2016 Kathleen L. Miller Fellow

Alexandra Tsitsiklis, UC Berkeley PhD Candidate in Infectious Diseases and Immunity Program, Robey Lab

Alexandra is a graduate student in UC Berkeley's Infectious Diseases and Immunity program. A native of Greece, Alexandra graduated from McGill University with a Major in biology, and a minor in Environmental Science. While at McGill, she spent a semester studying healthcare access issues in East Africa, and led a student fundraising group focused on African healthcare and education. She is studying T-cell responses to the parasite *Toxoplasma gondii* in Professor Ellen Robey's lab.

Fellowship Proposal

Humans exhibit an incredible diversity of immune responses, largely due to the structure and functions of the major histocompatibility complex (MHC). T-cells, which orchestrate immune responses, recognize pathogen-derived peptides presented by MHC via their T cell receptor (TCR). Differences in peptide presentation by allelic forms of MHC underlie susceptibility or resistance to HIV, cancers, and autoimmune disorders.

While most MHCs are "generalists" that broadly bind peptides and allow for adequate responses to many pathogens, it has been proposed that others are "specialists" that display limited peptide binding, leading to potent "jackpot" T-cell responses to certain pathogens. The mechanism of this action however, remains unknown. Studies of T-cell responses to the parasite *Toxoplasma gondii* in mice have revealed an unusually potent T-cell response that relies on a specialist MHC. The MHC molecule L^d exhibits limited peptide binding, but binds strongly to the *T. gondii* peptide GRA6.

Alexandra's project has two goals. The first, is to investigate how atypical peptide binding contributes to high affinity GRA6-specific T-cell responses *in vivo*. This goal will test the hypothesis that structural properties of specialist MHCs set the stage for "jackpot" T-cell responses by allowing for more extensive interactions between TCR and peptide-MHC. The second goal will determine whether low self-reactivity contributes to the maintenance of a protective response during chronic infection with *T. gondii*. This goal is based on the hypothesis that T-cells of high vs. low self-reactivity fill separate niches, and weakly self-reactive T cells are particularly suited to provide protection against persistent infections.

T. gondii poses a significant disease burden at a global level, and has been classified by the CDC as a Neglected Parasitic Infection. Alexandra's work seeks not only to elucidate how a protective T-cell response to *T. gondii* is made, but also develop an enhanced the broader mechanistic understanding of how MHC polymorphisms drive T-cell responses and correlate with disease outcome. Understanding the "rules" for inducing such a response will translate directly into improvements of the control of myriad chronic infectious diseases, including HIV.