

**Smith Family Foundation: Odyssey Award**  
*A program of the Richard and Susan Smith Family Foundation*  
**2021 Award Recipients**

- **Edward Chouchani, Ph.D.**

Assistant Professor of Cancer Biology

*Dana-Farber Cancer Institute*

“Systematic Chemical Manipulation Of Redox Sensitive Cysteines To Regulate Inflammatory Processes”

Key Words: Mass spectrometry, Cysteine, Chemoproteomics

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Mammalian tissues engage in specialized physiology that is regulated through reversible covalent modification of protein cysteine residues. Despite the widespread importance of redox regulation of tissue physiology, there is a persistent lack of information regarding the specific protein modifications that explain the molecular basis for these processes in vivo.

My lab recently developed a mass spectrometric (MS) technology for the first comprehensive and quantitative mapping of the mouse cysteine redox proteome in vivo. For the first time, we defined hundreds of protein cysteine modification networks that underlie distinct physiological responses across different tissues. Our “big picture” aim is to leverage this newfound regulatory landscape for an overarching mechanistic and therapeutic goal: systematic functional annotation and manipulation of redox regulated cysteines on proteins that play major roles in human diseases of aging. To do so, we will combine new MS methods, and chemical and biochemical approaches, to systematically develop covalent pharmacological manipulators of these redox regulated cysteines. Herein, we will prioritize newfound regulatory cysteines present on proteins that control macrophage cytokine production and inflammasome activation. Through systematic development of covalent chemotypes targeting these residues, we aim to engineer first-in-class manipulators for disease-relevant proteins that are currently undrugged. Successful completion of our aims will define mechanisms of redox regulation of effector proteins that control cytokine production and inflammasome activity, while developing new therapeutic chemotypes for treatment of inflammatory diseases.

- **Marcelo Dietrich, M.D.**

Associate Professor

*Yale School of Medicine*

“Opioid-Producing Neurons that Mediate the Attachment of Infants to their Mothers”

Key Words: Development, Behavior, Emotions, Neuronal circuits, Mother-Child bond

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Children’s bonds with caregivers in early childhood drive their physiological, emotional, and behavioral development. During the early postnatal period, mothers provide infants with their basic physiological needs, such as warmth, nutrition, and sensorial stimulation. The emotional bond between infants and their mothers ensures these physiological needs are met. Disruptions in mother-infant bonding—as it occurs in institutionalized children and in child abuse—can lead to irreversible lifelong consequences for an individual’s health. These negative consequences include an increased incidence of mental health problems. Despite the importance of the early postnatal period, the fundamental question of how the infant brain encodes rewards to reinforce maternal attachment remains elusive. Here, we advance the hypothesis that neurons in the infant hypothalamus that produce the strong opioid beta-endorphin encode early-life rewards, facilitating the healthy attachment of infants to their mothers. To test this hypothesis, we will apply new technologies to record and manipulate the activity of neurons in the brain of infant rats that engage in reward-related behaviors with their mothers. This study can significantly advance our understanding of the brain mechanisms that control early emotional development, which may unlock entirely new paradigms for the identification and treatment of mental health disorders in children.

- **Jenna Galloway, Ph.D.**

Assistant Professor of Orthopaedic Surgery  
*MGH Center for Regenerative Medicine*

“Identifying the molecular and cellular determinants of exercise-driven tendon remodeling”

Key Words: Musculoskeletal system, Tendon, Progenitor cells, Exercise

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Tendons transduce force from muscles to bone, enabling movement. Embedded within their highly organized extracellular matrix are tendon cells, which respond to changes in mechanical load and maintain the tissue. Altered loading conditions such as increased or decreased exercise affect tendon properties: underuse and overuse can lead to pathologies such as tissue degeneration or ectopic cartilage and bone, leading to injury. In contrast, moderate loading or exercise positively affects tendon properties. However, the molecular pathways and specific cell types that sense and respond to changes in load to regulate tendon cell function are largely unknown. To address this knowledge gap, we have two main goals: (1) to use an unbiased approach through single cell and bulk RNA-sequencing to identify novel pathways and cell types that respond to altered loading conditions; and (2) to test the role of a newly identified tendon progenitor cell population and candidate pathways in sensing and organizing tissue properties upon altered loading conditions. An improved understanding of the molecular and cellular mechanisms governing tendon mechanobiology would greatly impact our knowledge of how movement regulates tissue function and would lead to new targets for the treatment of tendon disease and injury.

- **Sebastian Lourido, Ph.D.**

Assistant Professor of Biology

*Whitehead Institute for Biomedical Research*

“Controlling the developmental transitions of a eukaryotic pathogen”

Key Words: Transcriptional regulation, Microbiology, Parasitology, *Toxoplasma gondii*, High-throughput genetics, Functional genomics

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A defining feature of eukaryotic parasites is their ability to restructure their cell biology to promote key transitions along their complex life cycles. Apicomplexan parasites depend on such developmental transitions to propagate between tissues and hosts and survive as the most widespread parasitic infections on earth. We propose to develop high-throughput approaches to investigate the molecular origin of key developmental transitions. Our recent work uncovering the master regulator of chronic differentiation suggests that relatively simple gene-expression networks underlie major developmental decisions in these parasites. We now propose to expand this conceptual framework to uncover the largely unknown regulators of the sexual cycle. Using CRISPR-based methods our lab has developed for *Toxoplasma*, we will be able to site-specifically install synthetic gene expression circuits to conditionally alter the function of all transcription factors in the cell. By manipulating collections of conditional mutants we will screen for perturbations to the regulatory network that elicit defined developmental transitions. As part of this work, we will characterize the binding of novel master regulators through the versatile chromatin-profiling method CUT&RUN. This work will allow us to study stages that are currently inaccessible to cell culture-based methods transforming our understanding of parasite cell biology.

- **Sarah McMenamin, Ph.D.**

Assistant Professor

*Boston College*

“Mechanisms by which shape is specified and remembered during development and regeneration of the zebrafish fin”

Key Words: Regeneration, Positional information, Positional memory, Developmental disorders, Limb malformations, Zebrafish fins, Fin regeneration

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To build an organ such as a limb or a fin, developing tissues must use positional information to generate appropriate shapes. Changes in these relationships underlie certain congenital malformations. Moreover, in order to regenerate following an amputation, tissues must re-deploy positional information. Nonetheless, the nature of positional information is incompletely understood; this lack of understanding limits our ability to treat congenital disease, and restricts the potential of regenerative therapies. The long-term goal of this research program is to determine the mechanisms by which vertebrate tissues establish, interpret and remember position. We have discovered a way to abolish medio-lateral positional information in zebrafish caudal fins, fundamentally changing the shape of the adult organ from a forked morphology into a truncate shape, with no distinction between medial and lateral fin regions. We will leverage this novel fin shape towards a better understanding of positional information, asking how fins are capable of remembering and regenerating shapes. In Aim 1, we ask how position is established during ontogeny, testing a mechanism by which expression of a developmental pathway pre-patterns adult shape during larval stages. In Aim 2, we ask how shape is remembered by adult tissues, testing if local cell populations store remembered positional information.

- **Andrew Wang, M.D., Ph.D.**

Assistant Professor of Medicine and Immunobiology  
*Yale University*

“Understanding the Role of Brain T-cells in Defending Sleep”

Key Words: T-cell, homeostasis, sleep, brain, inflammation

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How the central nervous system and immune system communicate to regulate our physiology is incompletely understood. Neuroimmune control of both normal homeostatic processes and defensive responses to danger is emerging as a key regulatory node in inflammatory responses. To better understand the neuroimmune circuit, we profiled immune cells in the brain and brain-draining lymph nodes. Unexpectedly, we discovered that T-cells, immune cells that are required to coordinate immune responses, trafficked in and out of the brain and brain-draining lymph nodes in a pattern that was opposite to that in peripheral tissues. Activated T-cells were found in their highest number in the brain during sleeping hours. This normal circadian oscillation was disrupted when sleep was fragmented. In this proposal, we will use an integrative approach in mouse models, combining techniques from immunology, physiology, and neurobiology, to test the hypothesis that T-cells are essential for the biology of sleep and that disruption of this neuroimmune circuit causes inflammation, where disruption of sleep/wake cycle is a common clinical feature. Since inflammation is a terminal outcome in disease states ranging from autoimmune diseases to psychiatric diseases to cancer, a better understanding of neuroimmune interactions will provide new clinical therapeutic targets.