Abstract of proposed student project (1 page limit. This should mirror the aims page of a grant and CLEARLY indicate the student's role.)

Malaria infection caused by *Plasmodium falciparum* during pregnancy produces profound placental dysfunction, leading to poor birth outcomes such as intrauterine growth restriction and preterm labor, yielding low birth weight infants. In non-pregnant patients, malaria negatively impacts other organs, including brain, lung, liver, kidneys and spleen, in severe cases resulting in organ failure and death. Severe malaria shares common features with other infections, including those caused by bacteria and viruses, and is similar to sepsis in that it is characterized by disrupted hemostasis, and tissue inflammation and oxidative stress. Understanding these phenomena – how they are initiated, propagated, and interrelated to yield organ damage and dysfunction – forms the foundation of the work in my laboratory. We use a combination of human samples (from women naturally exposed to malaria in Kenya), in vitro culture systems, and mouse models to probe mechanisms in placental malaria pathogenesis.
Previous work in my laboratory has shown that genetic disruption of the extrinsic coagulation pathway (namely, tissue factor (TF)) and the inflammatory mediator, tumor necrosis factor (TNF), independently improve pregnancy outcomes in mice infected with *Plasmodium chabaudi* in early gestation. Likewise, genetic disruption of these pathways in mice infected with another parasite species, *Plasmodium berghei*, mitigates the impact of this infection on the brain and protects against the neurological signs of severe malaria. How these genetic modifications alter the expression of genes associated with inflammation, coagulation and oxidative stress remain to be explored. Because all of these processes are regulated through gene expression, and are known to cross-regulate each other, there is strong rationale to explore how malaria impacts regulation of these pathways.

We hypothesize that inflammation, coagulation and oxidative stress are inexorably linked in malaria pathogenic processes, such that disruption of inflammatory pathways driven by TNF will impact expression of coagulation regulatory genes as well as antioxidant genes and disruption of TF will impact expression of inflammatory genes as well as antioxidant genes.

Research Aim: To characterize expression of TNF, TF and superoxide dismutases (SODs) in spleens of intact (C57BL/6J), TF-modified and TNF knockout mice exposed to malaria.

The proposed project for an FVSP student is to work with cryopreserved samples collected from previously conducted experiments in the above-described mouse models to advance the work proposed in the Aim above. The student will be guided through the processes of isolation of messenger RNA from the tissue and conduct of quantitative reverse transcriptase PCR to assess gene expression changes induced by the genetic modifications (comparing intact and modified mice) and infection (comparing infected and uninfected mice). Initial experiments will focus on spleen, and time permitting, will include work with other organs such as placenta, brain, lung or liver. The student will learn how to analyze and graphically represent the data and will be encouraged to engage in preparation of a manuscript to describe the experiment.