Biomedical Physics (BMP) Program
PhD Dissertation Defense

Samantha Reyes

From *In Silico* to Human: Translational PET Imaging of Immune Activation and Mitochondrial Function in Neurological Disorders

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Abstract: Inflammation is a hallmark of many diseases, including cancer, neurodegenerative disorders, and demyelinating conditions such as multiple sclerosis (MS). In the central nervous system, neuroinflammation arises from complex interactions between resident and peripheral immune cells that drive disease onset and progression. Despite growing recognition of maladaptive immune responses as key disease drivers (and the parallel development of immunomodulatory therapies), current methods for quantifying inflammation and dynamic immune activity *in vivo* remain limited. This constrains our ability to stage disease, stratify patients, and assess therapeutic response. Positron emission tomography (PET) is a powerful tool for imaging immune processes *in vivo*, and the 18 kDa translocator protein (TSPO) has long been the most widely used biomarker of neuroinflammation. However, TSPO is expressed across multiple cell types, and its expression in human myeloid cells does not increase with inflammation. Instead, TSPO appears to play a broader role in mitochondrial function, including regulation of bioenergetics, reactive oxygen species production, membrane potential, mitophagy, and calcium signaling. In my PhD work, I first investigated the utility of TSPO-PET in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a disease associated with immune dysregulation and changes in mitochondrial function. I will present my findings from the first whole-body TSPO-PET study of ME/CFS, revealing altered signal in the bone marrow, brain, and skeletal muscle. These changes correlate with clinical symptoms such as fatigue and pain, suggesting systemic alterations in immune activity and mitochondrial bioenergetics. Complementary plasma cytokine data further support these findings, highlighting the potential of TSPO-PET as a diagnostic tool and as a means to monitor therapeutic response.The second part of my thesis focused on identifying novel neuroinflammation biomarkers with improved

cell-type specificity, particularly for innate immune cells that act as early responders in disease. This led to the development of PET radiotracers targeting GPR84, an immunometabolic G protein–coupled receptor upregulated during pro-inflammatory responses. I will present preclinical evaluation of a GPR84-targeted radiotracer in a mouse model of MS, demonstrating its ability to track disease severity and detect response to fingolimod treatment *in vivo*. Together, these findings highlight the promise of TSPO-PET and GPR84-PET as complementary imaging approaches for improving diagnosis, patient stratification, and therapeutic monitoring in ME/CFS, MS, and other inflammatory diseases.