**Smith Family Awards Program for Excellence in Biomedical Research**
**2018 Award Recipients**

- **David Breslow, Ph.D.**
  Assistant Professor of Molecular, Cellular & Developmental Biology
  *Yale University*

  "Deconstructing the Cellular Antenna: Primary Cilium Disassembly and Control of Cell Growth"

  Key Words: Primary cilia, Cell cycle, Centrosome, Centriole, Cancer, Signaling, CRISPR, Functional genomics, Ciliopathy, Cell proliferation

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The primary cilium is a protrusion from the cell surface that serves as an organizing center for diverse signaling pathways. Cilia are required for embryonic development, and inherited ciliary defects cause pediatric disorders known as ciliopathies. Consistent with the many tissues impacted in ciliopathies, cilia are found on most cells in the human body. However, cilia are not constantly present; rather, they undergo regulated disassembly prior to mitosis and re-assemble after cell division. This regulated disassembly is observed across evolution and appears to be a key event in the cell cycle, as cilia are never observed on mitotic cells. Recent evidence further indicates that cilium disassembly controls cell cycle progression, acting like a checkpoint that blocks proliferation until disassembly is completed. Like other cell cycle checkpoints, deregulation of cilium disassembly may contribute to uncontrolled cell growth and cancer.

The possibility that cilium disassembly represents an uncharacterized cell cycle checkpoint raises many questions, including: what signals trigger cilium disassembly, what factors enable disassembly of the cilium's complex structural elements, how does an intact cilium delay cell cycle progression, and how do errors in these processes contribute to cancer and other diseases? Here, we plan to systematically investigate cell cycle-regulated cilium disassembly through high-resolution imaging of cilium disassembly, identification of gene products that control cilium disassembly, and mechanistic characterization of novel cilium disassembly factors. Together, these studies will provide a foundational characterization of cilium disassembly and of the critical connections between this process, the cell cycle, and disease.

- **Alan Brown, Ph.D.**
  Assistant Professor
  *Harvard Medical School*

"Structural Basis of Intraflagellar Transport"

Key Words: Cilia; Ciliopathy; Intraflagellar transport; Axoneme

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Cilia are slender projections on the surface of almost all eukaryotic cells. Their large membrane-to-volume ratios create ideal microenvironments to concentrate transmembrane receptors and their downstream effectors, and some signaling pathways reside exclusively within cilia. As a result, primary cilia dictate how we sense our environment: sight through the ciliated photoreceptor cells of the retina, smell through the cilia present on olfactory epithelia and sound through the kinocilium-propagated hair bundles of the inner ear. Some cilia are motile and beat rhythmically to produce a driving force for locomotion or fluid flow. In the human body, motile cilia have roles in fertility (propelling sperm and transporting the egg to the uterus), the immune system (clearing the respiratory tract of mucous), and the central nervous system (generating the flow of cerebrospinal fluid). Cilia are also essential for embryonic development.

My group aims to understand how molecules are transported within cilia to establish cilium-specific signal transduction pathways. To do this, we combine biochemical and structural approaches with an emphasis on high-resolution electron cryomicroscopy (cryo-EM). Here, we propose to reconstitute the dedicated transport mechanism of cilia known as intraflagellar transport (IFT) in vitro to build a testable platform from which we can interrogate the interplay between the microtubule doublets of the axoneme, motors, adaptor complexes, and cargoes. This system will be used to program complexes for cryo-EM analysis. Ultimately, we aim to build time-resolved, three-dimensional atomic movies of ciliary transport. These movies will be used for the development of therapeutics to manipulate IFT to repair cilia function in human ciliopathies.

- **Paul Greer, Ph.D.**
  Assistant Professor in the Program of Molecular Medicine
  *University of Massachusetts Medical School*

"Exploring the Role of a Novel Population of Microglia in Alzheimer's Disease"

Key Words: Microglia, Alzheimer's Disease, Chemoreceptor, single cell RNA sequencing, Neurodegeneration

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder that exacts a devastating toll on the individual with the disease, their family, and our society. In addition to being the fifth leading cause of death in the United States, current estimates suggest that the annual global costs associated with AD could soon exceed one trillion dollars. Nevertheless, despite considerable effort, existing therapeutic strategies targeting AD are highly limited in both number and efficacy, suggesting that novel approaches for preventing or treating AD are needed.

Recent human genetic studies have identified a small number of mutated AD susceptibility genes, which might be new drug targets for AD. At the top of this new list of AD-associated genes are members of the Ms4a gene family. In dozens of large-scale human genetic studies comparing individuals with AD to people without AD, mutations in Ms4a genes are amongst the most strongly and reproducibly linked genetic abnormalities that lead to altered susceptibility to AD. However, the physiological function of MS4A proteins and how Ms4a gene mutations alter susceptibility to AD are not known.

As a postdoctoral fellow, I recently uncovered the first clear function of MS4A proteins (Greer et al., Cell, 2016). I found that Ms4a genes encode a novel family of chemoreceptors, proteins that detect small molecules outside of the cell and relay the presence of those molecules to the cells in which they are expressed. Intriguingly, I have also recently discovered that MS4A receptors are expressed in microglia, the resident immune cells of the nervous system. While the specific role of microglia in AD is the subject of active debate, it is now widely accepted that these cells play a crucial role in AD, and thus the finding that Ms4as are expressed within these cells is of great interest. My goal in this proposal is to understand the biological role of MS4A proteins in microglia and to explore how Ms4a gene mutations lead to increased risk of AD. These experiments will both enhance our basic understanding of microglial biology and provide insight into how Ms4a mutations contribute to AD. Importantly, as MS4A receptors are potentially highly druggable targets, these experiments could offer a new therapeutic approach to treating or preventing AD.

- **Ankur Jain, Ph.D.**
  Assistant Professor of Biology
  *Whitehead Institute for Biomedical Research*

  "Identifying Cellular Suppressors of RNA Aggregation"

  Key Words: RNA aggregation, RNA chaperones, Helicases, Neurodegenerative disease, Trinucleotide expansion diseases

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Protein aggregation underlies numerous human diseases such as Alzheimer disease and Parkinsonism. In an analogous manner, RNA may also aggregate. Relatively little is known about the role of RNA aggregation in disease and how it is abated under physiological conditions. In previous research, I found that in diseases caused by nucleotide repeat expansions such as Huntington disease (CAG repeat expansion) and amyotrophic lateral sclerosis (GGGGCC repeat expansion), the mutant RNAs form aberrant intermolecular base-pairs and aggregate in cells (Jain & Vale, Nature, 2017).

Intriguingly, the aggregation propensity of RNA is lower in cells in comparison to pure RNA in test-tubes. Drawing parallels from protein aggregation, my hypothesis is that living systems may have developed mechanisms to keep RNA aggregation in check. I propose to identify and characterize the cellular factors that exhibit RNA disaggregation activity. I will use the pathogenic CAG-, and GGGGCC-repeat containing RNAs as model aggregation-prone transcripts. Using proteomics and genetic screens, I will investigate the putative cellular RNA disaggregases. These candidates will be evaluated for their functional activity in cells. Finally, I will develop biochemical assays to reconstitute the disaggregase activity in vitro using purified components. These assays will provide a stepping stone for future studies on the mechanisms of RNA disaggregases.

This work will help reveal the general principles that a cell employs to keep biomolecules soluble in the crowded sub-cellular environment. In addition, we may discover new genetic modifiers of repeat expansion disorders. Mutations in RNA chaperones are commonly observed in many neurodegenerative diseases, and our findings may have a direct impact on our understanding of disease mechanisms.

- **Tami Lieberman, Ph.D.**
  Assistant Professor of Medical Engineering and Science
  *Massachusetts Institute of Technology*

"Determinants of Bacterial Colonization of Facial Skin"

Key Words: Microbiome, Bacteria, Skin, Colonization, Mutations, Genomics, Population Biology

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Rational probiotic therapies for our gut, skin, and other microbiomes have the potential to treat a wide range of diseases and promote wellness. However, we remain limited in our ability to employ them, as we cannot predict which bacterial strains will stably colonize an individual. My lab seeks to close this knowledge gap, developing an understanding of how individual species and strains colonize in human microbiomes. We overcome the limitations of animal models by inferring recent bacterial behavior on and within individual people using mutations bacteria accumulate during colonization, and we overcome the limitations of metagenomics by using high-throughput culturing to achieve 'single-organism' resolution.

In the proposed study, we will use sebaceous skin (face, chest, back), as a tractable model system for mechanistic understanding of the determinants of colonization in human microbiomes. Adult sebaceous skin is dominated by Propionibacterium acnes, with many strains of P. acnes stably coexisting on each person, and this low species-level diversity makes exhaustive characterization feasible. Further, it can be interrogated non-invasively and at several spatial scales, down to the level of individual pores. We will: 1) Determine the timing and source of new colonizations by comparing the number and composition of P. acnes strains between children of different ages, their family members, and their classmates and by tracking these subjects as they age; 2) Use whole-genome evolutionary reconstruction to infer spreading dynamics on healthy adults intensively sampled at multiple spatial scales; and 3) Identify de novo mutations critical to long-term colonization. These studies will develop a population genetics paradigm for mechanistic understanding in the microbiome, bound interpretations of metagenomic data, and offer clues on how to manipulate human microbiomes, with the potential to lay the groundwork for the selection of long-lasting probiotic strains for the treatment of skin diseases and promotion of health.

• **Sibongile Mafu, Ph.D.**
Assistant professor of Biochemistry
*University of Massachusetts Amherst*

"Discovery and Mechanism of Plant-Derived Antifungals"

Key Words: Plant Natural Products, Antifungals, Fusarium, Cell Culture

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Each year invasive fungal infections affect over 1 billion people and claim around 1.5 million lives. This poses a serious health risk aggravated by an increasing community of immunocompromised individuals and a limited range of drug classes that effectively control fungal pathogens. Plants provide a rich source of natural biologically active products and a renewed opportunity for improving human health. Nearly 25 % of current drug applications are derived directly from or inspired by plant natural products and continue to show potential as building blocks for the development of more effective next generation therapeutics.

We are screening a diverse plant cell culture collection housed at UMass Amherst, a unique resource for investigation of plant natural product chemistry, that opens opportunities for drug discovery. Utilizing this collection, our lead compound discovery currently focuses on antifungals where limited chemical drug classes including azole inhibitors are facing reduced efficacy due to drug resistance. This research proposal seeks to discover and develop novel lead compounds through 1) high throughput screening of plant cell cultures against fungal causative agents such as Fusarium oxysporum. 2) natural product identification, biosynthetic pathway elucidation and bioengineering of analogs of lead compounds 3) and identification of the targets of inhibitory molecules through differential transcriptomics and proteomics combined with yeast chemical -genetic screens.

At the completion of these studies we expect to identify plant natural products that mitigate the action of Fusarium and their potential mechanism of action. We anticipate development of a screening platform that can be applied to other pathogens of interest.