- **Josefina del Marmol, Ph.D.**

  Harvard Medical School

  "Structural Determinants of Odor Transduction in the Disease Vector Mosquito Anopheles gambiae"

  Key Words: Olfactory receptors, Mosquito olfaction, Cryo-EM, Malaria

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Animals can detect and discriminate millions of odors using a small number of olfactory receptors, yet the molecular basis of this process remain obscure. My work aims to elucidate the structural and molecular mechanisms of olfaction. The research proposed here focuses on the olfactory system of the mosquito Anopheles gambiae, the major vector of malaria, a disease that takes the lives of more than half a million people every year. An. gambiae mosquitoes rely on their sense of smell to find and navigate towards human hosts to secure a bloodmeal, however, the identity of the olfactory receptors and pathways that mediate this process remain unknown, preventing modern drug-discovery efforts towards improved mosquito repellents. My work will combine structural and functional studies of An. gambiae olfactory receptors with in vivo behavioral assays of human-preference in An. gambiae mosquitoes to characterize the molecular mechanisms that enable mosquitoes to detect and discriminate natural odors such as the scent of humans. We will then use these insights to develop new pharmacological tools to manipulate An. gambiae ORs in vivo. This research will illuminate the fundamental principles of olfactory detection and discrimination, while providing new pharmacological avenues for the containment of vector-borne diseases.

- **Josué Flores Kim, Ph.D.**
  Assistant Professor
  University of Massachusetts Chan Medical School

"Bacterial Cell Envelope Remodeling as a Conserved Strategy for Modulating Antibiotic Tolerance and Virulence Factor Assembly."

Key Words: Antibiotics; Autolysins; Lysis; Drug-resistance; S. pneumoniae; Cell Envelope; Signal Transduction; Capsule; Wall Teichoic Acids; Virulence

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A fundamental goal of microbiology is to understand the mechanisms underlying the biogenesis and remodeling of the bacterial cell envelope, a complex structure essential for cell growth. The envelope also serves as the scaffold for the assembly of several virulence factors, and is the target of host immunity and our most effective antibiotics. Thus, envelope studies have also significant consequences for human health. Surprisingly, little is known about the mechanisms underlying the construction of the cell envelope, especially in pathogens like Streptococcus pneumoniae (Sp), a major cause of life-threatening antibiotic resistant and tolerant infections. Our research tackles these problems by characterizing an essential, widely-conserved envelope remodeling pathway in Sp that is important for cell growth and division, the assembly of virulence factors, and whose corruption by antibiotics is critical to induce bacteriolysis. In Aim 1 we will define the biochemical function and regulation of a novel enzyme critical for the remodeling of cell envelope polymers and identify how antibiotics short-circuit its activity to induce bacteriolysis. In Aim 2 we will uncover how the host environment triggers envelope remodeling processes to induce antibiotic tolerance and modulate the assembly of a surface-exposed virulence factor. Our studies will provide a holistic understanding of bacterial cell envelope assembly and remodeling processes, to inform the development of new treatments for antibiotic resistant and tolerant infections.

- **Richard Liu, Ph.D.**
  Assistant Professor of Chemistry and Chemical Biology
  Harvard University

  "Breaking the Metal Barrier: Safe and Rapid Radiopharmaceutical Synthesis Using Organic Pseudometals"

  Key Words: Chemical Synthesis, Radiotracers, Positron Emission Tomography, Medical Imaging, Drug Discovery, Organocatalysis, Late-Stage Functionalization, Green Chemistry

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Positron Emission Tomography (PET) is a promising precision imaging technology with both clinical and basic science applications. In PET, a radioisotope-tagged tracer compound is injected into a subject and its distribution, metabolism, and/or target is investigated by observing gamma ray emission from radioactive decay. A longstanding obstacle toward the widespread adoption of this technique has been the challenging synthesis of desirable radiopharmaceuticals. The most general approaches involve toxic transition metals such as palladium and copper, which necessitates cumbersome purification and analysis steps to ensure complete metal removal before administration.

We propose an unconventional approach to late-stage tagging of pharmaceuticals with radioisotopes, primarily 18F, involving the design of bio-inspired organic catalysts capable of mimicking the redox reactivity of transition metals. Using a combination of in silico screening and high-throughput experimentation, we will discover molecules that efficiently mediating the synthesis of aryl fluorides and cyanides (Aim 1). By immobilizing these mediators on solution-processable, porous organic polymer scaffolds that we have previous developed, we will develop a streamlined "load-and-release" continuous-flow synthetic scheme with minimal purification required (Aim 2). In collaboration with the Hooker Research Group (MGH), we will then optimize these methods with positron-emitting radionuclides (Aim 3). The proposed work aims not only to accelerate tracer production and circumvent the metal-toxicity risk, but also to greatly expand the scope of accessible radiopharmaceutical agents and hence the applicability of PET as a biomedical tool.

- **Jessica Spinelli, Ph.D.**
  Assistant Professor
  University of Massachusetts Chan Medical School

  "Elucidating Novel Circuits of Electron Flow in the Mammalian Electron Transport Chain"

  Key Words: Mitochondria, Metabolism, Hypoxia, Stable Isotope Tracing, Liquid Chromatography Coupled to High Resolution Mass Spectrometry, Biochemistry, Chemical Biology

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Textbook depictions of the mammalian ETC involve a single circuit, in which electrons enter at complexes I and II, are carried by ubiquinone, and deposited on oxygen as the terminal electron acceptor via complexes III and IV. In preliminary work, I discovered a novel and tissue-specific circuit of electron flow in the ETC that is facilitated by a previously uncharacterized mammalian metabolite. The proposed work will elucidate the fundamental role of distinct ETC circuits in mammals. First, my lab will determine the impact of each ETC circuit on canonical mitochondrial functions and explore potential novel mitochondrial functions that this metabolite may promote. Second, we will leverage genetic and pharmacologic tools optimized in preliminary work to create a mouse model in which electrons can be redirected on a different ETC circuit in tissues. This model will be instrumental in understanding the physiological and disease relevance of distinct ETC circuits. Third, this proposal tests a novel strategy to treat mammalian disease whereby electrons are redirected on a new path in the ETC to mitigate hypoxia-induced tissue damage. Taken together, this work sets the stage for a new field of mammalian biology on the physiological and disease relevance of distinct ETC circuits.

- **Meg Younger, Ph.D.**
  Assistant Professor
  Boston University

  “Non-Canonical Odor Coding in Mosquitoes”

  Key Words: Olfaction, Mosquito, Sensory neurobiology, Chemosensation, Odor coding, Non-model organism

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Detection of humans by mosquitoes relies heavily on olfaction. Understanding the mechanisms through which the mosquito olfactory system detects human odor is the inroad to preventing mosquitoes from smelling humans and therefore preventing mosquito biting behavior and disease transmission. We found that the olfactory system of the Yellow-fever mosquito, Aedes aegypti, is organized in a way that completely breaks with the dogma of olfactory system organization that was established in model species. Unlike flies and mice, which only express a single type of olfactory receptor in each olfactory sensory neuron, Aedes aegypti mosquitoes express multiple different chemosensory receptors in individual olfactory sensory neurons. The goal of this project is to understand how the atypical olfactory system of mosquitoes detects human odor. Once we learn how mosquitoes detect our odor we will develop novel approaches to systematically disrupt an olfactory system that has shown surprising resilience to human efforts to deceive it.