Specific Aims

American Indian (AI) populations have some of the poorest sexual and reproductive health outcomes in the United States. Rates of sexually transmitted infections (STIs) including gonorrhea, chlamydia, and HIV are substantially higher than co-located non-AI populations and the overall US population. AI communities also exhibit higher rates of pre-term birth and low-birth weights. One critical factor underlying urogenital health and of potential importance to AI reproductive and gynecologic complications is the state of the vaginal microbial community. Reproductive age women are vaginally colonized by one of five microbial community state types (CSTs). While four of these CSTs are dominated by Lactobacillus spp. and are generally regarded as healthy, CSTIV is associated with increased risks of various reproductive and gynecologic morbidities. Approximately 1/3rd of women with a CSTIV microbiota exhibit symptomatic BV, the most common vaginal disorder among reproductive age women and have increased risks of acquiring various STI, urinary tract infections, and pelvic inflammatory disease, or being infertile. In pregnant women, CSTIV and BV dramatically increase the risks of pre-term birth and spontaneous abortion. Given the clinical relevance of the vaginal microbiome to host health, it is important to determine its role in the exacerbation of AI reproductive and gynecologic morbidities and the social, environmental, cultural, and behavioral factors of AIs that potentially underscore its dysbiosis. We will achieve this by building upon a recently elucidated mechanistic hypothesis that connects the microbiome, to known risk factors, and CSTIV-associated morbidities through metabolic pathways of the host and microbiome. In a recent NIH-NIAID R21-funded study, we have shown that several biogenic amines are significantly higher in CSTIV women compared to other CSTs and increase immediately prior to a transition to a CSTIV state. This is an important observation that connects CSTIV to symptomatic BV and the associated increased risks of STI. Two clinical signs of BV are an elevated vaginal pH (normal <4.5 vs. BV>4.5) and malodor. The typically low pH of the vagina results from lactobacilli-produced lactic acid and is considered the primary barrier to the outgrowth of potential pathogens. Biogenic amine (BA) production is a well-described bacterial acid resistance and mitigation mechanism, and in sufficient concentrations BAs are responsible for vaginal malodor. Data published elsewhere has shown that BAs can alter pathogen virulence, and can protect pathogens, including Neisseria gonnorhea, from antimicrobial peptides of the innate immune defenses and protective lactic acid. We have shown BAs are produced by several bacteria that bloom early in the transition to CSTIV. We have also shown BAs are higher in populations who display known risk factors for CSTIV and BV, such as smoking. Interestingly BAs are affected by the host in response to stress, a currently unknown variable in the risk of CSTIV, BV, or STI. We therefore will test the hypothesis that AIs are exposed to higher rates of stress, and display risk factors that lead to increases in vaginal BA concentrations resulting in a higher prevalence of CSTIV vaginal microbiota and increased risks for the various reproductive and gynecological morbidities exacerbated in these populations.