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

Sexually transmitted infections (STI) in the U.S. are at an all-time high, with 20 million new cases each year directly costing the U.S. healthcare system $16 billion. While not currently a reportable STI, *Mycoplasma genitalium* (MG) is an emerging pathogen in men and women and increasingly more prevalent in STI patients. MG is becoming more recognized as a major public health issue, especially as antibiotic resistance is increasing. Understanding of its pathogenicity is limited primarily to epidemiological studies as MG lacks an easily tractable animal model, is difficult to culture, and the few animal studies reported have not fully defined the lesions or interactions with the host immune system. Because the host response to infection is a critical component of mycoplasmal disease pathogenesis, strong model systems should mirror that response as well as induce similar pathology and lesions. *Mycoplasma pulmonis* (MP) causes natural genital disease in rats, and the infection closely mimics many of the key aspects of MG infection of humans. A characteristic of MG clinical disease in humans is induction of a polymorphonuclear leukocyte (PMN) response to MG, as seen in chimpanzees, which are no longer supported as biomedical research models. Similarly, a strong PMN response is seen with MP in rats but not in mice. Like MG, MP can ascend to the female upper tract, causing endometritis, salpingitis, and oophoritis. Males bred to infected females become infected in urogenital tract. Existing models of reproductive infections in males are limited; most use multiple intraurethral inoculations of microbes or direct injection of LPS into reproductive tissues. A notable exception is the murine model using *Chlamydia muridarum* which, like our model, uses a pathogen in its natural host. Our MP model for infections in the male is noninvasive, permitting evaluation of STIs and ascending infection in the male reproductive tract by natural mating without external interventions that, independent of infection, may induce tissue damage.

We recently combined our rat model of intrauterine infection with prenatal nicotine exposure. Nicotine dramatically enhanced the ability of MP to cross the placental barrier and infect the amniotic fluid and fetus, perturbing the normal immune response and resulting in site-specific maternal and fetal pathology. This interaction between nicotine and infection led us to hypothesize that nicotine, a modifiable risk factor, also might impact genital infections in nonpregnant females as well as alter the susceptibility of males for acquisition of an STI from infected females. Although use of traditional cigarettes and/or electronic nicotine delivery systems is linked to risky behaviors that put users at increased risk of STI, nicotine has rarely been considered as a biological risk factor for STI as our model proposes.

Our central hypothesis is that nicotine alters the susceptibility of females to genital infections and increases the potential for males to become infected during sexual contact. Even if the impact of nicotine is limited, the establishment of a noninvasive model of ascending infection in the male urogenital tract using a natural mucosal pathogen is likely to provide critical knowledge on the mechanisms by which a pathogen establishes in the male genital tract and induces damage. We will determine the impact of nicotine on microbial load, lesion severity, and the host inflammatory immune response (Fig. 1) and use targeted gene microarray and inflammatory mediator analyses as well as tissue-specific receptor studies to answer the following questions:

Aim 1. Does nicotine increase the spread of infection to the female upper genital tract? What are the site-specific impacts on the host response to infection?

Aim 2. Are males exposed to nicotine at higher risk for acquisition of a pathogen during mating? What are the site-specific impacts on the host response to infection?

The Veterinary Scholar will be involved in animal procedures to include vaginal cytology, vaginal infection; setting up mating pairs and checking copulatory plugs; potentially anesthesia, surgery, and euthanasia. Laboratory techniques performed by the student will include mycoplasma culture, cytologic and histologic interpretation, immunohistochemical staining and interpretation, and molecular techniques as budget permits. Student will be involved in data handling and manuscript preparation.

Development of this model system to understand how nicotine and infection alone or in concert alters the immune environment in the male and female genital tracts as well as alters acquisition of infection during sexual contact will facilitate new approaches to study other STI pathogens and the adverse effects resulting from exposure to these risk factors. The Veterinary Scholar will come away with new skills in laboratory animal procedures, microbiologic procedures, and histopathologic procedures and interpretation. Student will also participate in data compilation, interpretation, and manuscript preparation experience.