**The Impact of Tobacco Exposure on the Lung’s Innate Defense System**  
Mouse Models of Human Smoking-related Diseases: What is the Best Mimic of Human Disease? (Project 3)  
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**Abstract:**

Tobacco smoke is the most common cause of chronic obstructive lung disease (COPD). Most mouse models of tobacco smoke related lung disease expose mouse strains to tobacco smoke, which results in mild-to-moderate emphysema, but with little or no evidence of the chronic bronchitis, a large component of COPD in humans. Recently, we began modeling tobacco smoke exposure by exposing transgenic mice overexpressing Scnn1b, the gene that codes for the epithelial Na+ channel subunit (βENaC), to tobacco smoke exposure. These initial studies suggest that this model mimics human injury more closely than mouse models to date. This project will test the hypothesis that smoke exposure in Scnn1b-tg mice is an excellent model of human disease and can be used more effectively than either wild type (WT) mice or other mouse models of COPD to study particular components of smoke or to compare tobacco products or substitutes. The first aim of this project is to establish this mouse model by exposing Scnn1b-tg and WT mice to tobacco or sham smoke and analyzing the following parameters related to disease: (i) pulmonary immune cell populations and cytokine production; (ii) immunophenotypes of cells in the lungs and mediastinal lymph nodes; (iii) protein and miR content of mucus and airway exosomes; (iv) mucociliary clearance and clearance of H. influenza; (v) mRNA and miR expression in whole lungs and isolated lung cells, including macrophages, neutrophils, and epithelial cells; and (vi) the activity of five critical intracellular signaling pathways in epithelial cells including the NF-κB pathway and the Keap1/Nrf2 pathway using bioluminescent in vivo reporters. In addition to comparing the results of the two models (smoke exposure in WT and Scnn1b-tg mice) to each other, we will also compare their results to the data generated from our human studies and from the literature to define the degree of similarity of these mouse models to tobacco smoke-induced lung injury in humans. After establishing the best mouse model for human smoke exposure, we will then determine the adverse health consequences of new and emerging tobacco products (NETPs), such as little cigars and hookahs, using the same parameters listed above. Finally, these results will be compared to the results generated from our cigarette studies to help define the adverse health consequences of NETPs.