

## Smith Family Awards Program for Excellence in Biomedical Research 2019 Award Recipients

- **Judith Agudo, Ph.D.**

Assistant Professor

*Dana-Farber Cancer Institute*

“Novel platform to increase dendritic cell function and antigen-specific T cell responses to cancer”

Key Words: innate immunity, antigen presentation, dendritic cells, viral vectors, gene editing, immunotherapy

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Immunotherapy has revolutionized cancer treatment as it has achieved remission in patients in which nothing else had worked. Despite many successful results, some patients do not respond or just do it temporarily. Thus, immunologists and cancer biologists are investigating mechanisms controlling resistance to immunotherapy. In this regard, T cells have drawn most of the attention from the scientific community as they are the major final effectors that can kill cancer cells. However, T cell mediated adaptive immune responses relies on the capacity of innate immune cells, such as dendritic cells, of picking up antigen, process it and present it to them. Notably, T cells are much more abundant in the tumor microenvironment than dendritic cells, which often represent just a minuscule population, but a lack of dendritic cells completely abrogates anti-tumor immunity. Despite their obvious importance, studies on dendritic cells are minimal compared to those on T cells, mostly in a cancer setting. A major reason is the difficulty to work with such a minute population and the lack of suitable tools for their genetic manipulation. Indeed, delivery of genetic tools, such as viral vectors, results in dendritic cell activation prior to their response to cancer or infection, as they sense them as pathogens. To overcome this limitation, here we propose to take advantage of a novel platform we have established to safely transduce dendritic cells in order to uncover key molecular underpinnings governing their ability to respond to danger signals. Moreover, we will also exploit a unique technology that we recently developed to unequivocally identify dendritic cells with a cancer-derived cargo and identify new regulators of antigen uptake and presentation to T cells. Our work will enable the discovery of new relevant factors in DC function, setting the path to new therapeutic avenues to improve current immunotherapies and vaccines.

- **Lillian Fritz–Laylin, Ph.D.**

Assistant Professor of Biology

*University of Massachusetts Amherst*

“Defining Mechanisms of Pathogenesis of the “Brain–eating Amoeba””

Key Words: Cell biology, Pathogenesis, Cytoskeleton

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The “brain–eating amoeba” *Naegleria fowleri* is an NIAID Priority Category B Pathogen that carries a 95% fatality rate, yet the mechanisms underlying its pathogenic behaviors remain largely unstudied. Because of the urgent need for safe therapeutics, our long–term goal is to define the cellular and molecular basis of *Naegleria* pathogenesis. Unlike human cells, from which *Naegleria* diverged 1–2 billion years ago, these amoebae do not possess cytoplasmic microtubules. This suggests that the actin cytoskeleton, assembled by the Arp2/3 complex and formin family proteins, is the primary driving force for cellular behaviors that are essential to cell survival and pathogenesis. The overall objective of this application is to test the hypothesis that actin cytoskeletal rearrangements promote three key pathogenic behaviors: cell motility, which is important for establishing infection, contractile vacuole pumping, which is required for surviving osmotic pressure, and cell division, which is critical for robust colonization in the brain. To test this hypothesis, we will carry out the following specific aims: (Aim 1) determine the contributions of the Arp2/3 complex and its activators to cell motility, (Aim 2) define the formin–based mechanisms governing contractile vacuole dynamics, and (Aim 3) identify the actin nucleators and molecular mechanisms responsible for cytokinesis. For each aim, we will use multiple orthogonal cellular perturbations, including small molecule inhibitors to impair the Arp2/3 complex and formin family proteins, individual gene targeting using morpholinos, and physical environmental perturbations. We will measure phenotypes of individual cells in detail using fluorescent microscopy, and complement this high–resolution approach by collecting quantitative data on entire cell populations with flow cytometry and gene expression assays. Because the cell biology underlying pathogenesis and basic functions in *Naegleria* is severely understudied, defining how actin orchestrates motility, division, and contractile vacuole dynamics is critical for uncovering drug targets to treat these deadly infections.

- **James Jeanne, Ph.D.**

Assistant Professor of Neuroscience  
*Yale University*

“Cracking the neural code for perception by writing spikes into neural circuits”

Key Words: Neuroscience, Olfaction, Neural coding, Synapse, Circuit, Optogenetics, 2-photon microscopy, Electrophysiology, *Drosophila melanogaster*.

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The long term objective of this project is to understand the relationship between sensation and action. Key to this relationship is the transformation of sensory stimuli into a “neural code,” a pattern of electrical activity across neurons that encodes information. Subsequently, downstream networks must decode (interpret and transform) this information to drive perception and behavior. Linking neural codes to their decoding by cellular and synaptic mechanisms has proven difficult. This is due to two challenges: causally perturbing the neural code with spatiotemporal precision and measuring the resulting activity from identified postsynaptic neurons.

Here, I propose to overcome these challenges by investigating how an olfactory neural code is decoded by its downstream network in a tractable experimental system: the fruit fly, *Drosophila melanogaster*. I have developed new approaches to “write” spike patterns into populations of central neurons with cellular resolution while recording from their postsynaptic target neurons. This enables direct causal control of precise spiking features of the olfactory neural population code. In Aim 1, I will identify the role of spike synchrony in driving downstream activity. In Aim 2, I will determine how postsynaptic neurons integrate presynaptic spiking over brief time gaps. In Aim 3, I will determine how postsynaptic neurons adapt their decoding to changing olfactory contexts. Together, these studies will reveal mechanisms by which the brain decodes its own neural code for olfaction.

Although there are differences between flies and mammals, the basic logic of neural coding is remarkably conserved. These similarities suggest that discoveries made in the fruit fly will be relevant to the mechanisms of neural decoding in other animals. A more thorough understanding of the principles of neural decoding within the brain has the potential to transform the development of novel brain-machine interfaces that could improve the outcomes of patients with brain injuries.

- **Laura Lewis, Ph.D.**

Assistant Professor of Biomedical Engineering  
*Boston University*

“Whole-brain dopamine dynamics underlying sleep and wakefulness”

Key Words: Neuroscience, Multimodal imaging, Arousal, Sleep, Neuromodulation, Networks

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Sleep transforms nearly every aspect of cognition and behavior. However, how and why sleep causes these complex cognitive and behavioral changes is still unclear. Small brainstem nuclei control sleep and wakefulness by releasing neuromodulatory substances such as dopamine. How dopamine acts upon large-scale brain networks to create the electrophysiological oscillations and behaviors that define sleep and wakefulness is not known.

This project aims to bridge neurochemistry and electrophysiology, to identify the links between release of neuromodulatory substances and large-scale brain network function in sleep and wakefulness. A major barrier to addressing this question is that conventional imaging techniques cannot simultaneously measure whole-brain dopaminergic tone and dynamic network activity. We will develop a multimodal imaging approach to simultaneously measure brainwide time-varying dopamine dynamics, electrophysiology, and activity in deep brain structures. We will then use this new technique to test a hypothesis for how dopamine acts on large-scale thalamocortical networks to alter perception and cognition.

This project will result in a new dynamic imaging method that can be broadly used to study the neuromodulatory activity that shapes brain network function and cognition, with the potential to illuminate many questions in systems neuroscience. It will also identify the relationship between the dynamics of dopamine release and the electrophysiological and behavioral signs of sleep, providing new insight into how the deep brain nuclei that control sleep and wakefulness lead to altered brain network function and behavior.

- **Jose Ordovas–Montanes, Ph.D.**

Assistant Professor of Pediatrics  
*Boston Children's Hospital*

“Inflammatory Memory and Adaptation in Human Intestinal Epithelial Stem Cells”

Key Words: Stem Cell, Cytokine, Inflammatory Memory, Human Immunology, scRNA-seq, Inflammatory Bowel Disease, Crohn's Disease, Organoids, Epithelial, Intestine

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For a barrier tissue to effectively learn from previous immunological experiences, it must sense, adapt, and store this information (i.e. memory), in readily accessible cell types. The baseline architecture of the human intestinal epithelium includes specialized cell subsets that collectively perform key tissue functions and arise from intestinal stem and progenitor cells (ISCs). This design principle is critical for responding to induced demands, together with the support of stromal and immune cells. However, this system becomes dysregulated with significant deviations from homeostasis in chronic inflammatory disease states driven by immune effector cytokines such as inflammatory bowel disease (IBD, including Crohn's disease). In recent experiments, I have set out to address whether inflammatory cytokines may also act directly on, and be remembered by, the tissue parenchyma. Using scRNA-seq and stem cell-based models, my work has provided the first-in-human evidence for cytokines acting to rewire tissue stem cells, which may serve as repositories for inflammatory memories, contributing to the persistence of disease.

The proposed Aims of this Smith Family Foundation Award will address whether and how human ISCs are capable of integrating and remembering immune effector cytokines during pediatric Crohn's disease. The successful completion of Aim 1 will position ISCs as key stores of inflammatory memory, and nominate intrinsic/extrinsic drivers. The successful completion of Aim 2 will unravel the intersection of canonical developmental and immunological pathways in mediating cell fate decisions at epithelial barriers, identifying decision points to target. More broadly, results derived from this Smith Award will enable these specific aims to turn into emergent principles of how inflammatory memory shapes tissue biology. Working towards these short- and long-term aims will aid in realizing a framework for inflammatory adaptation by mammalian tissues, with direct implications for chronic human diseases—an area in need of therapies beyond those targeting traditional immune mechanisms.

- **Lauren Orefice, Ph.D.**

Assistant Professor of Genetics  
*Massachusetts General Hospital*

“Development, Function and Dysfunction of Peripheral Sensory Neurons: Insights for Autism Spectrum Disorders.”

Key Words: Neuroscience, Development, Autism Spectrum Disorders, Somatosensation, Gastrointestinal System, Peripheral Sensory Neuron

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Autism spectrum disorders (ASD) are prevalent neurodevelopmental disorders defined by social impairments and restricted, repetitive behaviors. While ASDs are heterogeneous in etiology and severity, the majority of individuals with ASD also exhibit an array of co-morbid symptoms, including hypersensitivity to light touch and gastrointestinal dysfunction.

Previously, we used mouse models of ASD combined with behavior, anatomy, and electrophysiology to define the etiology of aberrant tactile sensitivity in ASD. We found that genetic mutations only in peripheral sensory neurons, and not neurons in the brain, account for touch over-reactivity in ASD models. Developmental touch hypersensitivity contributes to aberrant brain development, as well as anxiety and social interaction deficits in adulthood in three mouse models we studied. Selective restoration of peripheral sensory neuron function, using genetic, viral or pharmacological strategies, improves tactile hypersensitivity, anxiety-like phenotypes, and social deficits in mice. My work has revealed a novel locus of dysfunction in ASD and how aberrant function in peripheral sensory neurons can link multiple ASD phenotypes, leading to the exciting possibility of a therapeutic target.

I will study how peripheral sensory neuron dysfunction impacts brain development, core ASD features (anxiety, social impairments), and co-morbid ASD traits (tactile hypersensitivity, gastrointestinal disturbances). I will also develop therapeutic strategies targeting peripheral sensory neurons as a tractable approach for improving ASD core and co-morbid symptoms. My research program will iteratively combine genetics, behavior, anatomy, and electrophysiology in mice with induced pluripotent stem cell (iPSC)-based experiments. Specifically, my research will: 1) use animal models and ASD patient-derived iPSCs to study the prevalence, mechanisms and impact on brain development and behavior of peripheral somatosensory neuron dysfunction in ASD; 2) study gastrointestinal-nervous system interactions in ASD, focused on dysfunction of extrinsic spinal afferent sensory neurons; 3) develop therapies focused on peripheral sensory neuron abnormalities, using studies in mice and patient-derived iPSCs.