Smith Family Foundation: Odyssey Award

A program of the Richard and Susan Smith Family Foundation

2018 Award Recipients

- **Lydia Bourouiba, Ph.D.**
  Esther and Harold E. Edgerton Assistant Professor
  Massachusetts Institute of Technology

  "Respiratory Disease Transmission: Mechanistic Understanding for Control and Prevention of Epidemics"

  Key Words: Biophysics, Fluid dynamics, Rheology, Microbial ecology, Virology, Sequencing, Transmission, Super-spreaders, Respiratory diseases, Influenza and co-infection

---

Despite widespread vaccination programs, the healthcare and economic burdens of respiratory diseases remain enormous. Influenza returns every year, and the increase in urban population density will only exacerbate its burden worldwide. Epidemics and pandemics start with and are fueled by one key event: transmission from one individual to another. Yet, this very fundamental process is poorly understood. Additionally, there is evidence that some individuals appear more efficient at transmitting than others. Nothing is known about the mechanisms involved for such outlier behavior, yet, such outliers can in fact drive the onset and severity of epidemics. At this time, such outliers are only typically detected a posteriori at the end of an epidemic. Hence, we know even less about what makes such individuals efficient at transmitting, and even less about how to detect them during an epidemic. This research seeks to fill this important fundamental gap using a new paradigm that is distinct from traditional tools of epidemiology and statistics. We aim to gain a mechanistic understanding of respiratory transmission rooted in quantitative biophysics and combining complex fluid dynamics and rheology, and microbial and viral dynamics in particular. Our central hypothesis is that combinations of host respiratory physiology at various scales – from microbial ecology that can shape mucosalivary and sputum fluid properties, to biophysics of air-flow and fluid breakup during exhalations – drive host-to-host transmission. We propose that quantifying and understanding the interaction between physiology and pathogenesis can allow to define novel detection approaches. This unique marriage of traditionally separate fields will enable a shift in current paradigm on transmission and allow to define and detect predisposition for super-spreading that can be used for taking action during epidemic onset and development, rather than a posteriori analysis which does not lead to solutions for mitigation and control. The impact of this research will also include opening new directions of research on point-of-care early transmission tests and efficient prophylactics, not only managing symptoms for patients, but also ensuring that their ability for transmission to others is also simultaneously reduced.

- **Benjamin de Bivort, Ph.D.**
  Assistant Professor
  Harvard University

"Mapping Loci of Individuality for Spontaneous and Stimulus-Evoked Behaviors"

Key Words: Behavior, Neural Circuits, Stochasticity, Personality, Individuality, Variation, Drosophila, Disease Penetrance, Stimulus-Evoked, Spontaneous, Olfaction, Vision, Locomotion

---

Behaviors vary among individuals, and these differences, taken together, constitute our personality and underpin our sense of individuality. Genetic and environmental differences are well-appreciated determinants of such behavioral differences. But a third source of variation — stochastic fluctuations in the wiring of the brain and in its post-developmental dynamics — are a major, largely uncharacterized, source of behavioral individuality, and our lab's long-term research focus. Using the genetic model system Drosophila melanogaster, custom automated instruments for behavioral characterization, and modern transgenic and optogenetic tools, we are seeking the specific cellular-level features within neural circuits that give rise to behavioral differences. For example, we have preliminary evidence that individual-level morphological asymmetries (in the axonal arbors of interneurons in a pre-motor area of the brain) predict individual-level locomotor biases.

We call such predictors "loci of individuality," and we aim to test three hypotheses relating to their role within circuits that coordinate behavior: 1) In stimulus-evoked behaviors, there is a progressive increase in the predictability of individual behavior from activity across successive stages of the sensorimotor transformation. 2) In spontaneous behaviors, predictors of individual behavior arise immediately downstream of recurrent networks which are the site of multisensory integration and internal state representation. 3) Neurons harboring loci of individuality for both stimulus-evoked and spontaneous behaviors will be the targets of neuromodulation, by which the animals can tune their individuality in response to internal states such as stress.

Being able to predict individual behavioral biases from microfeatures of neural circuits will be a significant advance for systems neuroscience and the study of behavior in general. Identifying loci of individuality will enable important mechanistic follow-up projects to characterize the molecular variations at each locus, e.g., using single cell RNA-seq or in situ sequencing. Along with connectomics and whole-brain recording, these are techniques of the individual. For biomedicine, explaining behavioral outcomes at this causal level is likely key to understanding why psychiatric diseases seem to strike at random among individuals with identical risk-factors.

- **Elena Gracheva, Ph.D.**
  Assistant Professor of Neuroscience and Cellular and Molecular Physiology
  Yale University

"Regulation of Fluid and Ionic Balance Under Extreme Physiological States in a Mammalian Hibernator"

Key Words: Mammalian hibernation; fluid-ionic balance; osmosensitivity; molecular adaptations; torpor; hypothermia; ion transporters; ion channels; hypothalamic axis

---

Mammalian hibernation is a fascinating phenomenon, characterized by prolonged alternating periods of hypothermia (when core body temperature drops from 37°C to 2-4°C), hypometabolism, and low tissue perfusion. Even during such an extreme physiological state, hibernators do not experience cold-induced pain, and their organs continue to function despite being cold, hypo-perfused and oxygen-deprived for 8 months of the year! Moreover, during hibernation animals must rely solely on the management and utilization of internal resources for long-term survival. Despite decades of research, the molecular mechanisms that support mammalian hibernation remain enigmatic. Furthermore, it is not well understood whether and how homeostatic mechanisms, such as those controlling fluid-ionic balance, operate under torpor-arousal states, and how excitable cells are protected from perturbation in ionic gradients. Here, we aim to examine the neuronal, hormonal, and molecular strategies that hibernators employ to retain water and ionic gradient during prolonged periods of deep torpor.

Our main hypothesis is that hibernators evolved modifications at different levels, including tight regulation of hypothalamic axis controlling body homeostasis, and primary and secondary transporters that move ions against their gradient at low body temperature. We propose to address these fundamental biological questions by applying new expertise to hibernation research and engage interdisciplinary perspectives: cell- and function-specific transcriptomics; de novo cloning and in vitro biophysical analysis of hibernation-specific isoforms of ion transporters; state-specific analysis of organic and inorganic osmolytes, neuropeptides and hormones; live-cell functional imaging, electrophysiology and behavioral paradigms.

Molecular and cellular insights into these processes will have multiple and far-reaching medical implications, such as organ transplantation, recovery from ischemia, stroke or brain injury. Moreover, understanding molecular prerequisites for hibernation will be extremely useful for long-time space travel, such as that required for human missions to Mars—a highly ambitious (yet achievable) goal, which will mark a pivotal milestone for the humankind. At this moment, we know very little about the nature of long-term hibernation. Our lab's studies will provide fundamental information about this process.

- **Ya-Chieh Hsu, Ph.D.**
  Assistant Professor
  Harvard University

"Cellular and Molecular Mechanisms of Fetal Skin Regeneration"

Key Words: Regeneration, Stem Cell, Wound Healing, Skin

The ability to regenerate complex organs composed of multiple tissues varies greatly among different organisms and with different developmental stages, but the basis for this differential regeneration ability remains one of the greatest mysteries. Many mammalian organs, including the heart, digit tip, and the skin, retain some capacity to regenerate following damage during neonatal or fetal development, but the ability to regenerate declines drastically as animals develop. Discovering the mechanistic underpinnings of this differential regeneration ability is key to understanding principles of regeneration control and to therapeutic reactivation of organ regeneration upon injury.

Here, we use the mammalian skin as a model to elucidate mechanisms behind developmental influences on regeneration potential. Healing of full thickness injuries to postnatal skin is accompanied by excessive scarring. However, injuries to fetal skin heal without scar formation, a phenomenon that has fascinated biologists for a century but the underlying mechanisms remain elusive. My lab has developed tools and approaches to study regeneration of the fetal skin including robust surgical procedures to perform fetal skin wounding in mice, and has established viral-mediated strategies to manipulate gene expression in skin. Together, these technologies put us in a unique position to answer this century-old problem with powerful new tools. Our central hypothesis is that the differential regeneration ability in fetal versus postnatal skin is a consequence of changes in programs of gene expression between these two stages. In Aim1, we will use lineage-tracing and single cell RNAseq to determine the cellular and molecular differences between wound healing at fetal vs. postnatal stages. In Aim2, we will take both a candidate gene approach and an in vivo screening approach to identify signaling pathways and secreted factors that are crucial for the regeneration ability of fetal skin. Results from the proposed experiments will provide critical insights into how the regeneration ability is blocked or lost as an organ develops, will open new research direction to study whole organ regeneration in mammals, and will lay the foundation for new therapeutic strategies that promote regenerative healing under challenging conditions including burns and chronic non-healing wounds.

- **Jing-Ke Weng, M.D., Ph.D.**
  Member; Assistant Professor of Biology, MIT
  Whitehead Institute for Biomedical Research

  “Novel Psychiatric Therapeutics Inspired by Bioactive Plant Polyketides”

  Key Words: Kavalactone, Anxiolytics, Anxiety, Insomnia, Psychiatric therapeutics, Polyketide

---

Anxiety is among the most common psychiatric disorders affecting children and adults, affecting more than 40 million adults in the US. However, we currently lack safe and effective treatment for such disorder. The tropical shrub kava kava (Piper methysticum) has traditionally been used in the Pacific islands to prepare a strong beverage for social, ceremonial, and medical purposes. Kavalactones are the main bioactive principles in kava that trigger a multitude of amnestic, analgesic, and sedative effects in the human central nervous system. Identifying the bioactive compounds from kava kava, understanding their mechanism of action, and further devising biosynthetic strategies to produce these compounds will open up new avenues for developing new therapeutics for treating various psychiatric disorders. Our preliminary work has identified several key enzyme-encoding genes from kava kava underlying kavalactone biosynthesis, revealing the exact molecular evolutionary trajectories that led to the emergence of this very specialized metabolic trait in kava plant. In this proposed research, we aim to 1) resolve the complete kavalactone biosynthesis in kava as well as in several other unrelated plant species that reportedly to also contain kavalactones, 2) generate E. coli and yeast strains with engineered kavalactone biosynthetic pathways to produce natural kavalactones and additional unnatural kavalactone analogs, and 3) elucidate the action mechanism underpinning the anxiolytic activities of kavalactones in the animal brain. A diverse set of cutting-edge techniques, including enzyme structural biology, multi-omics-guided de novo metabolic pathway elucidation, crystalline-sponge-based natural product structural elucidation, will be used to help us achieve our aims.