2016 Irving H. Wiesenfeld Fellow

Daisy Ji, UC Berkeley PhD Candidate in Molecular and Cell Biology, Vance Lab

Daisy obtained her undergraduate degree in Immunology from McGill University, for which she received the Governor General's Silver Medal. After graduation, she moved to UC Berkeley's Molecular and Cell Biology PhD program, joining the lab of Professor Russell Vance in 2014. Daisy is studying host-pathogen interaction and mechanisms of pyroptosis, a form of cell death. She has focused her studies on the effect of host cell death response on *Mycobacterium tuberculosis* infection. In her free time, she enjoys opera and writings of author Jenny Lawson.

Fellowship Proposal

Tuberculosis (TB), a disease caused by the acid-fast bacterium *Mycobacterium tuberculosis*, is currently the leading cause of death worldwide. While both incidence and mortality from TB has decreased steadily since 1990, in 2014 there were still 1.5 million deaths and an estimated 9.6 million new cases. Efficient control of TB has been hindered by the lack of effective vaccines and treatments. In addition, it is not completely understood what aspect of the immune response correlates with disease control in TB, further hampering vaccine and drug development. Research into the mechanisms of *M. tuberculosis* pathogenesis and understanding the host-pathogen interaction are essential for the eradication of this devastating disease.

Programmed cell death is an immune response against intracellular pathogens such as TB. For some pathogens, the death of a host cell interrupts the pathogen's replicative cycle and allows other immune cells (e.g. neutrophils) to clear the infectious organism. Various forms of programmed cell death play a role in immune responses to infections. In particular, necrotic cell death pathways such as pyroptosis induce inflammation and recruit immune cells to clear the infectious organism. While the protective role of cell death in most intracellular bacteria is clear, it is not so with *M. tuberculosis*. However, there is evidence suggesting that when induced early during infection, programmed host cell death may be protective against *M. tuberculosis* by halting pathogen replication.

Daisy's project seeks to enhance understanding of how cell death alters TB disease outcome. She intends to test three hypotheses:

1. That pyroptotic cell death is important to the host during *M. tuberculosis* infection *in vivo* by promoting pathogen dissemination.
2. That induction of early cell death specifically in host cells infected with *M. tuberculosis* will interfere with pathogen replication *in vivo*.
3. That a specific host protein, Ipr1, mediates resistance against *M. tuberculosis* infection *in vivo* by promoting early host cell death and clearance.

A better understanding of cell death as an immune response during *M. tuberculosis* infection may help identify new targets and strategies for TB therapy.