Abstract: Regulation of pulmonary inflammation by leukocytes and extracellular matrix
PI: Steven Ziegler
3P01HL098067-03S1

The parent grant (P01 HL098067; Regulation of Pulmonary Inflammation by Leukocytes and Extracellular Matrix) is exploring the idea that communication between lung epithelium and leukocytes directs inflammatory responses. Our overall hypothesis is that changes in local pericellular environments-such as would occur with chronic exposure to tobacco smoke and the accumulation of toxic particulates-provide signals that activate airway epithelial cells and resident and infiltrating leukocytes that shape the innate and adaptive immune responses.

For this FSPTCA supplement, we will expand our program in pulmonary toxicology and assess how specific tobacco products impact specific lung immune response. These new studies will focus on airway epithelium and macrophages complementing the goals of two projects: Project 2, TSLP and Lung Inflammation and Immunity (Ziegler), and Project 3, Role of MMP10 in Lung Immunity (Parks). TSLP is a critical epithelial-derived cytokine with established effector roles in Th2-type inflammation in humans and rodents, but its function in tobacco-related lung immune responses is unknown. MMP10 drives macrophage activation towards an immunosuppressive and has been linked to development and severity of COPD in human smokers. The Parks lab has found that MMP10 promotes emphysema via an ability to drive macrophages to a Th2-type immune profile. For the FSPTCA supplement, studies will be conducted in both mouse and relevant cell-based models to explore how TSLP and MMP10 shape influence the airway and macrophage response to smoke exposure. The planned studies will compare the effects mediated by inhalation of menthol cigarette smoke and menthol-flavored e-cigarettes and will interface closely with two groups at the University of Washington. One, the Center for Ecogenetics and Environmental Health will help with the evaluation of the toxicity of tobacco smoke constituents, with emphasis on genetic toxicology and toxic consequences on stress responses, cellular redox status, and phase II metabolism.

Two, our studies and models will be developed in collaboration with another UW group seeking an FSPTCA supplement (P01 HL094374, Stem Cells and Cardiovascular Repair, PI: CE Murry).