- **Carolyn Elya, Ph.D.**
  Assistant Professor of Molecular and Cellular Biology
  Harvard University

"Leveraging Nature's "Zombies" to Understand Mechanisms Driving Animal Behavior"

Key Words: Behavior manipulation, Host-parasite interactions, Neural mechanisms

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Parasites that hijack the behavior of animal hosts are incredible neuroscientists. As a result, studying the mechanisms by which they puppeteer their hosts offers a complementary strategy to understanding how nervous systems encode and produce behavior. However, these systems have not been leveraged for this purpose, largely because most are not experimentally tractable. Recently, we have established a laboratory-based system in fruit flies for studying behavior manipulation by the obligate fungal pathogen Entomophthora muscae. Thanks to the extensive fruit fly genetic toolkit, this system provides a unique platform to gain mechanistic insights into behavioral manipulation. This work focuses specifically on defining the molecular "fungal-fly interface" of summiting behavior, namely: 1) What fungal genes drive summiting?, 2)What are the molecular triggers of summiting?, and 3) How does E. muscae interact with the host nervous system? We aim to answer these questions using an interdisciplinary experimental approach that combines behavior, calcium imaging, the extensive genetic fruit fly toolkit, transcriptomics, metabolomics, and the development of novel genetic manipulation strategies in E. muscae.

- **Zoe Hilbert, Ph.D.**
  Assistant Professor of Biology
  Boston College

"Defining the Molecular Determinants and Evolution of Pathogenicity in a Human Fungal Pathogen"

Key Words: Fungal pathogen, Cryptococcus neoformans, Evolution, Pathogenicity, Strain variation, Genetics, Ancestral reconstruction

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Fungi are an understudied class of microbial pathogens capable of infecting a diverse range of animals, including humans, with truly devastating effects on the health of these species. Despite their impact on human health and mortality, there still remain many open questions about the fundamental biology of these organisms and the mechanisms that drive their pathogenicity. One powerful method for revealing genes that control a trait, like pathogenicity, is to exploit naturally existing sequence and phenotypic variation across diverse isolates of species of interest that have adapted to unique environments and niches. For the clinically relevant pathogenic yeast, Cryptococcus neoformans, hundreds of genetically diverse clinical and environmental isolates have been collected and sequenced, but attempts to map determinants of pathogenicity or other disease-relevant traits have been hampered by the inability to easily utilize this resource's full potential. To overcome this limitation, my lab has adapted a high-throughput genetic barcoding method that will allow us to simultaneously measure the growth, infectivity, and pathogenicity of 300+ C. neoformans isolates in a single experiment. This will exponentially increase our ability to study the complex relationship between genetic variation and pathogenicity and infection outcomes in this species. Blending this powerful natural resource with high-throughput phenotyping and mechanistic studies promises to reveal not only what makes this fungus a successful pathogen but also how genes that control this trait naturally vary across strains and have evolved to give rise to the pathogens we encounter today.

- **Julia Li, Ph.D.**
  Investigator
  Boston Children's Hospital
  Assistant Professor of Genetics
  Harvard Medical School

"A Previously Missing Link between Repeat DNA, Genomic Instability, and Viruses"

Key Words: Repeat DNA, Chromosomes, Translocations, Genome Stability, Viral infection, Epstein Barr Virus, Cancer

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1) Identify the molecular mechanisms of protein binding-induced breakage at repeat sequences. I will solve how binding of Epstein Barr Virus Nuclear Antigen 1 (EBNA1) to repeat DNA sequences induces unstable structures prone to breakage. I will determine the functional domains on EBNA12 required for inducing breakage. Using END-seq3, I will explore which chromatin-associated activities play a critical role in breakage. I will also use ectopically inserted EBV-like DNA repeats to define determinants of repeat instability. I will establish an unbiased proteomic approach to identify host and viral proteins enriched at the EBV-like repeats that either promote stability or mediate breakage.

2) Determine the impact of the breakage of repeats on genome stability. I will define the role of EBNA1-induced breakage at 11q23 in shaping abnormalities on chromosome 11 and elsewhere in the genome. I will identify breakage-induced repeat junctions and translocation hotspots using high throughput, genome-wide translocation sequencing (HTGT)4. I will also use single cell-derived clones to identify molecular features of chromosome 11 rearrangements. Finally, I will analyze cancer genomes to establish the role of EBNA1-induced repeat junctions in generating abnormalities in chromosome 11.

3) Determine pathological conditions that trigger breakage of virus-like repeat sequences. I propose that genetic variation of virus-like repeats1 as well as the availability of EBNA1 determine the threshold critical for EBNA1 binding-induced breakage in cells latently infected with EBV. I will use genomics datasets to determine genetic variation of repeats in the human population5. I will also perform a genome-wide screen to identify and test host factors that can trigger an increase in EBNA1 abundance.

Long term: This work will 1) define unknown mechanisms surrounding the instability of virus-like repeats, 2) implicate EBV in potentially any human disease with chromosome 11 abnormalities, and 3) identify risk factors for development of EBV-associated cancer.

- **Rachel Wolfson, M.D., Ph.D.**
  Assistant Professor of Cell Biology
  Harvard Medical School

  “Defining the Cellular Basis of Pancreatic Sensation”

  Key Words: Neurobiology, Sensory, Pancreas, Interoception

Visceral organs have a dense amount of sensory innervation, though the diversity and function of these neurons in many organs, including the pancreas, is unclear. Sensory neurons that innervate the pancreas are those whose cell bodies reside in the dorsal root ganglia, the DRG sensory neurons. Our previous work identified multiple genetic subtypes of DRG neurons that innervate the colon with distinct morphologies, electrophysiologic response properties, and behavioral outcomes when activated. Here, we propose to identify the genetic subtypes of DRG neurons that innervate the pancreas. Using mouse genetic tools and whole mount immunofluorescence, we propose to characterize the morphologies of these neurons within the pancreas, shedding light on their underlying heterogeneity and possible functions. Additionally, using established and novel mouse behavior paradigms, we propose to characterize the role of these neurons in physiologic and pathophysiologic pancreatic functions. This work will lead to significant advances in our understanding of the peripheral nervous system in an understudied internal organ and potentially identify therapeutic targets for diseases such as diabetes and pancreatitis.

- **Gregory Wyant, Ph.D.**
  Assistant Investigator
  Massachusetts General Hospital
  Assistant Professor of Medicine
  Harvard Medical School

  “Nutrient and Oxygen Control of Skeletal Muscle Size”

  Key Words: Hypoxia, Nutrients Skeletal Muscle, HIF, Fasting, Atrophy, Autophagy

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Nutrients and oxygen are sensed within our muscle to control muscle growth. Disruption of either signal is sufficient to promote muscle atrophy and is driven by a common transcriptional program via the Forkhead box O (FoxO) and Hypoxia Inducible Factor (HIF) transcription factors, which sense nutrient starvation and oxygen, respectively, to control muscle homeostasis. While the critical transcription factors that control muscle size have been identified, the downstream mechanisms that initiate muscle loss are complex and still only partly understood. Muscle atrophy occurs when protein degradation rates exceed protein synthesis. Autophagy is an intracellular degradation pathway that is activated in skeletal muscle under starvation or hypoxia, and autophagy activation is sufficient to promote muscle atrophy. How, mechanistically, these signals activate autophagy remains unknown. Here, we identify C10orf10/Depp1, a protein of unknown function, that we find to be a key component to the muscle’s autophagy response to FoxO and HIF activation in vivo. We hypothesize C10orf10/Depp1 is a essential mediator of muscle homeostasis that when activated controls muscle loss. In Aim 1, we will test the role of C10orf10/Depp1 in the context of fasting or hypoxia-induced muscle atrophy. In Aim 2, we will determine whether autophagy inhibition reduces muscle loss in the context of C10orf10/Depp1 overexpression. In Aim 3, we will determine whether C10orf10/Depp1 is a key muscle atrophy factor in multiple pre-clinical models of muscle atrophy, such as denervation, glucocorticoids, diabetes, and cancer cachexia. As therapeutic targets for prevention of muscle atrophy are not known, these studies will provide fundamental insight into the mechanisms of muscle atrophy and how to inhibit it.