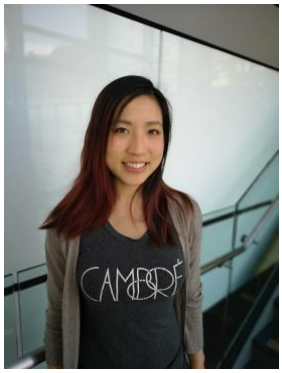
# 2019 Kathleen L. Miller Fellow

**Robyn Jong, UC Berkeley PhD Candidate in Molecular and Cell Biology, Stanley Lab**



Robyn Jong is a PhD candidate in the UC Berkeley Molecular and Cell Biology program. She received her B.S. from Tufts University in Biology and French. As a graduate student, she studies the host immune response to *Mycobacterium tuberculosis* infection in the laboratory of Dr. Sarah Stanley at UC Berkeley. Her project centers on the role of neutrophils during infection and which host and bacterial factors determine resistance to the disease.

**Fellowship Proposal**

Tuberculosis (TB) is the top infectious killer in the world, causing 1.6 million deaths in 2017. Antimicrobial resistance is of particular concern, as hundreds of thousands of cases of drug resistant TV continue to be diagnoses every year. This public health crisis highlights the urgent need to shift the focus from antibiotic treatment towards host-directed therapy. To best develop therapies that augment natural immune defenses, however, it is crucial to understand which aspects of the host immune response are most and least beneficial for host outcome.

Neutrophils are known to be one of the most abundant innate immune cell types responding to the causative agent of TB, *Mycobacterium tuberculosis (Mtb)*. However, there is much debate over whether neutrophils are protective or pathogenic for the host. Neutrophil effectors may positively influence cell-intrinsic host control but may also cause immunopathology *in vivo*. Human blood transcriptional profiling shows that a neutrophil-driven response to type I interferon correlates with active disease. Antibody-mediated neutrophil depletion has been shown to reduce hyperinflammation and promote resistance to *Mtb* infection in some susceptible mouse strains but does not always increase survival. The type of cell death the neutrophil undergoes may influence this switch between a positive and negative outcome for the host. Virulent *Mtb* induces human neutrophil necrosis to promote mycobacterial growth, while attenuated ESX-1-deficient mutant infections results in apoptotic cell death and control of infection after subsequent phagocytosis by an uninfected macrophage. The ESX-1 secretion system is a key virulence factor for *Mtb*. The function of ESX-1 has not been fully elucidated, although it is known that it is necessary for *Mtb* access to the cytosol rom the autophagosome formed within the phagocytic cell. Neutrophils can therefore act as restrictors of attenuated bacterial growth yet serve as a permissive replicative niche when infected with virulent *Mtb*. In this project, I will investigate how ESX—deficient *Mtb* is sense in the cytosol of infected neutrophils. I will further test whether bacterial cytoscolic access determines neutrophil survival during infection. Additionally, I will further explore

which host pathways are necessary for induction of longer-term survival during ESX-1 mutant *Mtb* infection and how this response may differ with virulent *Mtb*.