng will tether fragments that bind to adjacent RNA sites to improve binding affinity and selectivity. These experiments will be conducted in Dr. Eric Kool's lab at Stanford University. Dr. Feng's research will explore a new route for inhibiting an important target in oncology and represents a general method for inhibiting other difficult protein targets.

As a graduate student in Dr. Stephen Buchwald's lab at the Massachusetts Institute of Technology, Feng developed copper hydride-catalyzed bond forming reactions that are highly regio- and stereoselective. Such reactions produce important substructures for pharmaceuticals, agrochemicals, and natural products. Dr. Feng's background in organic chemistry has prepared her to design and prepare small molecule ligand libraries for targeting c-Myc mRNA.

FELLOW

MICHELLE FRY, Ph.D.

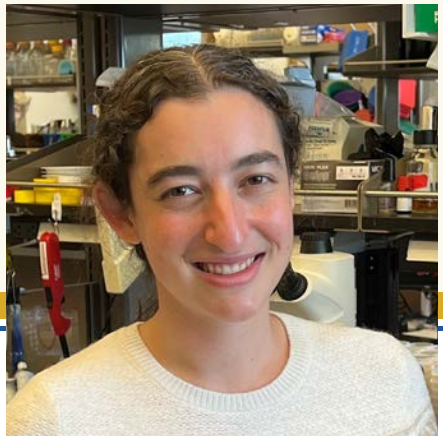
LABORATORY OF DR. LUKE CHAO
DEPARTMENT OF MOLECULAR BIOLOGY
MASSACHUSETTS GENERAL HOSPITAL

JANE COFFIN CHILDS FELLOW

Mitochondria generate energy needed to power cells and multicellular organisms. Wrinkles in the inner mitochondrial membrane, known as cristae, concentrate molecular motors for energy production. However, it is unclear how the wrinkly cristae are formed. Dr. Michelle Fry will use a clever approach to investigate cristae formation in cells. She will introduce candidate protein/protein complexes into parasitic protist mitochondria. These mitochondria are smooth, making them amenable for testing with proteins are sufficient to generate cristae. Dr. Fry will use advanced electron microscopy techniques to image changes in mitochondrial morphology. Fry will conduct these studies in Dr. Luke Chao's lab at Massachusetts General Hospital. These experiments will provide fundamental insights into mitochondrial biology and may provide clues for mitochondrial pathological dysfunction.

As a graduate student in Dr. Bil Clemons lab at the California Institute of Technology, Fry used structural biology to study the targeting of membrane proteins to the endoplasmic reticulum. Specifically, Dr. Fry captured several structural conformations of a protein chaperone, Get3. Fry demonstrated how conformational flexibility is important for Get3 to integrate multiple regulatory signals (binding partners, client proteins, nucleotide binding and hydrolysis). Dr Fry is now excited to use cryo-electron tomography to capture the conformational landscape of proteins that regulate mitochondrial cristae formation in cells.

FELLOW



NAOMI GENUTH, Ph.D.

LABORATORY OF DR. ANDREW DILLIN
DEPARTMENT OF MOLECULAR & CELL BIOLOGY
UNIVERSITY OF CALIFORNIA, BERKELEY

JANE COFFIN CHILDS-HHMI FELLOW

Aging is a complex physiological process coordinated across tissues within an organism. Loss of protein homeostasis is a hallmark of aging, yet it is not understood why dysregulation in protein synthesis occurs, and if this dysregulation drives aging pathologies. Dr. Naomi Genuth will investigate these questions in Dr. Andrew Dillin's lab at the University of California, Berkeley. Dr. Genuth will use *C. elegans* to visualize protein synthesis patterns in vivo in different tissues during the aging process. Ultimately, Genuth aims to define the molecules that contribute to dysregulation of protein synthesis and see whether manipulation of these molecules can delay and/or prevent the aging process. Dr. Genuth's research will improve our understanding of changes in protein synthesis during aging at the molecular, cellular, and organismal levels, and may reveal new therapeutic strategies for aging pathologies.

As a Ph.D. student in Dr. Maria Barna's lab at Stanford University, Genuth investigated the role of translational regulation in gene expression. Specifically, she developed a quantitative roadmap of how ribosome composition changes during human embryonic stem cell differentiation. Dr. Genuth will now investigate protein synthesis during aging in Dr. Dillin's lab.

FELLOW

NITSAN GOLDSTEIN, Ph.D.

LABORATORY OF DR. FAN WANG
McGOVERN INSTITUTE FOR BRAIN RESEARCH
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

JANE COFFIN CHILDS FELLOW

Medication for chronic pain often leads to addiction. Dr. Nitsan Goldstein thinks this may be because around one third of people experiencing chronic pain also suffer from anxiety. Additionally, anxiety is a strong predictor of chronic pain development. Dr. Goldstein predicts that targeting pain and pain-induced anxiety together may reduce chronic pain symptoms. She has identified neurons that are anxiolytic and will test their functional relationship with pain-induced anxiety and a chronic pain-like state. Goldstein will conduct her experiments in Dr. Fan Wang's lab at the Massachusetts Institute of Technology. Dr. Goldstein hopes that investigating both the central and peripheral causes of chronic pain and anxiety will open avenues for more effective pain treatments.

As a graduate student in Dr. J. Nicholas Betley's lab at the University of Pennsylvania, Goldstein investigated how the brain regulates food intake. Specifically, Dr. Goldstein discovered that the activation of hunger circuits enhances dopamine release, which is critical for motivating humans to seek rewards like food. These studies helped reveal new relationships between neural programs and have prepared Dr. Goldstein to investigate the relationship between chronic pain and anxiety.

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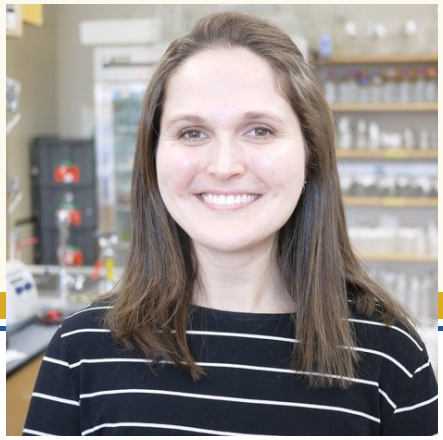

CHANTAL GUEGLER, Ph.D.

LABORATORY OF DR. L. STIRLING CHURCHMAN
DEPARTMENT OF GENETICS
HARVARD MEDICAL SCHOOL

JANE COFFIN CHILDS FELLOW

mRNA degradation is an important step in gene expression that is traditionally thought to occur in the cytoplasm. However, a recent genome-wide study uncovered a class of genes whose transcripts are predicted to be primarily degraded in the nucleus. Yet, it is unclear how and why these mRNAs undergo nuclear degradation. Dr. Chantal Guegler will use both candidate- and screening-based approaches to determine which pathways are important for nuclear mRNA degradation, and how this process influences cellular physiology. Dr. Guegler will conduct this research in Dr. Stirling Churchman's lab at Harvard Medical School. This work will reveal the key determinants of nuclear mRNA degradation and how this process contributes to gene expression regulation.

As a graduate student, Guegler studied bacterial toxin-antitoxin (TA) systems and their role in protecting against bacteriophage infection in Dr. Michael Laub's lab at the Massachusetts Institute of Technology. There, Dr. Guegler demonstrated that the RNase toxin ToxN cleaves phage mRNAs to disrupt the translation and assembly of viral particles. Interestingly, Guegler also demonstrated that T4 phage can combat ToxN using the phage-encoded antitoxin TifA that sequesters RNA-bound ToxN to prevent it from degrading additional phage mRNAs. With her background in RNA degradation in bacterial TA systems, Dr. Guegler will now investigate nuclear mRNA degradation in eukaryotic cells.

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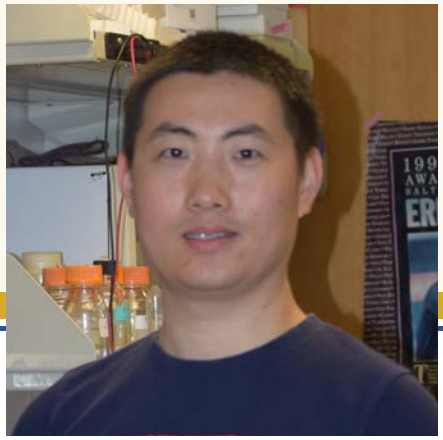

CHANGKUN HU, Ph.D.

LABORATORY OF DR. SUE BIGGINS
BASIC SCIENCES DIVISION
FRED HUTCHINSON CANCER CENTER

JANE COFFIN CHILDS-HHMI FELLOW

Aneuploidy is a hallmark of cancer development and occurs due to defects in chromosome segregation. The kinetochore, a complex consisting of over 100 different types of proteins, is required for the proper segregation of chromosomes. However, we lack an in depth understanding of the step-by-step assembly process resulting in a functional kinetochore due to the extreme molecular and temporal complexity of this complex. Dr. Changkun Hu will reconstitute kinetochore assembly in vitro and use TIRF microscopy to measure individual kinetochore protein recruitment times in Dr. Sue Biggins' lab at the Fred Hutch. This approach will allow Dr. Hu to determine rate-limiting steps and key regulating mechanisms in kinetochore assembly and will serve as a blueprint for future studies examining the assembly of other large complexes. Furthermore, this work may reveal novel trouble points in chromosome segregation that lead to aneuploidy in cancer.

As a PhD student in Dr. Nicholas Wallace's lab at Kansas State University, Dr. Hu's research focused on the repair of DNA double-strand breaks (DSBs). Dr. Hu demonstrated that beta human papillomavirus type 8 protein E6 (8E6), long known to impair traditional DNA-repair pathways, also promotes DNA repair via a mutagenic DSB repair pathway termed alternative end joining. In this way, 8E6 promotes cancer development by increasing genomic instability. Dr. Hu will now pivot to study genome stability at the chromosome level in Dr. Biggins' lab.

FELLOW

ALLISON KANN, Ph.D.

LABORATORY OF DR. MANSI SRIVASTAVA
DEPARTMENT OF ORGANISMIC AND EVOLUTIONARY BIOLOGY
HARVARD UNIVERSITY

JANE COFFIN CHILDS FELLOW

Many animals are capable of whole-body regeneration, enabling the regrowth of missing structures to their original size and shape after major amputation. Most studies investigating this phenomenon have focused on the transcriptional control of differentiation from adult pluripotent stem cells. However, Dr. Allison Kann predicts that an important, yet underappreciated, aspect of regeneration is the role of cell adhesion. Regeneration from stem cells requires free progenitor cells to unite and integrate into multicellular tissues and organs. Dr. Kann will use *Hofstenia miamia*, a genetically tractable invertebrate model system to investigate the disassembly, formation, and remodeling of cellular junctions during regeneration. Kann will conduct these studies in Dr. Mansi Srivastava's lab at Harvard University. These studies will reveal new principles of regeneration and identify mechanisms that cells use to converge into multicellular structures.

As a graduate student in Dr. Robert Krauss' lab at Icahn School of Medicine at Mount Sinai, Kann investigated the activation of muscle stem cells. She identified that cytoskeletal regulation is a key driver of muscle stem cell fate decisions and demonstrated how stem cells transduce injury signals into activation. With her background in adult stem cell biology, Dr. Kann is now ready to investigate how cellular interactions between progenitor cells regulate organismal regeneration.

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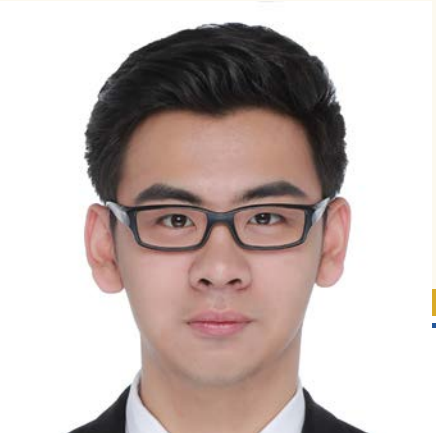


XINYU LING, Ph.D.

LABORATORY OF DR. SIDI CHEN
DEPARTMENT OF GENETICS
YALE UNIVERSITY

JANE COFFIN CHILDS-MERCK FELLOW

Dr. Xinyu Ling aims to improve cellular immunotherapies targeting solid tumors in Dr. Sidi Chen's lab at Yale University. To date, cellular immunotherapies have shown unsatisfactory results in treating solid tumors due to the immunosuppressive tumor microenvironment. Furthermore, CRISPR screening is a powerful tool for the identification of new cancer immunotherapy targets. However, existing approaches are limited in which types of cells can be targeted and in understanding the spatial arrangement of those cells. Dr. Ling will develop a versatile CRISPR screening method that will allow for simple "plug-and-play" targeting of many different cell types. The resulting platform will expand the use of CRISPR screening tools for cancer immunotherapies and may lead to the discovery of novel immunotherapy targets.

As a PhD student in Dr. Tao Liu's lab at Peking University, Ling used unnatural amino acid technology to improve the genome-editing and cost efficiencies of CRISPR Cas9/Cas12a genome editors. This prior experience in optimizing genome engineering strategies will assist Dr. Ling in developing an agile cellular targeting platform to identify novel cancer immunotherapy targets.

FELLOW

JOSE OROZCO, M.D., Ph.D.

LABORATORY OF DR. LEWIS CANTLEY
DEPARTMENT OF CANCER BIOLOGY
DANA-FARBER CANCER INSTITUTE

JANE COFFIN CHILDS FELLOW

Organisms adapt to scarce and bountiful nutrient environments by employing nutrient signaling pathways. Sugar is a rich source of energy and carbon for organisms, Dr. Jose Orozco will explore sugar-sensing pathways using biochemical and genetic approaches to discover sugar-regulated kinases and their roles in metabolic adaptation. Dr. Orozco will conduct his work in Dr. Lewis Cantley's lab at Dana-Farber Cancer Institute. These studies may reveal a new therapeutic target to alleviate metabolic maladaptive responses to the chronic overconsumption of sugars and carbohydrates.

As a graduate student in Dr. David Sabatini's lab at Massachusetts Institute of Technology, Orozco investigated the nutrient-regulated pathway that controls the target of rapamycin complex 1 (mTORC1) kinase. Specifically, Dr. Orozco discovered a new amino acid sensor that integrates S-adenosylmethionine levels, identified a metabolic product of glycolysis that communicates with mTORC1, and discovered new genes in the mTORC1 pathway. Dr. Orozco will continue pursuing his interests in the link between metabolism and signal transduction pathways in his investigations of MondoA .

FELLOW

MARK PLITT, Ph.D.

LABORATORY OF DR. YVETTE FISHER
DEPARTMENT OF MOLECULAR AND CELL BIOLOGY
UNIVERSITY OF CALIFORNIA, BERKELEY

JANE COFFIN CHILDS FELLOW

As we learn new behaviors, we still have to remember old behaviors as well. Thus there is a tension between the flexibility in learning and the stability of maintaining behaviors. Dr. Mark Plitt proposes that neural circuits resolve this tension by using neuromodulation to adaptively switch between stable and labile states. He will investigate these questions in Dr. Yvette Fisher's lab at the University of California, Berkeley. There, Dr. Plitt will use a fly's head direction circuit – a neuronal representation of the fly's orientation in space – to investigate the tradeoffs between flexibility and stability. Dr. Plitt predicts that different neurotransmitters will reinforce learning and maintenance of memory. By developing this powerful model system, Dr. Plitt hopes to uncover physiological and computational principles that govern flexible learning.

As a graduate student in Dr. Lisa Giocomo's lab at Stanford University, Plitt investigated hippocampal "place" cell remapping – a cellular process that encodes an animal's memory-guided navigation. Specifically, Dr. Plitt demonstrated that hippocampal remapping patterns are predictably driven by an animal's prior experience. This expertise in memory establishment will assist Dr. Plitt in investigating the tradeoff between stability and flexibility during adaptive learning.

FELLOW

CHINMAY PURANDARE, Ph.D.

LABORATORY OF DR. MASSIMO SCANZIANI
DEPARTMENT OF PHYSIOLOGY
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

JANE COFFIN CHILDS-HHMI FELLOW

The hippocampus is a mental GPS that uses visual information to determine relative location. However, the neural pathways that convey visual information to the hippocampus are unknown. Dr. Chinmay Purandare will investigate this information transmission in Dr. Massimo Scanziani's lab at the University of California, San Francisco. Dr. Purandare will use a novel set of visual cues, developed during his graduate studies, to directly activate hippocampal neurons and determine which visual brain regions are informing the hippocampus. Furthermore, Purandare would probe if the visual information conveyed is different depending on whether the subject is moving versus externally generated visual motion. Dr. Purandare's research will further our understanding of circuit level connections between visual pathways and the hippocampus.

As a graduate student in Dr. Mayank Mehta's lab at the University of California, Los Angeles, Purandare explored the minimal set of cues necessary for driving hippocampal responses. He developed novel visual stimuli and found that the hippocampus responds like sensory cortices when presented with these cues. This research led Dr. Purandare to the question of how these visual cues reach the hippocampus, which he will now explore in Dr. Scanziani's lab.

FELLOW

SAHANA RAO, Ph.D.

LABORATORY OF VAMSI MOOTHA, M.D.
METABOLISM PROGRAM
BROAD INSTITUTE OF MIT AND HARVARD

JANE COFFIN CHILDS-HHMI FELLOW

Oxidative phosphorylation is a central metabolic pathway that occurs within mitochondria. Decline in oxidative phosphorylation capacity is observed during aging and in many diseases. Dr. Sahana Rao aims to investigate how a tumor suppressor gene also suppresses mitochondrial biogenesis. Dr. Rao will also use a genome-wide screen to identify novel regulators of mitochondrial biogenesis. Rao will conduct these studies in Dr. Vamsi Mootha's lab at the Broad Institute. Collectively, these studies will provide insight into the regulation of mitochondrial biogenesis. They may also inform on mitochondrial dysregulation in aged or diseased states.

As a graduate student in Dr. Daniel Bachovchin's lab at Memorial Sloan Kettering Cancer Center, Rao investigated inflammasomes – innate immune sensors that detect pathogenic signals and form large signaling complexes to alert immune cells. Dr. Rao's studies elucidated molecular mechanisms of the activation of two inflammasome proteins, NLRP1 and CARD8, and established new tools to activate inflammasomes. With her extensive training as a chemical biologist, Rao will now study cellular metabolism and mitochondrial biogenesis in her postdoc.

FELLOW

ALEXANDRA SCHNELL, Ph.D.

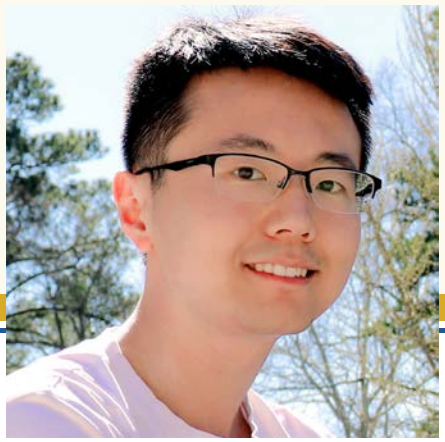
LABORATORY OF DR. JONATHAN WEISSMAN
WHITEHEAD INSTITUTE

JANE COFFIN CHILDS-HHMI FELLOW

Tumor-associated macrophages (TAMs) are the most abundant innate immune cell type in tumors. TAMs can either inhibit or support tumor progression, though it is unclear how their dichotomous functions are regulated. Dr. Alexandra Schnell predicts that the functional heterogeneity of TAMs may be due to distinct lineage origins and cell plasticity. To investigate these hypotheses, Dr. Schnell is developing a myeloid-specific lineage tracing tool to track TAM heterogeneity in tumors, and in response to immunotherapies. Schnell will conduct these experiments in Dr. Jonathan Weissman's and Dr. Kipp Weiskopf's labs at the Whitehead Institute. By better understanding TAM heterogeneity, Schnell hopes to enable the development of TAM-targeted cancer immunotherapies that specifically target tumor-promoting macrophages.

During her PhD, Schnell studied the fundamental mechanisms of the immune system in Dr. Vijay Kuchroo's lab at Harvard Medical School. There, Dr. Schnell performed lineage tracing of immune cells during autoimmune inflammation. Her studies provided a mechanism for how homeostatic intestinal immune cells act as a reservoir for pathogenic inflammation elsewhere in the body. With this background in immunity and lineage tracing, Dr. Schnell will now investigate how the heterogeneity of tumor immune cells can be leveraged to generate new cancer immunotherapies.

FELLOW



HONGLUE SHI, Ph.D.

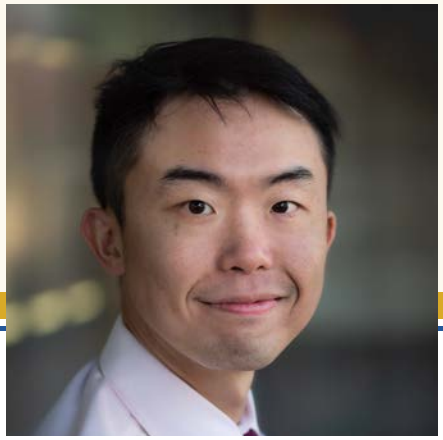
LABORATORY OF DR. JENNIFER DOUDNA
CALIFORNIA INSTITUTE FOR QUANTITATIVE BIOSCIENCES
UNIVERSITY OF CALIFORNIA, BERKELEY

JANE COFFIN CHILDS-HHMI FELLOW

CRISPR-Cas enzymes are versatile tools for gene editing and research applications such as transcriptional regulation and imaging. The speed and accuracy of CRISPR-Cas enzymes are crucial, yet how they identify a unique ~20-base-pair target within billions of base pairs in the genome is still unclear. Dr. Honglue Shi aims to obtain a more quantitative and predictive understanding of how natural and engineered CRISPR-Cas enzymes rapidly and accurately target specific DNA sequences in Dr. Jennifer Doudna's lab at the University of California, Berkeley. Shi will use structure-guided biochemistry to develop a kinetic model for CRISPR-Cas9 search speed and accuracy. He will then test the generality of the model on additional CRISPR enzymes and ancestral RNA-guided TnpB enzymes. This research is fundamental to understanding both the evolutionary history of RNA-guided enzymes and the utility of these systems for genome editing. In the future, these results will enable predictions and design of genome editing functions that are not possible or practical today and will greatly accelerate the field as well as the precision and outcomes of next-generation genome editing tools.

As a Ph.D. student in Dr. Hashim Al-Hashimi's lab at Duke University, Shi focused on the development of biophysical approaches such as NMR spectroscopy to extend the description of nucleic acids from static structures to dynamic ensembles, which results in a deeper and more predictive understanding of how nucleic acids are being recognized by other biomolecules. Having developed this expertise in nucleic acid biophysics and perspectives in dynamic ensembles, Dr. Shi is ready to elucidate the properties that define the best genome editors in Dr. Doudna's lab.

FELLOW



ADAM WEI JIAN SOH, Ph.D.

LABORATORY OF DR. DAVID SHERWOOD
DEPARTMENT OF BIOLOGY
DUKE UNIVERSITY

JANE COFFIN CHILDS FELLOW

Dr. Adam Wei Jian Soh will investigate how the basement membrane (BM), a sheet-like extracellular matrix that encloses tissues, stretches in mechanically-active tissues in Dr. David Sherwood's lab at Duke University. Dr. Soh will use C elegans ovulation as a novel model system for examining BM stretching and recovery. Soh has performed a localization screen and identified candidate proteins that are likely important for BM dynamics. He will follow up on these findings by determining which proteins are functionally important for the stretching and recovery of BMs. Soh hypothesizes that type IV collagen is critical for stretching tissues as genetic defects in this gene lead to vasculature hemorrhaging and muscle dysfunction. This research may also identify novel genes that are critical for tissue support and are mutated in human disease.

Previously, Dr. Soh investigated the mechanics of motile cilia beating as a PhD student in Dr. Chad Pearson's lab at the University of Colorado Anschutz Medical Campus. Specifically, he discovered a novel intracellular mechanism involving the cortical cytoskeleton network that regulates cilia beating synchronization. Through this research Soh developed expertise in imaging techniques and cellular biophysics. This experience has prepared Dr. Soh for his current project dissecting basement membrane dynamics.

FELLOW

XULU SUN, Ph.D.

LABORATORY OF DR. LOREN FRANK
DEPARTMENT OF PHYSIOLOGY
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

JANE COFFIN CHILDS-HHMI FELLOW

When planning or troubleshooting, we often contemplate possible actions and imagine their outcomes based on prior knowledge. The hippocampus has been implicated in our ability to imagine possible futures, yet it is unclear how future representations are regulated and what functions they subserve. Dr. Xulu Sun will explore the anatomical underpinnings, mechanistic control, and functional significance of hippocampal future representations in Dr. Loren Frank's lab at the University of California, San Francisco. Dr. Sun will use behavioral tasks and multiregional electrophysiology to explore how the hippocampus interacts with other brain regions to enable future representations and how these representations may support flexible planning. This process is impaired in many neuropsychiatric disorders such as schizophrenia. Thus, Dr. Sun's research of the underlying neuroscience may reveal new strategies for treating such disorders.

As a PhD student in Dr. Krishna Shenoy's lab at Stanford University, Sun investigated dexterous movement control. There she used behavioral tasks and large-scale neural recordings to show how the cortical motor system implements a behavior-organizing map in rhesus monkeys. Dr. Sun will now use her strong foundation in neural computations to explore the neural basis of future representations.

FELLOW

JEFFREY SWAN, Ph.D.

LABORATORY OF DR. ELIZABETH H. KELLOGG
DEPARTMENT OF MOLECULAR BIOLOGY AND GENETICS
CORNELL UNIVERSITY

JANE COFFIN CHILDS FELLOW

CRISPR-associated transposons (CASTS) enable programmable DNA insertion, yet there is a limited understanding of how they recognize specific DNA sequences and activate DNA insertion. Dr. Jeffery Swan will conduct structural and kinetic studies of CASTs in Dr. Elizabeth Kellogg's lab at Cornell University. Dr. Swan will investigate the AAA+ (ATPases Associated with diverse cellular Activities) regulator TnsC which influences both ATP hydrolysis and DNA deformation. He will use cryo-electron microscopy to structurally characterize the fully assembled integration complex, and single-molecule and ensemble kinetic experiments to better understand transpososome assembly and activation. Swan anticipates that these studies will guide future attempts to rationally engineer CASTs for gene-editing and therapeutic applications.

As a Ph.D. student in Dr. Carrie Partch's lab at the University of California at Santa Cruz, Swan investigated the role of the KaiC, an AAA+ protein that effectuates circadian timing. Dr. Swan demonstrated that the ATPase activity in KaiC imparts cooperativity to the transition between autophosphorylation and autodephosphorylation, which is an important feature of the circadian clock. With his expertise in AAA+ proteins, Dr. Swan is ready to investigate how TnsC enables the programmable DNA insertion of CASTs.

FELLOW

MABEL TETTEY, Ph.D.

LABORATORY OF DR. MICHAEL GRIGG
SECTION OF MOLECULAR PARASITOLOGY
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

JANE COFFIN CHILDS FELLOW

In disease-causing organisms, hybridization allows for the transfer of traits such as virulence and drug resistance. Dr. Mabel Tettey will investigate how hybridization impacts African trypanosomiasis outbreaks caused by the parasite *Trypanosoma brucei*. Dr. Tettey will assess the degree of hybridization occurring in African trypanosome endemic areas, explore the impact of hybridization on virulence, and identify the key molecules involved in this process. She will conduct these experiments in Dr. Michael Grigg's lab at the National Institute of Allergy and Infectious Diseases. These studies may enable the development of effective disease control strategies against African trypanosomes.

As a graduate student in Dr. Keith Matthews' lab at the University of Edinburgh, Tettey examined the function of released peptidases in the transmission of African trypanosomes. Specifically, Dr. Tettey identified the genes that dominate quorum sensing signal in African trypanosomes. With her extensive background in trypanosome biology, Dr. Tettey will now examine the role of hybridization in trypanosome virulence.

FELLOW

PETRA VANDE ZANDE, Ph.D.

LABORATORY OF DR. ANNA SELMECKI
DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY
UNIVERSITY OF MINNESOTA

JANE COFFIN CHILDS FELLOW

The human pathogen *Candida albicans*' genome varies substantially between clinical isolates, yet it is currently unknown how this variation affects infection. Since many genetic variants are located in gene regulatory sequences, Dr. Petra Vande Zande predicts that there is substantial divergence in gene-regulatory networks between different *C. albicans* isolates that modifies their fitness. Dr. Vande Zande will use gene expression data from different isolates to model gene regulatory networks and identify key differences that impact fitness. Vande Zande will conduct these experiments in Dr. Anna Selmecki's lab at the University of Minnesota. This research will provide direct insight into genetic differences that impact *C. albicans* infections. It may also provide clues into other genetically diverse systems with differences in gene-regulatory networks, including human cancers.

As a graduate student in Dr. Patricia Wittkopp's lab at the University of Michigan, Vande Zande studied gene expression in the context of adaptive evolution. In particular, Dr. Vande Zande discovered that mutations affecting a gene's expression from a distance are more pleiotropic and more detrimental to fitness than mutations occurring proximally to the gene of interest. With her experience in the evolution of gene expression, Dr. Vande Zande is now interested in understanding divergence in gene-regulatory networks between different clinical isolates of yeast infections.

FELLOW

PABLO VILLAR, Ph.D.

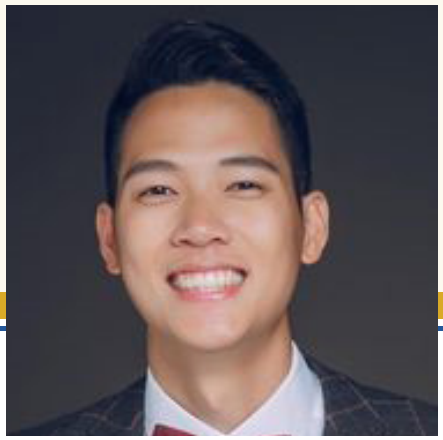
LABORATORY OF DR. NICHOLAS BELLONO
DEPARTMENT OF MOLECULAR AND CELLULAR BIOLOGY
HARVARD UNIVERSITY

JANE COFFIN CHILDS FELLOW

Cells detect and transform specific external stimuli into precise biochemical functions in a process termed signal transduction. Sensory systems are one example of signal transduction. Dr. Pablo Villar will investigate a unique sensory system: octopus chemotactile receptors that mediate contact-dependent aquatic chemosensation. Dr. Villar will use single-cell sequencing, cryo-EM, and physiology to investigate the molecular logic of receptor expression, complex formation, and physiological function in cephalopods. These experiments will be conducted in Dr. Nicholas Bellono's lab at Harvard University. Villar's studies will reveal general principles for the evolutionary fine tuning of signal transduction and help connect adaptations in protein structure with octopus behavior.

As a graduate student in Dr. Ricardo Araneda's lab at the University of Maryland, Villar examined how neuromodulatory brain regions regulate circuits that process sensory information. Specifically, Dr. Villar showed that the basal forebrain activates shortly after the onset of a sensory stimuli, and in a stimulus-specific manner. With this experience in neuroscience and sensory stimuli, Villar will now examine the signal transduction of stimuli at a molecular level in cephalopods.

FELLOW



KEVIN WU, Ph.D.

LABORATORY OF DR. EUNYONG PARK
DEPARTMENT OF MOLECULAR AND CELL BIOLOGY
UNIVERSITY OF CALIFORNIA, BERKELEY

JANE COFFIN CHILDS FELLOW

The endoplasmic reticulum (ER) is a critical organelle for maintaining protein quality control in cells; misfolded proteins are targeted for degradation through the ER-associate degradation (ERAD) pathway. Dr. Kevin Wu will study the ER-membrane bound E3 ubiquitin ligase Doa10 in Dr. Eunyong Park's lab at the University of California, Berkeley. Doa10 is conserved from yeast to humans and identifies and targets many misfolded proteins for degradation. However, it is unclear how Doa10 recognizes a wide range of client proteins. Dr. Wu will use biochemical and structural approaches to reveal how Doa10 recognizes and processes a range of substrates, and how Doa10 cooperates with other quality control factors to maintain protein homeostasis. Protein misfolding and aggregation are associated with aging and diseases such as neurodegeneration. Thus, Wu's studies may have implications for developing future therapies to improve protein homeostasis in human disease.

As a graduate student in Dr. James Bardwell's lab at the University of Michigan, Wu investigated chaperone-mediated protein folding. There, he discovered that weak binding between ATP-independent chaperones enable the refolding of client proteins, whereas stronger binding hinders refolding. Dr. Wu's background in protein refolding set him up for exploring how Doa10 E3 ubiquitin ligase recognizes unfolded protein targets.

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