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*Department of Molecular Biology and Microbiology* *2006 Program*
*University of Central Florida* *New Investigator (3-year project)*

**Project Title:** Prostasin Protects Lung Epithelial Cell Integrity From Cigarette Smoke Induced Stress

**Project Summary**: Cigarette smoking is associated with an increased incidence of airway infection and numerous diseases including lung cancer and chronic obstructive pulmonary disease (COPD). The epithelium of the lung, a layer of cells that cover the airway and in direct contact with the "outside" environment, functions as a selective barrier. Cigarette smoke damages the lung epithelium barrier and causes increased permeability of the epithelium by disrupting the natural "sealant" of the tissue, known as intercellular tight junctions (TJ), a complex of interacting proteins. Prostasin is a proteolytic enzyme (of the serine protease family), and is present on the normal lung epithelial surface. Previous research in this laboratory has led to the finding that prostasin is greatly reduced in quantity or absent in invasive breast cancer and prostate cancer cells. Re-introduction of prostasin in the breast and prostate cancer cells was sufficient to reduce their malignancy. Preliminary work performed for this project also established a loss of prostasin in human lung cancer cells. Prostasin has been shown to be necessary for maintaining the tight junction structure, protecting the natural "sealant" of the epithelial cell layer. Lung cancer cells with loss of prostasin do not properly assemble the TJ components into functional and effective TJ's/"sealant." Injured epithelium needs to be rapidly repaired. Appropriate repair requires adjacent epithelial cells to migrate, proliferate (grow), and differentiate (specialize, e.g., making the TJ proteins and sealing the tissue) so the injured sites are covered and sealed once again. The migration, proliferation, and differentiation of the repairing cells have to be tightly regulated through orchestrated execution of the cells' molecular programs. Failure of this repair process at any level is a direct cause of lung diseases, acute or chronic. A constant exposure to cigarette smoke makes the lung epithelial cells highly susceptible to development of lung cancer because of dis-orchestrated cellular migration, proliferation, and differentiation programs.

The study has shown in preliminary studies that cigarette smoke extract (CSE) greatly reduces prostasin presence in human airway epithelial cells, with concomitant reduction of TJ/"sealant" components. Given prostasin's proven pivotal role in maintaining TJ/"sealant" protein presence and organization, we propose that CSE-induced reduction or loss of prostasin in the short and long term will lead to disorganization of TJ's/"sealant" of the airway and produce a leaky epithelium. Further, because the proper production and organization of the tight junctions mark the end of the differentiation program at the molecular level for the injury repairing cells, a lack of this communication will promote further migration and growth of cells beyond their call of duty to repair the wound. These events will then eventually lead to the development of lung cancer.

This project will test 1) if prostasin protects tight junction structure and function under cigarette smoke stress, 2) if prostasin enhances epithelial cell differentiation thus suppressing tumor malignancy, and 3) if chronic cigarette smoke exposure to airway epithelial cells causes a selection for cells with a loss of prostasin by a common gene-

silencing mechanism in cancer known as DNA methylation (a chemical modification of DNA that renders genes inactive). The outcome of this research will establish prostasin as a potential therapeutic agent for use in preventing and treating lung diseases resulting from cigarette smoking.